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“Innovation through Cyclotron/ and Generator-based Positron Emission Tomography (PET) - Radiopharmaceuticals: Challenges and Barriers in Receiving Market Authorisation”

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München, 06.06.2019 Georg Konwalinka

„All I know is that I know nothing.“
(Socrates, * ~ 469 before Chr, † 399 AD)

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1.1 Introduction to the Research Topic:

Cancer is the leading cause of death in developed countries, with higher incidence and mortality rates compared to economically developing countries (Jemal et al., 2011). The latest global estimate from the International Agency for Research on Cancer (IARC), showed a total of 12.7 million new cancer cases worldwide in 2008, and this number is expected to increase to 21.4 million in 2030 (Ferlay et al., 2010).

Much effort was taken in the past ten years to fight this global burden. Several developed countries and global health institutes have implemented cancer control programs to reduce the incidence- and mortality rate and also to improve the quality of life of cancer patients. The World Health Organisation (WHO) aims member states to start a systematic implementation of evidence-based interventions for prevention, early detection, diagnosis, treatment and palliative care (World Health & Organisation, 2008). In the long term, prevention and thus raising the awareness of cancer risk factors seem to be the most cost-effective and promising strategy in avoiding cancer cases. The primary objective of early detection through screening is to detect precancerous changes or early stages of cancers when they can be treated most effectively (Jemal et al., 2011). Globally many screening programs (e.g. lung, breast, cervical, colon and prostate cancers) are in place, with varying interpretations of the effectiveness of specific screening programs (Hugosson et al., 2010).

Both in early detection and diagnoses of cancer, non-invasive imaging such as radiology (X-Ray), Computer Tomography (CT), Magnet Resonance Imaging (MRI), and Ultrasound (US) and nuclear medicine procedures (Single-photon emission computed tomography – SPECT; Positron Emission Tomography –PET) and their hybrid forms of PET/CT and PET/MRI have gained increasing importance. Since the discovery of x-rays by Wilhelm Conrad Roentgen in 1895, new imaging techniques have emerged rapidly over the years. X-ray and CT, using ionising radiation, and MRI, using a strong magnetic field and radio waves, now enable a precise inspection of on the body's anatomical structures (Buzug, 2005). SPECT and PET use short- and ultra-short-lived radionuclides, which are connected to a specific biological active substance and therefore accumulate in a region of interest. With a detector, this emitting radiation (SPECT) and positrons (PET) can be detected and therefore give a three-dimensional picture of the functional processes in the human body (Granov, Tiutin, & Schwarz, 2013).

Imaging has, therefore, become an indispensable tool in cancer research, clinical trials and medical practice (Weissleder & Pittet, 2008). The underlying medical question and the field of investigation mainly drives the use of one or the other imaging technique, but imaging specific molecular targets should allow earlier diagnosis and better management of oncology patients (Gambhir, 2002). PET/CT is seen as a modality with high precision in the identification of early disease, the differentiation between benign from malignant lesions, the detection of metastases, and determination of therapeutic effectiveness of tumours (Massoud & Gambhir, 2003; Phelps, 2000a). PET is an imaging technique, which is thought to be new, the basis for PET was already laid in the 1970s (Granov et al., 2013). However, with the evolving knowledge of cancer biology, pharmacology and the clinical implications the number of radiolabelled tracers increase steadily and so the field of application in imaging. With the fusion of PET with CT (PET/CT Scanner) in 2002, it was then possible to get high-resolution functional and morphological images (von Schulthess, Steinert, & Hany, 2006) which considerably changed the management of patients with cancer (Fletcher et al., 2008; Juweid et al., 2007; Juweid & Cheson, 2006; Lardinois et al., 2003; Rohren, Turkington, & Coleman, 2004; Seam, Juweid, & Cheson, 2007; von Schulthess et al., 2006; Weber, 2006).

The heart of a PET (PET/CT) and SPECT procedure is its underlying radiopharmaceutical (RP). These drugs contain radioactive materials called *radioisotopes*, which target and accumulate in an affected area and are used for diagnosis or therapy. Because of the fractional amount of these substances in imaging tracers, these agents, which consist of a radionuclide and pharmaceutical part, do not show any pharmacological effect (World Health Organisation, 2008). The amount of activity will be aligned with the field of investigation and is expressed in units called Becquerel (Bq) or Curie (Ci). For decades the SPECT radionuclides ^{99} Mo (Molybdenum) and ^{99m} Tc (Technetium) have been the primary source of diagnostic RPs, covering approximately 80% of all nuclear medical procedures (Deutsch, Libson, Vanderheyden, Ketring, & Maxon, 1986; Liu & Edwards, 1999; Rösch & Baum, 2011). With the step-up of PET, more radionuclides are currently used for research and clinical practice: ^{11}C (Carbon), ^{13}N (Nitrogen), ^{15}O (Oxygen), ^{18}F (Fluor), ^{64}Cu (Copper), ^{124}I (Iodine) and ^{68}Ga (Gallium) (Schicha & Schober, 2013). Due to the convenient production of radionuclides via generators the ^{68}Ge/^{68}Ga generator has spread quickly and is now a routine source of positron emitting ^{68}Ga for PET/CT imaging (Velikyan, 2014). With the rising number of radionuclides and their specifics pharmaceuticals (e.g. monoclonal antibodies, peptides) individual diagnoses, treatment planning and control will lead to a patient-based treatment of the disease (Rösch, Herzog, & Qaim, 2017).

1.2 Statement of the Research Problem:

In the past decade, the term “personalised medicine” (PM) became the magic word for almost every player in the healthcare industry. It is the goal: “Provide the right patient with the right drug at the right dose at the right time” (Sadee & Dai, 2005). The National Academy of Sciences in the United States (NAS) defined personalised medicine as “*the use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment*.” (Committee on a Framework for Development a New Taxonomy of Disease National Research Council, 2011).

It is sure that medical diagnostics will play a significant role in PM and the treatment of oncological diseases, enabling the identification of the patient´s genetic, anatomical and physiological characteristics. Besides molecular diagnostic tests, anatomic imaging and molecular imaging (MI); the latter has the advantage to detect and characterises tumours based on their molecular alterations. With these new tools, it will be easier to understand the heterogeneity of metastatic diseases, and it can examine in-vivo and non-invasively (Kircher, Hricak, & Larson, 2012).

The current workhorse of PET is 2-[18F] fluoro-2-deoxy-D-glucose (^{18}F-FDG), a glucose analogue labelled with Fluor- 18, which allows assessing the glucose metabolism levels in tissues and the differentiation between healthy and disease levels (Coenen et al., 2010; Fletcher et al., 2008). Because of its non-patented status, this tracer quickly became a standard in the diagnosis of cancer (Schwaiger & Wester, 2011). However, ^{18}F-FDG alone cannot serve as a companion diagnostic for the discovery, development, and use of new molecular therapeutics. Increasing diversity of tracers beyond ^{18}F-FDG will be needed in the clinic to provide useful diagnostics with more specificity over a greater range of disease and injury (Coenen et al., 2010). Genome-wide association studies (GWAS) have enabled rapid discovery of genetic variants contributing to the pathogenesis of complex genetic diseases (Manolio, 2010). This knowledge of molecular biology shifted the way of research towards developing target-specific RPs based on receptor binding of a radiolabelled receptor ligand in the diseased tissue. This high receptor binding affinity and specificity makes PET and SPECT unique in comparison to any other imaging modality (Liu, 2004; Phelps, 2000a). ^{68}Ga is, for example, a promising new radioisotope in the field of neuroendocrine tumours, which improved the neuroendocrine tumour detection and are now widely applied in Europe (Johnbeck, Knigge, & Kjær, 2014; Maecke, Hofmann, & Haberkorn, 2005).

Because PET, and the hybrid systems PET/CT and PET/MRI, are such powerful and sophisticated tools, research facilities all around the world have established their centralised radiochemistry facilities to produce and develop new PET probes independently. At the moment thousands of radiolabelled molecules have been researched, several hundred tested in human, but only a few dozen received an international market authorisation for a diagnostic and therapeutic purpose (Zimmermann, 2013). Since radiopharmaceuticals are approved according to the same rules as pharmaceuticals, public universities and research organisations struggle with the high costs of running their research facilities, the lengthy process and the high costs associated with the regulatory approval (Schwaiger & Wester, 2011). Whereas ^{18}F-FDG was very versatile applicable for imaging, newer radiopharmaceuticals used in oncology (for imaging and therapy) tend to be more specific and have a narrower field of application. A drug´s specialisation subsequently decreases the sales market, the return on investment (ROI) and thus the investor´s market attractiveness (Henderson, Alexander, & Smith, 2005; Nunn, 2007a; Zimmermann, 2013). A guaranteed profit may not be easily achieved without taking a higher commercial risk (Zimmermann, 2013).

The pharmaceutical industry, as a fundamental investor for RPs, is currently struggling with several challenges: less revenue due to expiration of patented blockbusters (≥ 1 billion of annual sales); low productivity in new drug development (Khanna, 2012) and pressure on the reimbursement of new products (Kaitin & DiMasi, 2011). Thus many of the larger companies adjusted their strategies and risk-reward ratio and may not be invested in products with lower or moderate market size (< 300 million dollars) (Khanna, 2012).

The decreasing R&D budgets (for products with higher commercial risk) also affect the investor´s interest in nuclear medicine products and subsequently prevents the market authorisation of clinically useful drugs. Several barriers have been described in literature:

(1) Economic and Market-related Challenges
   i. The market is very small because imaging agents are undervalued, and current prices will not support a new drug unless it is used in high volume (Nunn, 2007b).
   ii. RPs have limited profitability even if they are proprietary (Zimmermann, 2013).
   iii. There is a limited possibility for commercial exploitation of academic discoveries (Mather, 1998).

(2) Research and Development
   i. High development costs for radiopharmaceuticals, ranging from 100-200 million dollars for an RP imaging agent (Henderson et al., 2005; Nunn, 2006; Zimmermann, 2012a) and around 800 million dollars for a new therapeutic drug (e.g. DiMasi, Grabowski, & Hansen, 2016; DiMasi, Hansen, & Grabowski, 2003; Prasad & Mailankody, 2017)
   ii. Some biological imaging markers are clinically not validated and adopted, because they do not measure a relevant biological feature nor enable disease diagnosis or outcome prediction (O´Connor et al., 2017).
   iii. Experimental RPs are used in the drug development process to investigate pharmacokinetic and to dose but are not developed further (Nunn, 2007a).
   iv. Intellectual property right (IPR) issues between public research groups and potential investors. Sharing IPRs may limit exclusive commercial rights and discourage commercial development for investors (Schelbert, 2011).

(3) Regulation and Marketing Authorisation
   i. There are many validation steps necessary to regulatory and safety approval in the development and production of RPs by national authorities (Henderson et al., 2005; Nunn, 2007a; O´Connor et al., 2017; Zimmermann, 2013).

ii. At the moment, the requirements by the FDA and EMA for the regulatory approval of imaging agents are the same as for therapeutics (Agdeppa & Spilker, 2009).

(4) Reimbursement and Revenue Planning

i. Shrinking revenue for investors based on the low or even decreasing reimbursement rates for diagnostic imaging tests (Nunn, 2007a; Zimmermann, 2013).

ii. Health Technology Assessment (HTA) is implemented in many developed countries, evaluating the benefit of a medicinal product and the data is used for price/ reimbursement negotiations. Imaging biomarkers are evaluated based on the same patient-related benefits indicators (mortality, morbidity and health-related quality of life) as pharmaceutical drugs (Institute for Quality and Efficiency in Health Care - IQWIG, 2017a).

(5) Different goals between the Scientific Community and Investors/Industry

i. Different goals in the industry- and academic research: The questions asked in academia generates data, which may not be helpful in the market authorisation process (Buscombe, 2015).

ii. Limited knowledge in the scientific community (outside of the nuclear medicine field) on the benefits of radiopharmaceuticals in the diagnosis and therapy of cancer (Zimmermann, 2013);

(6) Special Manufacturing, Distribution and Handling of Radiopharmaceuticals

i. Special manufacturing and distribution of RPs due to the usage of radioactive components (Bundesministerium für Justiz und Verbraucherschutz, 2017; Bundesministerium für Erwelt Naturschutz und Reaktorsicherheit, Bundesministerium für Gesundheit, & Bundesministerium für Verkehr Bau und Wohnungswesen, 2017; European Commission, 2017; International Atomic Energy Agency, 2008; Zimmermann, 2013)

These obstacles lead to fewer RPs receiving market authorisation, even if they could potentially significantly contribute to the treatment of specific diseases (Kratochwil et al., 2015). If new, efficient and innovative technology does not reach the market, it appears to be a market failure. The same phenomenon can also be observed in “neglected diseases” (Trouiller et al., 2002). Initially, Schumpeter assumed in his work of *Capitalism, Socialism, and Democracy* that large firms with industrial research laboratories enjoy a static market power and would use their economic profits to finance risky, large-scale R&D activities whereby the society and the company will profit (Schumpeter, 1975).

However, on the contrary, one could observe that less and less research-based pharmaceutical companies take the financial risk of drug R&D (Comanor & Scherer, 2013). Professional Institutions, such as the National Institute of Health (NIH) or the National Cancer Institute (NCI) in the United States identified the low investor´s interest and are trying to bring new investors into the market. With the success of the concept of public-private partnerships (PPP) in public infrastructure project, it was also suggested that this would be a suitable concept for life science and drug development sector (Lazdins-Helds, 2008; The European Commission, 2013; Vaudano, 2013; Yildirim, Gottwald, Schüler, & Michel, 2016). The concept pursues the goal to invite different players to participate in clinical trials actively, share financial risks and thus overcome the deficiency of authorised products (Aerts, Sunyoto, Tediosi, & Sicuri, 2017; Mercanoglu & Ozer, 2015).

1.3 Statement of the Purpose of this Study

Several barriers in the development and authorisation of new radiopharmaceuticals have been described in literature so far, but little is known about the real weight of each “obstacle” from the view of the investors and scientific community. Do stakeholders in Europe experience the same challenges? Are challenges seen differently in countries with regulatory approved in-house production? The studies

dealing with this topic are mostly written by a member of one stakeholder group such as the pharmaceutical industry, the scientific community, and the regulatory authorities. These studies can be described as "reviews", but so far no study could be identified, which surveyed the stakeholder´s (industry, scientific community, regulatory organisation) point of view empirically.

The purpose of the proposed study is to explore and explain the challenges of diagnostic and therapeutic radiopharmaceuticals with regards to receiving a marketing authorisation, and identifying the underlying disinterest from private investors ("Why"). The study will furthermore investigate the challenges and/or success factors for public-private- partnerships and how it could resolve some of the critical problems.

Research questions:

1. What is the clinical efficacy of Somatostatin Analogues and PSMA ligands in diagnostic and therapy?
2. What are the main challenges, why diagnostic and therapeutic Radiopharmaceuticals are currently mainly developed in public research organisations and don´t reach market authorisation?
3. What are potential alternatives to the "traditional" pharmaceutical drug development process and how could these address/solve the above problems? Can the concept of public-private partnerships (PPP) serve as an alternative to improve the number of diagnostic and therapeutic radiopharmaceuticals?

1.4 Methodology

For this research purpose, a quantitative and a qualitative research method will be used to triangle the problem from different perspectives and test the consistency of findings from one method to another. This research approach has its roots in the pragmatic worldview: "Instead of focusing on methods, researchers emphasise the research problem and use all approaches available to understand the problem" (Rossman & Wilson, 1985). Methodological pluralism can increase the scope and the level of possible analysis (Johnson & Onwuegbuzie, 2004).

The first theoretical framework of the mixed research method by Rossmann & Wilson in 1985 initially described three purposes: corroboration, elaboration and initiation. Soon this concept was extended by another purpose: development (Greene, Caracelli, & Graham, 1989; Rossmann & Wilson, 1991).

- Corroboration: A classical triangulation where different methods are employed to test the consistency of findings from one method to another (Rossman & Wilson, 1985).
  "*Pinpoint the values of a phenomenon more accurately by sighting in on it from different methodological viewpoints*" (Brewer & Hunter, 1989)
- Elaboration: Is a concept of complementarity and provides additional richness and detail if just one method is used. It "*enhances, illustrates, clarifies the results from one method with the results from the other*" (Greene et al., 1989; Rossman & Wilson, 1985; Rossmann & Wilson, 1991)
- Development: "*The results from one method shape the instrumentation, sampling and analysis strategies of the other method*" (Greene et al., 1989).
- Initiation: This purpose intends to uncover "paradox and contradiction", reframe the research question to challenge the original conceptual framework (Greene et al., 1989; Rossman & Wilson, 1985).

Dickson, C. and Wilson, B. significantly demonstrated the efficacy of the mixed research model in two social studies (Dickson, 1991; Wilson, Rossman, & Adduci, 1991).

The reason we analyse the efficiency of two of the most widely studied radiopharmaceuticals (neuroendocrine tumours and prostate cancer) in the first step: we need to make sure that the technology is efficient and does not fall short due to inferiority. Otherwise, the assessment of challenges/ barriers, and the reasons for the low investor interest is not reasonable.

1.4.1 Quantitative Research – Focused Literature Review

The aim of conducting a literature review is often to enable the researcher both to map and to assess the current intellectual territory, and to specify a research question to develop the existing body of knowledge further (Tranfield, Denyer, & Smart, 2003). It is nowadays well known that a good literature review is the basis of both theoretical and methodological detailing, and improves the quality and usefulness of the following research (Boote & Beile, 2005). Especially in medicine, where recommendations are based on solid clinical research, it is essential to achieve a certain level of evidence. Systematic reviews and meta-analyses are a crucial element of evidence-based healthcare, ensuring that clinical decisions are made by the most up-to-date, trustworthy, reliable scientific evidence (Khan, Kunz, Kleijnen, & Antes, 2003; Sackett, Rosenberg, Gray, Hynes, & Richardson, 1996).
We were guided by the requirements of the systematic literature review, but it was not the goal to create a systematic review of the cases NET and PSMA. Nevertheless, we tried to carry out a scientifically transparent process, to eliminate bias by extensive literature search and to refer to currently available, scientifically high-quality reviews.

Search Terms used for the identification of relevant literature:

I. Search terms to identify studies dealing with Radiopharmaceuticals and Neuroendocrine Tumours:
   - Diagnostic: "PET" OR "PET/CT" AND "neuroendocrine tumour" OR "carcinoid"
   - Therapeutic: "peptide receptor radiotherapy" OR "PRRT" OR "radiotherapy" OR "lutetium" OR "yttrium" AND "neuroendocrine" OR "neuroendocrine tumour"

II. Search terms to identify studies dealing with Radiopharmaceuticals and Prostate Cancer:
   - Diagnostic: "PET" OR "PET/CT" AND "prostate" OR "prostate cancer" OR "PSMA"
   - Therapeutic: "peptide receptor radiotherapy" OR "PRRT" OR "radiotherapy" OR "lutetium" OR "yttrium" AND "prostate" OR "prostate cancer" OR "PSMA"

III. Search terms to identify studies dealing with the challenges and barriers to get Radiopharmaceuticals approved:
   - "molecular imaging" OR "radiopharmaceutical" OR "imaging biomarker" OR "radiotracer" AND "constraints" OR "challenge" OR "uncertain" OR "economic"

Inclusion Criteria for Search Term I and II:

- Only full publications
- Only studies with the species "human"
- Studies in the field of oncology
- Studies needed to have a prospective, retrospective design. Case reports have been excluded.

Inclusion Criteria for Search Term III:

- Only full publications
- Studies in the field of oncology
- Studies discussing challenges, problems, opportunities or topics related to regulation and market authorization of radiopharmaceuticals
- Studies after 2001 (In 2001 the European Union introduced a new directive (EU 2001/83) on the use of medicinal products in human use, which affected the marketing authorization of radiopharmaceuticals (Decristoforo & Peñuelas, 2005)

Exclusion criteria:

- Studies with focus on medical efficacy, technical implementation, and health efficacy assessments, paediatric, nanoparticles, animal studies, ultrasound, Magnet Resonance Imaging and all studies not related to the above research question and the field of oncology.

All included studies were screened for additional relevant references.

The primary databases for both literature reviews were: PubMed, Science Direct, EMBASE and Google Scholar.

1.4.2 Qualitative Research – Expert Interviews

While quantitative research tools identify the causal mechanism with statistical methods, qualitative research looks into the causal mechanism and identify the scope´s determination (Gläser & Laufel, 2009). For decades there is an ongoing methodological debate, whether scientific conclusions can be made based on qualitative research methods or quantitative research, such as the gold standard Randomised Controlled Trials (RCTs), are the only valid scientific procedure in health studies, education, social work and social sciences (Cochrane Collaboration & Campbell Collaboration, 2017). There is a long history of criticism that qualitative research does not adequately justify its assertions and that the creation of theory is based on rather thin evidence (Gioia, Corley, & Hamilton, 2013).

The different views are hieratic, and so in the last decades, a mixed methods research approach has emerged as an alternative in social and behavioural science (Creswell, Klassen, Plano, & Smith, 2011). This new methodical approach should improve the quality and scientific power of data, by investigating complicated health problems with a multi-level approach (Creswell et al., 2011). In this context multi-level means that investigators, with knowledge of the social and health word, gather evidence via various sources and levels that influence a given problem. The opportunity to integrate a variety of theoretical perspectives (Creswell et al., 2011).

Quantitative methods are used to measure the depressiveness of a known phenomenon, whereas qualitative research methods build on the gathered evidence. One can identify previously unknown processes and explanations of why and how phenomena occur, and the range of their effects (Creswell et al., 2011; Pasick et al., 2009). The strength is the focus on the context, the intentional collection of both quantitative and qualitative data and the interpretation of qualitative data to understand processes.

> *"It is a systematic and rigorous form of inquiry that uses methods of data collection such as in-depth interviews, ethnographic observation, and review of documents. Qualitative data help researchers understand processes, especially those that emerge over time, provide detailed information about setting or context, and emphasise the voices of participants through quotes. Qualitative methods facilitate the collection of data when measures do not exist and provide a depth of understanding of concepts."* (Creswell et al., 2011)

We used the qualitative research tool "interview", what we find to be a suitable method for collecting data and answering the research questions. Interviews, in general, are useful to generate valued scientific knowledge, also because it has become one of the most widespread knowledge-producing practices across the human and social sciences in general (Brinkmann, 2014). Knowledge is generated through the interaction between the interviewer and an interviewee, with the purpose of obtaining descriptions of the living world and describing the phenomena (Brinkmann & Kvale, 2017). Interviews techniques have been extensively described in literature, ranging from focused-, biographic-, narrative, qualitative-, problem- centred-, standardised-, partly standardised interviews and many more (Gläser & Laufel, 2009).

In this thesis, we have opted for a semi-structured expert interview approach. The idea is that the researcher provides some structure to the interviewee, based on the research interest, but allows for more spontaneous descriptions and narratives (Brinkmann, 2014). The rationale to interview "experts" is that those persons should be better informed, have a unique source of inside information and are more motivated compared to mass surveys (Dorussen, Lenz, & Blavoukos, 2005). Experts are seen as individuals, who are part of the sphere of activity and are responsible for the development, implementation or control of solutions, strategies or policies (Audenhove, 2007; Meuser & Nagel,

1991). Furthermore, interviews with experts allow the researcher to have control over the dimensions that are central to the related research topic (David, 1996; Dorussen et al., 2005).
Even this approach is commonplace in medicine, management and marketing, communication, political science and education studies (Dorussen et al., 2005), there is some debate on whether qualitative research data is reliable. For example, there is criticism that the results rely upon few data points, that experts do not have the same knowledge, interviewees may report on their thoughts or actions which could be incomplete or even deceitful, and the interpretation of the data is affected by the researcher´s subjectivity (Brinkmann, 2014; Brinkmann & Kvale, 2017). Indeed, an interviewee can provide a convincing narrative of a situation, but also other things could be said about the topic. Therefore, it is necessary to be suspicious, as these narratives could be constructed. The argument about the researcher's subjectivity could be countered by the argument that all research involves interpretation, even data from statistical tests need to be interpreted based on pre-existing theories, personal preferences and contextual understanding (Brinkmann, 2014).

> *"Qualitative research procedures are explicitly interpretive in their approach, striving to make sense of data and often expressing great caution about generalizability."* (Brinkmann, 2014)

Dorussen et al. (2005) used the Condorcet Jury Theorem to evaluate the quality and reliability of the expert-opinion data. In the most basic form of the Condorcet Jury Theorem, a group of individuals independently make a binary decision that is either "right" or "wrong", with each has a fixed probability of being right. The asymptotic part of the theorem states that "it becomes extremely likely that the majority is right when the number of individuals increases", and the non-asymptotic part assumes that "the majority is more reliable than each citizen" (Dorussen et al., 2005). And as a result this research group has revealed that expert interviews are an attractive data collection method, but the validity of the information depends on the quality of the experts. They also clarified that:

> *"Any theoretical link between the reliability and validity of data cannot simply be assumed. However, the Condorcet Jury Theorem can be used to argue for the existence of such a link. More coherent, i.e. reliable, experts are also more likely to be right, i.e. provide valid information, under some quite general and reasonable assumptions. The Condorcet Jury Theorem does not require all experts to be equally knowledgeable, and they may be better informed on some issues rather than others."* (Dorussen et al., 2005)

The limitations are apparent: Only with high-quality data sophisticated assumptions can be made, and the experts need to be willing to participate (Dorussen et al., 2005).

1.4.2.1 Qualitative Content Analysis

The starting point of the Qualitative Content Analysis is the Quantitative Content Analysis. In this case, the quantitative content analysis is our focused literature review, which was our basis to systematically draft the qualitative research questions. The generated dataset is subject to the analysis of the researcher, with the main purpose to reach for statements about the subject matter. "*Because without a specific line of inquiry or established direction of analysis any content analysis would be unthinkable*" (Mayring, 2014). Based on the nature of the research question we have selected the qualitative content analysis approach based on the methodology of Bryman & Bell (2011) and Philipp Mayring (2000).

Because qualitative data is related to concepts, values, opinions and behaviours of people, the data cannot be reduced to numbers but is processed in some form of explanation and understanding (Lewins, Taylor, & Gibbs, 2010). Different methods are described in the literature, associated with specific approaches or traditions such as grounded theory (Strauss & Corbin, 1998), narrative analysis (Andrews,

Squire, & Tamboukou, 2013), phenomenology (e.g. Sokolowski, 2000), and discourse analysis (e.g. Brown & Yule, 1983). The basis for Strauss, Corbin´s ground theory is recognised as the inductive analysis approach, a systematic procedure for analysing data guided by specific evaluation objectives (Thomas, 2006). *"The researcher begins with an area of study and allows the theory to emerge from the data"* (Strauss & Corbin, 1998). The analysis is "goal-free", the extensive and varied raw data is condensed into a brief, summary format. Clear links are established between research objectives and the raw data´s findings to show transparency and defensibility, and to develop a model or a theory about the underlying structure (Thomas, 2006).

The second approach is called deductive analysis used to test whether data is consistent with prior assumptions, theories, or hypotheses. Researchers very often use both methods to analyse their data. A central element in the analysis is the "category system", which can be either deductive or inductive. The latter emerge out of the analysis itself, whereas in the deductive approach the theoretical considerations are the basis for the categories (Mayring, 2000).

1.4.2.1.1 Category System and Coding:

For the analysis of the semi-structured interview qualitative data set, we have chosen to use the deductive as well as the inductive method. The benefit of the inductive approach: frequent, dominant, or significant themes can emerge from the raw data, without being restrained by structured methodology (Thomas, 2006). In the concept of content analytical procedures, the text is not interpreted as a whole but split into segments, which are defined (in advance) into categories. This segmentation is also called "coding into units", it is distinctive and offers a second reviewer the possibility to come to similar results (Mayring, 2014). The author has used the approach by Gioia et al. (2013), stepwise identifying informant terms and categories via the 1st-order analysis, looking for similarities and differences among the many different categories and label them. In the 2nd –order analysis one is looking for emerging themes, which may help to describe and explain phenomena.

1.4.2.1.2 Unit level data and Coding unit:

In some cases, it made sense to classify responses in whether they "agree", "disagree" or were "neutral/ undecided". It is worth mentioning that due to the structure of the interview, the majority of questions was not towards receiving a "Yes" or "No" answer, but in some instances interposed questions led to answer such as "agree", "disagree" or "neutral/undecided".

The coding unit (Baxter, 1991) is a constellation of words or statements that relate to the same central meaning, also known as a keyword and phrase, a unit of analysis, and a theme (Graneheim & Lundman, 2004). So a coding unit can be words, sentences or paragraphs, and should be defined in advanced. In this thesis the coding unit is at least a sentence, more often we used paragraphs. These coding units had to contain a statement or a causal statement relevant to the research questions. After transcription of all interviews, those were reviewed several times to identify significant themes and categories.

1.4.2.2 Characteristics of the Study Population

The primary research interest of this study is to explore and explain the economically, regulatory, and developmentally challenges of diagnostic and therapeutic radiopharmaceuticals with regards to receiving marketing authorisation, and the future role of molecular imaging in patients with cancer disease. Typically, several stakeholders take part in the development of new drugs/ imaging biomarkers as outlined in Figure 1. Especially in nuclear medicine, new products have often been developed within a unique collaboration between national laboratories, academia, different research communities and the industry (National Research Council (US), Institute of Medicine (US), & Committee on State of the Science of Nuclear Medicine, 2007). The academic community was and still is the foundation for basic research, the translation from basic research to applied clinical research and has been driving many new pharmaceutical , radiopharmaceutical and biopharmaceutical innovations (Kaitin, 2010).

Figure 1 shows the main stakeholders involved in the approval, development and research of new radiopharmaceuticals.

Experts from the following fields were identified in advance to be most valuable to answer the research question:

1. Experts in nuclear medicine and/or molecular imaging
2. Experts in the treatment of patients with prostate and/or neuroendocrine cancer
3. Experts from the pharmaceutical industry with knowledge in imaging and/or companion diagnostics
4. Experts from the Radiopharmaceutical business with knowledge in Research & Development and/or General Management
5. Experts from the Molecular Imaging Equipment industry with knowledge in the nuclear medicine/ molecular imaging area
6. Experts from a national and/or cross-country regulatory authority responsible for the authorisation imaging biomarkers and/or implementation of new regulations.

1.4.2.2.1 Identification of Experts

For our study, we identify several experts from the stakeholder groups, who would be willing to take part in this study. In advance, we have defined the expert to be "a leading physician, leading manager, leading researcher, who is qualified because of his skill, knowledge, education, experience, or training. He/she knows the medical and healthcare professional field, beyond that of an average person."

i. <u>Identification of Medical Experts (Nuclear medicine physicist, medical specialist, and oncologist):</u>
"Must" criterion: high knowledge and experience in their field of specialisation; knowledge evaluated by the number of relevant publications in peer-reviewed, high-impact journals; currently high ranked job position in well-respected (mainly university) hospitals;
"May" criterion: Personal recommendation of a previously selected interview partner, if he/she is prevented.

ii. <u>Identification of experts in the industry:</u>
"Must" criterion: general knowledge and experience in the pharmaceutical, radiopharmaceutical and medical technology field; very sound knowledge in molecular imaging and/or the application of companion diagnostics; Perennial experience in the relevant industry;

high ranked position in the company, preferred in Research & Development or General Management;

“May” criterion: relevant publications in journals or speeches in relevant scientific congresses or engagement in industrial- or scientific associations related to the research topic;

Among other things, the academic research platform “research gate” and the professional job platform “LinkedIn” was used to identify these individuals.

iii. Identification of experts in the regulatory field:

The selection of interview partners has proofed to be provoking. Employees generally do not show their expertise on public platforms but could be identified through an indirect way based on official government documents such as code of practices, regulations and public Q&A sessions. Primary contact demonstrated to be not helpful, for example due to in-house allowance rules. We, therefore, had to use the proper contact path and experts, if even available, have been selected by the regulatory agencies by themselves. Nevertheless, the two interview partners seemed to have profound knowledge in the field of radiopharmaceuticals and/or companion diagnostics.

“Must” criterion: existing permanent employment with a regulatory authority involved in the approval/evaluation of marketing authorisation and/or other regulatory issues related to radiopharmaceuticals; Several years of experience in radiopharmaceuticals, molecular imaging or companion diagnostics;

1.4.2.3 Details on the Qualitative Interviews

The interviews have mainly been conducted by telephone (23/25), two interviews have been performed face to face. The average length of the interviews was around ~ 36 minutes, with a range from 16 minutes to 57 minutes. The distribution of interview partners from the specific segments is highlighted in Table 1.

Segment	Total number/ % of total interviews	Number of interview inquiries sent	The average duration of the interviews (min)
Senior Academics in the Nuclear Medicine Segment	7/35	9	~37
Specialist Physicians in Cancer Treatment	4/ 16	8	~29
Senior Managers from the Pharmaceutical Industry	3/12	12	~44
Senior Managers in the Radiopharmaceutical Industry	5/20	6	~35
Senior Managers from the Molecular Imaging Equipment Industry	2/8	6	~42
Specialists Regulatory Authority	3/10	7	~27
International Agency promoting the safe, secure and peaceful use of nuclear technology in Healthcare	1/ 4	5	~34

Table 1 shows the distribution of interviews within the speciality, the number of interviews performed, the number of interview inquiries sent to specialists in this field, as well as the mean duration of the talk

All interviewees were asked to give their consent to the recording of the interview at the written invitation. At the beginning of the interview, the interviewees have been asked again if they agree that the interview will be recorded if no written consent was available in advance of the interview. Written or oral consent is available from twenty-two (22) interviewees, disagreement by three (3) interviewees. If there was no consent, the participants were asked to give permission to take notes. This was confirmed by the three interviewees. In two cases, the quality of the recording was low, which meant that some parts of the conversation (not relevant to the analysis) were incomprehensible.

1.4.2.3.1 Transcription:

The interviews were transcribed word-for-word using the online software tool http://otranscribe.com/. The interviews were put down in writing promptly after the interviews were finished, allowing the researcher to get familiar with the data and also prepare for upcoming interviews.

All transcripts have been checked for mistakes.

1.4.2.3.2 Categories and Coding:

Since up to five different stakeholder groups, with different perceptions and views, answered analogical questions, there was a wide range of responses, terms and categories in the 1st-order analysis. Therefore, the data was first arranged in preliminary sub-categories (for each stakeholder group) using the program MS Excel. Specific text segments related to the objective have been identified and labelled, and subsequently, the essential categories have been incorporated in the program FreeMind. The original coding has been performed by the author; subsamples were independently read by MR, a well-experienced university staff member in qualitative research. MR also agreed with the author on the coding frame and together they conceptualise broad themes.

After a final critical re-reading, no new themes emerged suggesting that the major themes have been identified (Marshall & Rossman, 1999). Ineluctably, the findings are influenced by the questions outlined

by the researcher, as well as shaped and ranked according to their importance by the assumptions of the researcher

1.4.2.3.3 Remarks and Limitations:

The identification of the right interview partner in the pharmaceutical, radiopharmaceutical, molecular imaging technology, and regulatory group proved to be difficult, and time-consuming. We sent several interview inquiries, some had not been answered at all, and few had a negative answer (details in Table 1). In one case an interviewee had to refuse due to internal company restrictions (in the molecular imaging technology group) but has referred to a company brochure. The mobilisation of interview partners in the group of national/international regulatory agencies was particularly tricky. Here, the rate of refusals was the highest. During the research period, we identified another stakeholder group (Health insurance companies/ Health insurance policymakers), which could have eventually contributed to answering the research questions. Unfortunately, no interview was conducted since the interview inquiries were rejected or not answered (healthcare insurance companies: four interviews inquiries sent, two rejections, two pending requests; healthcare insurance policy makers: three interviews inquiries sent, one rejection, two pending requests).

Due to the inexperience of the interviewer, it sometimes happened that questions were skipped or evasively answered by the interview partners. In this case, the interviewees were contacted again and asked to answer the question. Unfortunately, this works only in two cases, in two other cases, we received no answer to our written request.

2 Role of Nuclear Medicine in Oncology

Early diagnoses may be a fundamental contributor to the reduction of morbidity and mortality by early identification of functional abnormalities (Higgins & Pomper, 2011b). When speaking about malignant diseases, nuclear medicine is an essential contributor to the detection, staging, therapy selection and planning stage (Velikyan, 2014). Diagnostic nuclear medicine procedures add value to standard diagnostic methods, by identifying essential and vital tissue segments (Bartenstein & Haug, 2011). Compared to contrast agents, which are non-specific and accumulate in the bloodstream and or in organs, many RPs are highly specific, have a high affinity to a specific receptor molecule (Figure 2) and thus only bind to specific molecules (Möllmann, 2006). Ideally, the target receptor is only found on diseased tissue, or the receptor is overexpressed in the region of interest relative to other tissues (Möllmann, 2006; Srinivasarao, Galliford, & Low, 2015). Newer anticancer drugs use a similar approach (Figure 3) substituting the radionuclide with a therapeutic agent and adding a spacer and a cleavable bridge to permit the drug release in the target cell. A variety of targeting therapy- ligands have been used so far: antibodies, aptamers, small protein scaffolds, peptides and low-molecular-weight non-peptidic ligands (Srinivasarao et al., 2015). The ongoing findings in proteomics and genomics further expand the knowledge about the function of receptors, enzymes, antigens and substrates (Velikyan, 2014). So newer RPs used in molecular imaging make it quite easy to adequately assess and understand the primary process of metabolism of elements and the more complicated metabolic system in organs (Müller in Schwiegk & Turba, 1961).

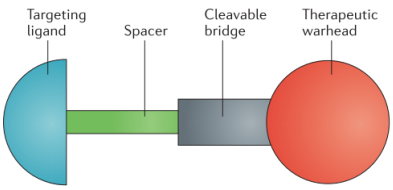


Figure 3 shows a new generation therapeutic agent using a target ligand to permit the drug release in the target cell (Source: Möllmann, 2006)

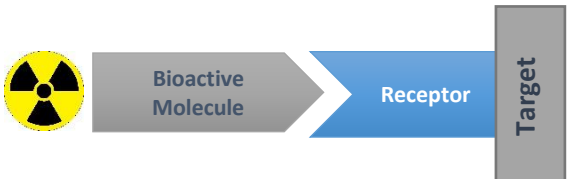


Figure 2 shows the components of a radiopharmaceutical complex using a bioactive molecule to bind to a receptor (Source: Möllmann, 2006)

Nuclear medicine therapy has successfully started with the use of radioiodine to treat thyroid disease disorders. In more than 50 years, millions of people have been treated with radioiodine to treat benign and malignant thyroid diseases (Oyen et al., 2007). In this approach primarily β emitting radionuclides are used since they are characterised by a small range, high linear energy transfer and subsequently a high biological efficacy (Bartenstein & Haug, 2011).

Two different types of nuclide therapy are available:

Systematic Nuclide Therapy:

The radionuclide is being administered oral or intravenous. It either follows a physiological uptake and accumulates in the target organ via metabolism or is coupled with receptors (receptor-ligand therapy/receptor peptide therapy) to reach the target region. The second way is used with RP such as somatostatin-analogue or marked antibodies (radioimmunotherapy). The efficacy of PRRT will be highlighted in the case study of ^{177}Lu- DOTATATE and ^{90}Y-PSMA.

Various clinical studies have confirmed the high value of Peptide receptor radionuclide therapy (PRRT) in patients with cancer and multiple inoperable metastases (see chapter 2.2 & 2.3). The success story of

PRRT started with the use of somatostatin analogues with the radionuclides Indium, Yttrium and Lutetium, especially ^{90}Y-DOTATOC and ^{177}Lu- DOTATATE (Bergsma et al., 2013; Teunissen, Kwekkeboom, Valkema, & Krenning, 2011). The new era of highly specific drugs (imatinib, trastuzumab, and epidermal growth factor–receptor inhibitors) it is increasingly important to select the right patients for the right drug as maybe just a few patients have the right target and the drug is effective (Tofilon, Saxman, & Coleman, 2003). The efficacy of PRRT will be highlighted in the case study of ^{177}Lu- DOTATATE and ^{90}Y-PSMA.

Local nuclide therapy:

The radionuclide is placed in the place of interest and is taking effect on the surrounding tissue. Effective therapy is radiosynoviorthesis, which is successfully used for local treatment of painful inflammatory joint disease for many decades. Also important is the "Selective internal radiation therapy" (SIRT) used to treat/ control inoperable cancer in the liver. Tiny microspheres, which contain a radioactive substance block small blood vessels and restrict the blood flow to the tumour.

2.1 Theranostics – combining diagnostics and therapy

Since a decade theranostics is thought to be a promising tool for drug - and diagnostic test developers. The idea of theranostics: administrating a specific targeted therapy based on a previously performed specific targeted diagnostic tests. The diagnostic test stratifies those patients, who are most likely to be helped or harmed by new targeted drug therapy using e.g. specific genomic expression profiles, semi-quantitative immunohistochemical (IHC) assays and molecular imaging tests. (Warner, 2004).

Probably the most well-known example in this field is trastuzumab (registered trade name: Herceptin). Trastuzumab is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2, c-erbB2). This receptor type is overexpressed in 25% to 30% of breast cancers. It inhibits the tumour cell proliferation by targeting the extracellular domain of the protein encoded by the HER2/neu gene (Boku, 2014; Dawood, Broglio, Buzdar, Hortobagyi, & Giordano, 2010). Patients are selected by HeceptTest and/or Path-Vysion, and so far several studies confirmed the clinical benefit of this approach showing a significantly prolonged overall survival and progression-free survival (Boku, 2014; Dawood et al., 2010). HER2 is also overexpressed in other forms of cancer, such as gastric cancer and seems to be effective, additionally to chemotherapy, in patients with advanced gastric or gastro-oesophageal junction cancer (Bang et al., 2010).

Theranostics/Theragnostic in Nuclear Medicine

While the term "theragnostics" is used to explain a treatment strategy that specifically combines therapeutics with diagnostics, the term "theranostics" explains more in general the ongoing efforts to develop more specific, individualized therapies for various diseases (Dobson, 2010; Pene, Courtine, Cariou, & Mira, 2009). In the case of nuclear medicine the targeting vectors (e.g. peptides) can be either labelled with a diagnostic radionuclide for PET or SPECT or with a therapeutic radionuclide. Some molecular targeting vectors allow a quantitative diagnosis of a disease, (personalised) treatment with the same vector but different radionuclides, with the option to consider patient-individual dosimetry (Rösch & Baum, 2011). This thesis will focus on two exemplary cases, which highlight the concept of Theranostics/ theragnostics and the contribution of nuclear medicine procedures in imaging and therapy.

2.2 Case 1 - Somatostatin Receptor Scintigraphy in Neuroendocrine Tumours (NETs)

Probably the best example of the successful implementation of a peptide-based radiopharmaceutical for diagnoses (and much later the use of a very similar vector for therapy) was in the field of neuroendocrine tumours.

Neuroendocrine tumours (NETs) are rare but a broad family of neoplasms, which mainly occur in the lungs, intestine and the pancreas. The originate in neural and diffuse endocrine structures of the gastrointestinal tract and pancreases and present many clinical challenges (Modlin et al., 2008; Öberg, 2015; Rindi & Wiedenmann, 2011). NETs are frequently sporadic, unpredictable, have an unusual biological behaviour and have a delayed diagnosis with poor outcome (Modlin et al., 2008; Öberg, 2015; Ramage et al., 2005). In earlier stages of the disease, patients often have non-functioning tumours or exhibit nonspecific symptoms, and once these tumours start to metastasize they often feature hypersecretory syndromes and release peptide hormones and bioactive substances such as gastrin, insulin into the bloodstream (Modlin et al., 2008; Vinik & Moattari, 1989). The tumours originate from pancreatic islet cells, gastroenteric tissue, neuroendocrine cells within the respiratory epithelium, and parafollicular cells within the thyroid (Öberg, 2015; Ramage et al., 2005).

> "*About 72 % of NETs arise in gastrointestinal structures, 25 % are bronchopulmonary in origin, and less than 5 % arise at other sites (e.g. thymus, breast and genitourinary system). Frequently, these tumours are discovered when metastatic or locally advanced and therefore inoperable.*" (Zaknun et al., 2013)

In the past, these tumours have also been called "carcinoids", named by Oberndorfer in 1907 to distinguish a tumour of the small intestine which is less aggressive than most carcinomas (Williams & Sandler, 1963). Until 2010 these tumours were classified based on their primary localisation (foregut tumours, midgut tumours, and hindgut tumours), but this classification system has been updated and is now based on the localisation and the eventual hormone production: NET G1 (Ki-67 <2%), NET G2 (Ki-67, 2-20%) and NEC (G3) with Ki-67 > 20% (Bosman & Carneiro, 2010).

The neoplasm varies from being well-differentiated endocrine tumours (WDET) and poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC) (Barbieri et al., 2014; Bosman & Carneiro, 2010). PDEC generally show a poorer outcome as the tumours are biologically more aggressive

Biological behavior	WHO classification (2000)	WHO classification (2010)	Metastases	Invasion	Tumor size, cm	Angioinvasion	Ki67, %
Benign	Well-differentiated endocrine tumor	NET G1 or NET G2	–	–	≤2	–	usually around 2
Benign or low-grade malignant	Well-differentiated endocrine tumor	NET G1 or NET G2	–	–	>2	±	usually around 2
Low-grade malignant	Well-differentiated endocrine carcinoma	NET G1 or G2	+	+	any	+	usually >2
High-grade malignant	Poorly-differentiated endocrine carcinoma	NEC or G3	+	+	any	+	>20

NET = Neuroendocrine tumor; NEC = neuroendocrine carcinoma.

Table 2 ENETS classification of pancreatic neoplasms (Falconi et al. 2012)

compared to WDET, which can be cured entirely or allow a long-term survival even in the presence of relapse or metastasis (Barbieri et al., 2014).

Some criticism came up on the existing WHO 2010 classification/staging systems by the European Neuroendocrine Tumour Society (ENETS) and the American Joint Committee on Cancer (AJCC). But a current study by Kim et al. 2016 evaluated the 2010 WHO, ENETS and AJCC grading system to predict survival after gastric neuroendocrine tumour (NET) resection. They retrospectively evaluated 175 gastric

NET patients and showed an overall low prognostic value of the ENETS and WHO classification, a low prognostic value for well-differentiated NETs (G1 or G2) but a high prognostic value for G3 or mixed tumours by the AJCC classification system.

2.2.1 Epidemiological data

Based on the Surveillance, Epidemiology, and End Results (SEER) Program registries in the USA the annual incidence of NETs have been rising from 1.09/100,000 to 5.25/100,000 over the past 30 years (Yao et al., 2008). An increase which may also be due to an increase in incidentally identified lesions (benign and malign) due to more performed diagnostic imaging tests (endoscopy and radiological procedures) (Modlin et al., 2008) The SEER data demonstrated that ~ 40% of the patients had a localised disease, 17% had regional disease and 20% had already distant metastases (Yao et al., 2008). The age-adjusted incidence of NETs of the small intestine therefore increase by 460% over 30 years, NETs in digestive system increase by 720% in the same period (Modlin et al., 2008). One has to keep in mind that SEER data only counts malignant tumours without having a standardised histopathological protocol. Consequently, the numbers from the SEER database could be underestimated.

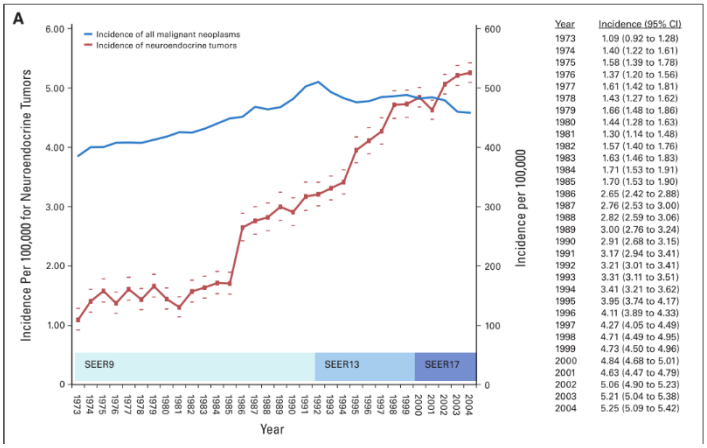


Figure 4 Incidence of all malignant neoplasms and neuroendocrine tumours from 1973 t0 2003 (Source: SEER database).

A study from Austria identified 1.49% of all malignant digestive tumours being classified as NETs. Based on the WHO 2010 classification, 46% of NETs had been classified as benign, 15% have been showing uncertain biological behaviour, and 39% marked as malignant (Niederle, Hackl, Kaserum, & Niederle, 2010). Studies from Switzerland and the Netherlands in 2000 and 2001 also estimated the incidence with approximately 1–2/100,000 patients (Levi, Te, Randimbison, Rindi, & La Vecchia, 2000; Quaedvlieg, Visser, Lamers, Janssen-Heijen, & Taal, 2001). Nevertheless, in a 30 year period, the incidence rate has annually increased by ~ 5.8% (Modlin et al., 2008; Yao et al., 2008).

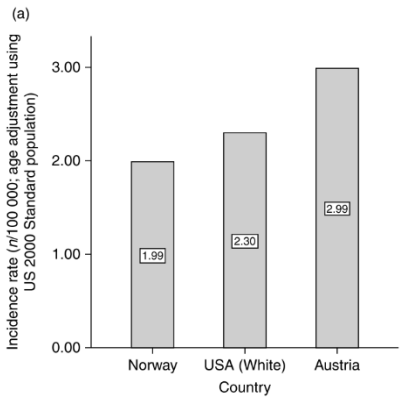


Figure 5 Incidence rates of GEP NET (n/100.000 per year); age-adjusted using the 2000 US standard population comparing the recent data with Norway, USA and Austria (Niederle et al. 2010; Hauso et al. 2008).

One has to keep in mind that NET- incidence data are mainly based on national cancers registries. Thus there could be substantial limitations in the accuracy of this analysis. Firstly benign or NETs with the uncertain clinical course may not be fully incorporated in these registries because of registries' specifications. Secondly, the definitions of these tumours have evolved over time, resulting in a change in the classification standards (Niederle et al., 2010).

2.2.2 Diagnostic workup of NETs –Biochemical Markers

Despite broad access to modern imaging methods, NETs still have a delayed diagnosis of several years (Modlin et al., 2008). There is a clear need for sensitive and specific biomarkers, which allow earlier diagnosis, identification of residual disease, minimal disease detection and demonstration of failure/efficacy of therapy. (Modlin et al., 2014)

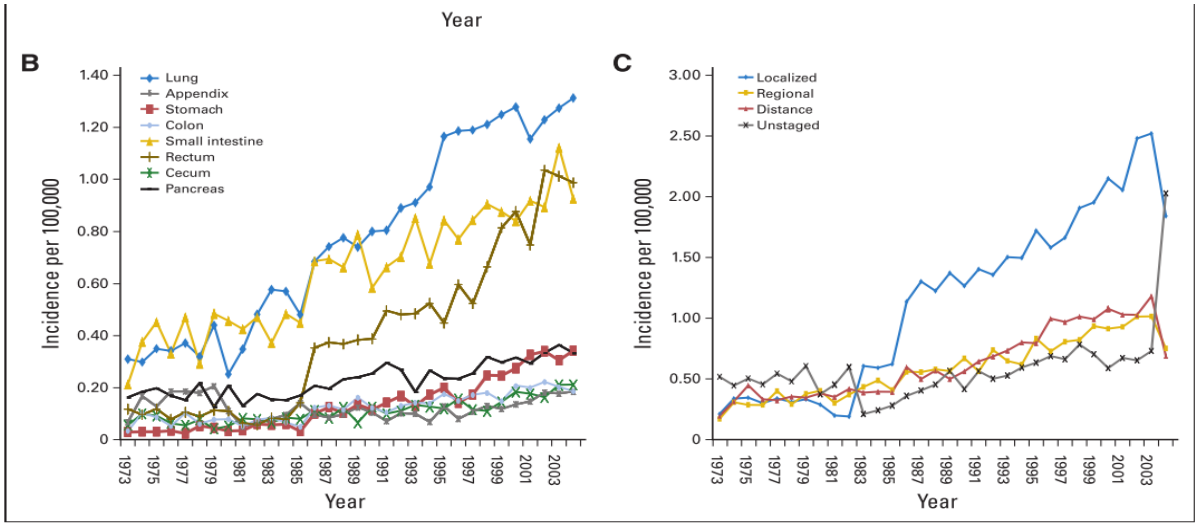


Figure 6 shows graphs of the incidence of NETs over time based on data from SEER database. Graph (B) shows a time- trend analyses of the incidence of NETs by primary tumour site (1973-2004) and (C) the incidence by disease stage at diagnosis (Yao et al. 2008)

NETs show a vast divergent biological behaviour and can be classified into non-functioning (e.g. besides local obstruction and bleeding) and function tumours. Tumours which are classified into functioning tumours release specific peptides and amines via the involved neuroendocrine cell types (e.g. beta cells, enterochromaffin-like cells, G-cells) and therefore cause special symptoms (Duque, Modlin, Gupta, & Wasif Saif, 2013; Modlin et al., 2008; Ramage et al., 2012).

The functional status of a tumour, the clinical symptoms and histological features can be assessed during the biochemical workup analysing specific substances, such as insulin, proinsulin, glucagon, calcitonin, gastrin, pancreatic polypeptide and VIP (vasoactive intestinal peptide) (K Öberg, 2012). Other biomarkers used in the work-up are chromogranin A (CgA), urinary 5-HIAA (Duque et al., 2013; Modlin et al., 2008), KI-67, and Placental growth factor (PGF) (Hilfenhaus et al., 2013).

2.2.2.1 Diagnostic workup of NETs -Imaging

The selection of the appropriate imaging method and therapeutic intervention is particularly dependant on the location of the primary tumour, the degree of differentiation and dissemination, the functional status and the tumour's grade (Modlin et al., 2008). The European Neuroendocrine Tumour Society (ENETS) extends these characteristics to the evaluation of tumour somatostatin receptor density, therapy monitoring and detection of recurrent disease (Sundin et al., 2009).

Based on the high diversity of NETs, also the imaging workup consists of a variety of different imaging modalities in the detection, characterisation and staging of NETs (Leung & Schwartz, 2013). Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) is the widely used imaging techniques in establishing the diagnosis and location of NETs. Modern CT systems reach a high spatial resolution of the whole abdomen and thorax, with hundreds or more of 1-mm or sub-millimetre transaxial images per second (Leung & Schwartz, 2013; Sundin et al., 2009). Imaging with a rapid bolus injection of intravenous (i.v.) contrast media can be beneficial in many NETs, as the tumours are visualised as enhancing or hypervascular lesion on the early and later arterial phase images (Leung & Schwartz, 2013).

CT is still the most commonly used modality with a low sensitivity ranging from 50% – 85% (see Table 3), and specificity from 25% - 99% (Sundin et al., 2009). Multidetector CT increased the detection of insulinomas to 94%, in combination with Endoscopic ultrasonography (EUS) the sensitivity reached 100% (Gouya et al., 2003)

Type of NET	Sensitivity mean (range)	Specificity mean (range)	Detection rate mean (range)	Number of patients/ studies	Reference
Endocrine pancreatic tumour	73% (63-82)	96% (83-100)	73% (39-94)	162/5 178/6	(Ferlay et al., 2013; Fidler et al., 2003; Procacci et al., 2001; Rossi et al., 1985; Stark, Moss, & Tumors, 1984; Van Hoe, Gryspeerdt, Marchal, Baert, & Mertens, 1995)
Liver metastases	82% (78-100)	92% (83-100)	81%	135/4 21/1	(Chiti, Fanti, Savelli, Romeo, Bellanova, Rodari, Graafeiland, & Bombardieri, 1998; Cwikla et al., 2004; Hubalewska-Dydejczyk et al., 2006; Kumbasar et al., 2004; Shi, Johnston, et al., 1998)
Extrahepatic abdominal soft tissue metastases	75% (63-90)	99% (98-100)	81%	77/4 21/1	(Chiti, Fanti, Savelli, Romeo, Bellanova, Rodari, Graafeiland, & Bombardieri, 1998; Cwikla et al., 2004; Hubalewska-Dydejczyk et al., 2006; Kumbasar et al., 2004)
Various NET lesions in abdomen and thorax	83% (61-100)	76% (71-80)	76%	164/3 25/1	(Cwikla et al., 2004; Gabriel et al., 2007; Koopmans et al., 2006; Shi, Buchanan, et al., 1998)
Small bowel NET at CT enteroclysis	50% 85%	25% 97%	n.a.	8/1 219[a]/1	(Johanssen, Boivin, Lochs, & Voderholzer, 2006; Pilleul et al., 2006)

a. Out of 219 patients included in the study, there were 19 subjects with carcinoids

Table 3 Sensitivity, Specificity and Detection Rate of NETs with Computed Tomography

Also, MRI is an essential tool in the visualisation of NETs, using mainly 1.5 or 3.0 Tesla systems. Currently the number of meaningful studies is limited, but generally supports the use of MRI in NET diagnosis with high sensitivity and specificity (see Table 5) (Sundin et al., 2009). Early studies showed a lower sensitivity for the detection of the primary tumour and their metastases compared to CT, however, newer studies evaluate MRI to be equal or superior to CT, especially in the visualisation of liver metastases (Ichikawa et al., 2000; Owen et al., 2001; Schraml et al., 2013; Semelka, Custodio, Balci, & Woosley, 2000). Larger lesions show a higher enhancement than smaller lesions but could be heterogeneous in hyperintensity on T2- weighted sequences (Leung & Schwartz, 2013). Liver metastases show a better lesion visualisation compared to CT scans (Rockall & Reznek, 2007).

Type of NET	Sensitivity mean (range)	Specificity mean (range)	Detection rate mean (range)	Number of patients/ studies	Reference
Endocrine pancreatic tumour	93% (85–100)	88% (75–100)	73% (50-94)	54/2 192/5	(Carlson, Johnson, Stephens, Ward, & Kvols, 1993; Ichikawa et al., 2000; Owen et al., 2001; Semelka et al., 2000; Shi, Johnston, et al., 1998; Termanini et al., 1997; Thoeni, Mueller-Lisse, Chan, Do, & Shyn, 2000)
Liver metastases	n.a.	n.a.	82% (80-85) 95%	74/3 64/1	(Carlson et al., 1993; Cwikla et al., 2004; Dromain et al., 2005; Seemann, Meisetschlaeger, Gaa, & Rummeny, 2006; Shi, Buchanan, et al., 1998)
Extrahepatic abdominal soft tissue metastases	89%	100%	68% (55-81)	34/1 58/2	(Carlson et al., 1993; Cwikla et al., 2004; Seemann et al., 2006; Shi, Johnston, et al., 1998)

Table 4 Sensitivity, Specificity and Detection Rate of NET diagnosis with Magnet Resonance Imaging (MRI)

Ultrasound is a helpful tool in the detection of the tiny NETs. Especially insulinomas, which are primarily located in the pancreas, could be easily missed with conventional imaging methods if their diameter is smaller than 2 cm, and located in the gastrointestinal wall (Zimmer et al., 1994). For example, transabdominal ultrasonography (US) shows a much lower sensitivity and specificity compared to Endoscopic ultrasonography (EUS) in the detection of insulinomas and gastrinomas (Zimmer et al., 2000; Zimmer, Stölzel, et al., 1996). Also, intraoperative ultrasonography/ultrasound (IOUS) is a sensitive method for the identification of tumours with a low density of somatostatin receptors (e.g. insulinomas). Contrast-enhanced ultrasonography (CEUS) has been shown to be more sensitive in

neuroendocrine metastases and liver lesions, compared to US (Mörk, Ignee, Schuessler, Ott, & Dietrich, 2007).

However, as US, EUS, IOUS and CEUS seem to miss or misdiagnosed some tumours/metastases, a combination of SRS, CT or MRI shows the best outcome during surgery or if no metastases have been detected by the first line diagnostic procedures (SRS, CT or MRI) (Hiramoto, Feldstein, LaBerge, & Norton, 2001; Zimmer et al., 1994, 2000; Zimmer, Stölzel, et al., 1996). It should be mentioned that EUS is an invasive and operator-dependent procedure, thus results vary from centre to centre (Ramage et al., 2012).

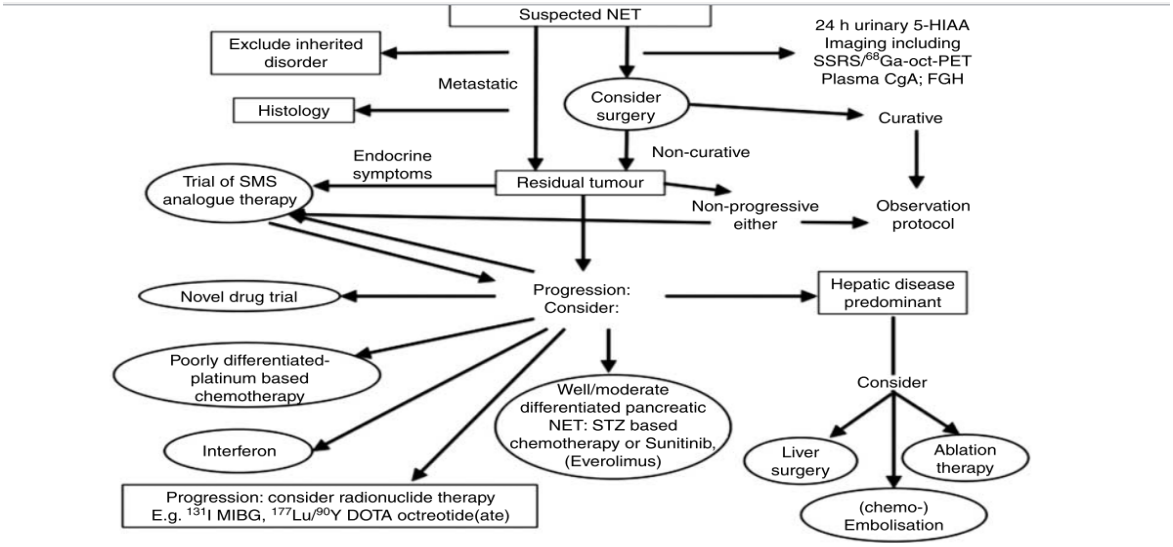
Type of NET	Sensitivity mean (range)	Specificity mean (range)	Detection rate mean (range)	Number of patients/ studies	Reference:
Endocrine pancreatic tumour:					
US (Transabdominal Ultrasonography)	n.a.	n.a.	39% (17-79)	153/6	Angeli et al., 1997; De Angelis, Carucci, Repici, & Rizzetto, 1999; Galiber et al., 1988; Pitre, Soubrane, Palazzo, & Chapuis, 1996; Zimmer et al., 1994; Zimmer, Stolzel, et al., 1996
EUS (Endoscopic ultrasonography)	93%	95%	90% (77-100)	261/10 75/1	Ariyama, Suyama, Satoh, & Wakabayashi, 1998; Celso Ardengh, Andrade De Paulo, & Paulo Ferrari, 2004; De Angelis et al., 1999; Gouya et al., 2003; Pitre et al., 1996; Proye, Malvaux, Pattou, Filoche, Godchaux, Maunoury, Palazzo, Huglo, Lefebvre, Paris, et al., 1998; T. Rösch et al., 1992; Zimmer et al., 1994, 2000; Zimmer, Stolzel, et al., 1996
IOUS (Intraoperative Ultrasonography/ ultrasound)	n.a.	n.a.	92% (74-96)	127/4	Galiber et al., 1988; Hiramoto et al., 2001; Huai et al., 1998; Pitre et al., 1996
Insulinoma:					
EUS	n.a.	n.a.	92% (88-94)	86/4	M. A. Anderson et al., 2000; Gouya et al., 2003; Zimmer et al., 2000; Zimmer, Stölzel, et al., 1996
IOUS	n.a.	n.a.	92% (84-96)	109/3	Galiber et al., 1988; Hiramoto et al., 2001; Huai et al., 1998
Duodenal tumours and lymph node metastases:					
US	n.a.	n.a.	18%	25/1	De Angelis et al., 1999
EUS	n.a.	n.a.	63%	59/2	De Angelis et al., 1999; Proye, Malvaux, Pattou, Filoche, Godchaux, Maunoury, Palazzo, Huglo, Lefebvre, & Paris, 1998
Liver metastases US:					
US	88%	95%	n.a.	131/1	(rturo Chiti et al., 1998
CEUS	82%	n.a.	n.a.	48/1	Mörk et al., 2007
US, Ultrasound; EUS, Endoscopic Ultrasound; IOUS, Intraoperative ultrasound;					

Table 5: Sensitivity, Specificity and Detection Rate for NET diagnosis by US, EUS, IOUS and CEUS

2.2.3 Therapy Options in the Treatment of NETs

There is a variety of therapy options available, but surgery is the foundation for curative treatment in various NET cancers types (Falconi et al., 2016). Due to the high prevalence of already metastatic disease stage at the time of diagnosis (Kianmanesh, O'Toole, Sauvanet, Ruszniewski, & Belghiti, 2005), surgical approaches for locally advanced or metastatic tumours (with or without new molecular targeted therapies) are generally more aggressive but seem to be safe and may offer long-term survival (Basuroy, Srirajaskanthan, & Ramage, 2012; Birnbaum et al., 2015). An analysis from the German NET registry showed that around 77% of patients with NET had surgery as first treatment,18.6% medical therapy, 2.7% radiotherapy and around 1.1% ablative therapy (Ploeckinger, Kloeppel, Wiedenmann, & Lohmann, 2009).

Since it is not the intention of this thesis to explain the surgical options for the treatment of NETs, we refer to the literature/ guidelines of M. S. Khan & Caplin, 2011 and Falconi et al., 2016, 2012 and the corresponding literature in the papers.



5-HIAA: 5-hydrixyindole acetic acid; SSRS: somatostatin receptor scintigraphy; CgA: chromogranin A; STZ: streptozocin; MIBG: metaiodobenenzylguanidine; chemoT: chemotherapy; ^{68}-Ga-oct PET; ^{68}-Ga-DOTA-octretotate positron emission tomography

Figure 7 Algorithm for the management of patients with NETs (Khan & Caplin, 2011)*; adapted from* (Ramage et al., 2005)

2.2.4 Specific Targeting via Somatostatin Analogues - Imaging

The groundwork for the successful use of somatostatin analogues was to a certain extent laid by Jean Claude Reubi, a pathologist emeritus from the University of Berne (Switzerland). In 1987 Reubi published a study showing the somatostatin receptor density in NETs and suggested that the chronically applied somatostatin receptors analogues, used to treat the symptoms in NET disease, are likely to bind to a tumour itself (Reubi, 1987).

Before, Krulich mentioned the inhibiting effect on the release of growth hormone from the hypothalamus by a small tetradecapeptide (somatostatin) in 1968 (Krulich, Dhariwal, & McCann, 1968). The group identified an inhibitor, which reduced the release of growth hormone in the pituitary in-vitro but may not have been aware of the significance. Brazeau (1973) later extracted a synthetic somatotropin release inhibiting factor (SRFI), which was biologically active in-vivo (Brazeau et al., 1973). Today, it is clear that SRIF, later named Somatostatin, acts though six G-protein coupled receptors (SSTR1, SSTR2a, SSTR2b, SSTR3, SSTR4 and SSTR5) acts on the biological activity on neurotransmission, inhibits cell proliferation & endocrine secretion, and affects smooth muscle contractility (Bronstein-Sitton, 2006).

Somatostatin is produced by neurons and secretory cells in various organs such as the central and peripheral nervous system, placenta, kidney, retina and cells of the immune system (Bronstein-Sitton, 2006). The distribution of the six different SSTRs differs depending on the tissue, but receptors can be found in varying degrees of intensity in almost all tissues (Table 6). In cases of a benign

	Tissue distribution	Antibodies
SSTR1	Brain Pancreas (ß cells) GI tract several human tumours	Anti-SSTR1 (extracellular)
SSTR2a	Brain Pituitary gland GI tract Adrenal gland Immune cells Several human tumours	Anti-SSTR2 (extracellular)
SSTR2b		
SSTR3	Brain GI tract Liver Spleen Several human tumours	Anti-SSTR3 (Intracellular)
SSTR4	Brain (less than other subtypes) GI tract Lung Heart Placenta Several human tumours	Anti-SSTR4 (Extracellular)
SSTR5	Brain (mainly hypothalamus) Pituitary gland Pancreas (ß and Ŏ cells) GI tract Several human tumours	Anti- SSTR5 (extracellular)
SSSTR – Somatostatin Receptor SST – Somatostatin GI tract – gastrointestinal tract		

Table 6 Distribution of Somatostatin Receptors in different tissues

and malignant disease, the expression of SSTR´s is considerably upregulated in the majority of tumour cell lines (Bronstein-Sitton, 2006; Krenning et al., 1993; Reubi, Maurer, & Von Werder, 1987). Table 7 represents an early study evaluating the incidence of SSTRs in tumours and comparing the results from the in-vivo scintigraphy with ^{111}In-DTPA-D-Phe1-Octreotide and in-vitro SSTR autoradiography. Nowadays we know that SSTR2 is the most widely expressed subtype in tumours, in particular in neuroblastomas, medulloblastomas, breast carcinomas, meningiomas, paragangliomas, lymphomas and renal cell carcinomas (Bronstein-Sitton, 2006; Reubi, Waser, Schaer, & Laissue, 2001). GEP NETs show a mixture of various SSTRs, but having a preference for SSTR2 or SSTR1. SSTR2 is omnipresent in breast cancer with a powerful expression of SSTR5 (around 30% of tumours) (Evans et al., 1997). The evidence that many neuroendocrine tumours have an overexpression of at least one somatostatin receptor subtype was strong enough to test the target for imaging- and therapeutic applications.

	In-vivo Scintigraphy[1]			In-vitro Receptor Status[2]	
GH producing pituitary tumour	7/10	70%		45/46	98%
TSH producing pituitary tumour	2/2	100%		-	-
Non- functioning pituitary tumour	12/16	75%		12/22	55%
Gastrinoma	12/12	100%		6/6	100%
Insulinoma	14/23	62%		8/11	72%
Glucagonoma	3/3	200%		2/2	100%
Unclassified APUDoma	18/18	89%		4/4	100%
Paraganglioma	33/33	200%		11/12	92%
Medullary thyroid carcinoma	20/28	72%		10/26	38%
Neuroblastoma	8/9	89%		15/23	65%
Phaeochromocytoma	12/14	86%		38/52	73%
Carcinoid	69/72	96%		54/62	88%
Small cell lung cancer	34/34	100%		4/7	57%
GH- Growth hormone					
TSH - Thyroid stimulating hormone					
APU- Amine Precursor Uptake					

Table 7 Incidence of Somatostatin Receptors in Neuroendocrine Tumours: Results of in-vivo ^{111}In-DTPA-D-Phe3 – Octreotide Scintigraphy (1), and in-vitro Somatostatin Receptor Autoradiography (2). Data from different patient groups

At the beginning, the synthetic somatostatin analogue was used for the treatment of symptoms in patients with NETs, but soon after the Iodine-123 marked analogue (^{123}I-Tyr^3-Octreotide) was used as an imaging agent (Lamberts, Bakker, Reubi, & Krenning, 1990). The radioiodinated synthetic derivate of somatostatin could visualise the primary tumour and metastases in endocrine pancreatic tumours very well (Krenning et al., 1989). The results from imaging were compared to ^{123}I-Tyr^3-Octreotide receptor autoradiography, a quantitatively, morphological technique with high (pharmacologically) specificity (Reubi, 2015). The in-vivo imaging results in detection were quite promising, but the use of the radioligand ^{123}-I had several drawbacks at that time:

- the labelling with ^{123}-I was exhausting, and special labelling skills were needed,
- ^{123}I in specific activity is expensive and rarely available,
- the production and distribution of Na- 123-I possessed a challenge, and
- ^{123}-I Tyr^3- Octreotide accumulated in the intestine and made the interpretation of planar and single-photon emission tomography difficult (Krenning et al., 1993).

Subsequently, Iodine-123 was replaced by Indium-111 and some of the obstacles have been solved. For an efficient binding of ^{111}-In, a diethylenetriaminopentaacetic acid (DTPA) conjugated derivative of octreotide was produced, which could bind around 95% of Indium in an easy and single step process, without further purification (Bakker et al., 1991). In animal studies of the rat, it was then suggested that the compound might show a lower affinity to SSTRs compared to the ^{123}I complex (Bakker et al., 1991). The first larger clinical study with this new radiopharmaceutical was conducted by Eric Krenning and his

colleagues from the University Hospital in Rotterdam, by the time the probably most advanced users and developers. They published the findings from 735 patients undergoing an ^{111}In- DTPA-o-Phel^{1}-octreotide (^{111}In-pentetreotide) scan, implying at least an unequivocal diagnosis and optimal anatomical information, whether provided by the common imaging modalities by histology and by autopsy (Krenning et al., 1993). The scan showed a high sensitivity for various somatostatin receptor positive tumours (NETs), granulomas and (autoimmune) diseases but less for insulinomas, as these tumours express more than one SST subtype with a different affinity of octreotide (Krenning et al., 1993). Especially in endocrine pancreatic tumours (gastrinomas, insulinomas, and glucagonomas) where surgery remains the best treatment choice, ^{111}In-pentetreotide scintigraphy showed to be very beneficial. Before SRS, the detection of a primary tumour and its metastases with conventional imaging methods was difficult or even impossible (Moertel, 1987). CT and MRI are well suited for sites where a tumour is clinically expected but aren´t that sensitive in the detection of distant metastases (Krenning et al., 1993). In endocrine pancreatic tumours ultrasonography and CT are usually limited to the pancreas and liver region, thereby missing possible metastases, e.g. in the chest, especially in the left supraclavicular region. Inconclusive results with US and CT, particularly with tumours less than 2 cm in diameter, are usually followed sequentially by invasive localisation methods, e.g. transhepatic selective portal venous sampling and selective visceral arteriography. These usual methods may fail to localise a tumour in 40%-60% of patients (Sloan, Schwartz, & Kenady, 1993)

2.2.4.1 ^{111}In-DTPA0- Octreotide (Octreoscan)

Up to now, ^{111}In- DTPA-o-Phel^{1}-octreotide (^{111}In- pentetreotide) is the most commonly used agent for SRS, using two-dimensional planar images and three-dimensional SPECT at 4, 24 and optionally 48hours

Peptides	hsst 1	hsst 2	hsst 3	hsst 4	hsst 5
SS-28	5.2±0.3 (19)	2.7±0.3 (19)	7.7±0.9 (15)	5.6±0.4 (19)	4.0±0.3 (19)
Octreotide	>10,000 (5)	2.0±0.7 (5)	187±55 (3)	>1,000 (4)	22±6 (5)
CH288	23±2 (3)	>10,000 (4)	>1,000 (3)	>10,000 (3)	>1,000 (4)
DTPA-octreotide	>10,000 (6)	12±2 (5)	376±84 (5)	>1,000 (5)	299±50 (6)
In-DTPA-octreotide	>10,000 (5)	22±3.6 (5)	182±13 (5)	>1,000 (5)	237±52 (5)
DOTA-TOC	>10,000 (7)	14±2.6 (6)	880±324 (4)	>1,000 (6)	393±84 (6)
Y-DOTA-TOC	>10,000 (4)	11±1.7 (6)	389±135 (5)	>10,000 (5)	114±29(5)
DOTA-LAN	>10,000 (7)	26±3.4 (6)	771±229 (6)	>10,000 (4)	73±12 (6)
Y-DOTA-LAN	>10,000 (3)	23±5 (4)	290±105 (4)	>10,000 (4)	16±3.4 (4)
DOTA-VAP	>10,000 (3)	29±7 (4)	419±104 (4)	743±190 (3)	80±19 (4)
Y-DOTA-VAP	>10,000 (4)	12±2 (5)	102±25 (5)	778±225 (5)	20±2.3 (5)
DOTA-OC	>10,000 (3)	14±3 (4)	27±9 (4)	>1,000 (4)	103±39 (3)
Y-DOTA-OC	>10,000 (5)	20±2 (5)	27±8 (5)	>10,000 (4)	57±22 (4)
Ga-DOTA-TOC	>10,000 (6)	2.5±0.5 (7)	613 ±140 (7)	>1,000 (6)	73±21 (6)
Ga-DOTA-OC	>10,000 (3)	7.3±1.9 (4)	120±45 (4)	>1,000 (3)	60±14 (4)
DTPA-[Tyr^3]-octreotate	>10,000 (4)	3.9±1 (4)	>10,000 (4)	>1,000 (4)	>1,000 (4)
In-DTPA-[Tyr^3]-octreotate	>10,000 (3)	1.3±0.2 (3)	>10,000 (3)	433±16 (3)	>1,000 (3)
DOTA-[Tyr^3]-octreotate	>10,000 (3)	1.5±0.4 (3)	>1,000 (3)	453±176 (3)	547±160 (3)
Y-DOTA-[Tyr^3]-octreotate	>10,000 (3)	1.6±0.4 (3)	>1,000 (3)	523±239 (3)	187±50 (3)
Ga-DOTA-[Tyr^3]-octreotate	>10,000 (3)	0.2±0.04 (3)	>1,000 (3)	300±140 (3)	377±18 (3)

All values are IC_{50}±SEM in n*M*. The number of experiments is in parentheses

Table 8 Affinity profiles (IC50) for human SST1-SST5 receptors with a series of somatostatin receptors (Source: J. C. Reubi et al., 2000)

after injection (Bodei, Sundin, Kidd, Prasad, & Modlin, 2014). Other forms of synthetic somatostatin analogues vary in the peptide sequences, chelators and chelator-peptide conjugate and consequently have different affinity profiles to the somatostatin receptor subtypes (Reubi et al., 2000). Reubi et al. identified that even small structural changes could have a significant impact on the affinity profile, e.g. marking DOTA-[Tyr3]-octreotate with the radioligand gallium improved the binding affinity by eight times (Reubi et al., 2000)

^{111}In-DTPA^{0}-Octreotide (trade name: Octreoscan) is registered for SSTR scintigraphy since June 1994 in the USA (FDA approval) and December 1994 in Europe (EMA approval).

At the time of registration ^{111}In-DTPA0-Octreotide has been clinically tested in nine unblended studies in a total of 365 patients, suspected of a neuroendocrine tumour. The results of the scan were consistent with the final diagnosis in 86.4% of patients, with lower success rates in insulinomas, neuroblastomas, pituitary adenomas and medullary thyroid carcinomas (Mallinckrodt Inc., 1994). A review of 1,200 patients with gastrointestinal NETs showed a median detection rate of 89% (67%-100%) and a sensitivity of 84% (57%- 93%) (Modlin, Kidd, Latich, Zikusoka, & Shapiro, 2005). Koopmans et al., 2009 further reviewed the use of ^{111}In-DTPA^{0}-Octreotide in abdominal carcinoid, pheochromocytoma, gastric carcinoid, Merkel cell tumour, medullary thyroid carcinoma, neuroblastoma, pancreatic islet cell tumour, paraganglioma, small cell lung cancer and bronchial carcinoid (see Table 9 Sensitivity with a calculated confidence interval for 111In-DTPA0- Octreotide in different neuroendocrine tumour subtypes (Koopmans *et al., 2009)*.

Abdominal Carcinoids	Sensitivity	Calculated confidence interval	Number of patients
Hoffman et al., 1992	58%	44% - 71%	57
Arturo Chiti et al., 1998	95%	82% - 100%	17
Krausz et al., 1998	86%	81% - 91%	87
Hoegerle et al., 2001	57%	46% - 67%	17
Shikano et al., 2003	100%	97% - 100%	22
Klaas P. Koopmans et al., 2006	46%	43% - 50%	53
Klaas P. Koopmans et al., 2008	49%	44% - 54%	23
Montravers et al., 2006	93%	78% - 99%	23
Orlefors et al., 2005	52%	42% - 62%	13
Raderer et al., 2000	92%	89% - 95%	133
W. Shi, Johnston, et al., 1998	87%	72% - 96%	25
Virgolini et al., 2001	87%	72% - 96%	38
Pheochromocytoma			
Tenenbaum et al., 1995	63%	51% - 73%	14
Gastric Carcinoids			
Gibril et al., 2000	75%	68% - 82%	162
V. Briganti et al., 2001	100%	68% - 100%	10
Orazio Schillaci et al., 2003	90%	84% - 95%	40
Merkel-cell-tumour			
Durani, Klein, Henze, Haberkorn, & Hartschuh, 2003	78%	39% - 98%	11
Guitera-Rovel et al., 2001	78%	40% - 95%	9
Medullary thyroid carcinoma			
S. Adams et al., 1998	29%	17% - 42%	18
Arslan et al., 2001	44%	29% - 60%	14
Bernà et al., 1998	75%	51% - 92%	20
de Groot, Links, Jager, Kahraman, & Plukker, 2004	41%	23% - 61%	26
Diehl et al., 2001	25%	16% - 35%	46
Belhocine et al., 2002	52%	32% - 71%	11
Kurtaran et al., 1998	71%	41% - 92%	14
Neuroblastoma			
Kropp, Hofmann, & Bihl, 1997	61%	35% - 83%	18
Schilling et al., 2000	64%	53% - 74%	88
Pancreatic Islet cell tumours			
V. Briganti et al., 2001	83%	34% - 100%	6
Corleto et al., 1996	93%	73% - 99%	24
Krausz et al., 1998	77%	56% - 91%	18
Rickes, Unkrodt, Ocran, Neye, & Wermke, 2003	54%	32% - 71%	29
Klaas P. Koopmans et al., 2008	46%	40% - 52%	22
Paraganglioma			
Duet et al., 2003	100%	91% - 100%	42

Muros et al., 1998	83%	74% - 91%	8
K. P. Koopmans et al., 2008	89%	75% - 97%	27
Small cell lung cancer			
Bohuslavizki et al., 1996	26%	15% - 39%	20
Bombardieri et al., 1995	86%	74% - 94%	20
Bronchial carcinoid			
Fanti et al., 2003	71%	52% - 86%	31

Table 9 Sensitivity with a calculated confidence interval for ^{111}In-DTPA^{0}- Octreotide in different neuroendocrine tumour subtypes (Koopmans et al., 2009)

^{111}In-DTPA^{0}-Octreotide´s sensitivity was good in most forms of the neuroendocrine tumours, additional information to morphological imaging was added and that SRS clearly influenced the patient e.g. surgical approaches in GEP-NETs (Briganti et al., 2001; Chiti, Fanti, Savelli, Romeo, Bellanova, Rodari, Graafeiland, & Bombardieri, 1998; Frilling et al., 1998; Gotthardt et al., 2003; Jamar, Fiasse, Leners, & Pauwels, 1995; Lebtahi et al., 1997; Termanini et al., 1997). Lebtahi et al., 1997 demonstrated that SRS massively changed the patient/tumour classification (in 24% of cases) and the surgical strategy (in 25% of cases) by identifying new primary tumour sites and metastases. Chiti et al., 1998 reported a change of the therapeutic schedule in 21% of patients, which means an exclusion of surgical procedures or the starting of palliative treatment with somatostatin analogues. However, SRS, as well as all other diagnostic methods alone, had an inferior sensitivity in patients with metastases but unknown primary tumour (Chiti, Fanti, Savelli, Romeo, Bellanova, Rodari, Graafeiland, Monetti, et al., 1998). Therefore actual guidelines for the management of GEP NETs (including carcinoids) recommend, with a level of evidence 3 and a grade of recommendation A/B, the use of a multimodality approach to detect the primary tumour with CT, MRI and somatostatin receptor scintigraphy (SRS) (Ramage et al., 2012). All imaging techniques can change the therapeutic management to a comparable extent, which is especially true in patients with advanced disease (Gotthardt et al., 2003).

The question remains if SRS is an efficient imaging technology under ideal conditions or effective in ordinary (not ideal) conditions in the sense of a change of outcome for the patient (Brook & Lohr, 1985). Fryback and Thornbury created a six-tiered model of efficacy to identify the usefulness of a diagnostic imaging procedure, even though diagnostic imaging is a step in an extensive process (Fryback & Thornbury, 1991). Based on this model a breakdown of the published studies of SRS in GEP NETs showed that every study (Briganti et al., 2001; G Cadiot et al., 1997; Guillaume Cadiot et al., 1996; Chiti, Fanti, Savelli, Romeo, Bellanova, Rodari, Graafeiland, & Bombardieri, 1998; De Kerviler et al., 1994; Frilling et al., 1998; Gibril et al., 1996; Gotthardt et al., 2003; Hammond, Arka, Peters, Bloom, & Gilbey, 1994; Jamar et al., 1995; Krausz et al., 1998; Lebtahi et al., 1997; Meko, Doherty, Siegel, & Norton, 1996; Proye et al., 1998; Raderer et al., 2000; Scherubl et al., 1993; O. Schillaci, Massa, & Scopinaro, 2000; O Schillaci et al., 1996; Schirmer et al., 1995; Termanini et al., 1997; Vezzosi et al., 2005; Weinel et al., 1993; Westlin et al., 1993; Zimmer et al., 1994; Zimmer, Stölzel, et al., 1996) contributed either to the level 1 (technical efficacy), level 2 (diagnostic accuracy efficacy), level 3 (diagnostic thinking efficacy) and level 4 (therapeutic efficacy) efficacy, but no study was designed to achieve level 5 (patient outcome efficacy) and level 6 (societal efficacy). It is therefore difficult to judge, how SRS influenced the disease outcome also because it took time for new treatment options to be available. Over the years some specialised centres reported increased survival over the time in GEP NETs; the SEER database could (for example) not show a better 5-year survival rate for carcinoids tumours of the small intestine since 1973 (Modlin et al., 2008). With the newly available therapy option this figure may change. A recently published randomized controlled Phase-3 registration trial showed a markedly increased progression –free survival with 177-Lu-DOTATATE compared to octreotide LAR in patients with well-differentiated,

metastatic midgut neuroendocrine tumours. CT, MRI were used for diagnosis and SRS to assess the somatostatin receptor status before therapy planning (Strosberg et al., 2017).

2.2.4.2 Gallium-68 PET/CT- advancement in Somatostatin Receptor Scintigraphy (SRS)

With the increased availability of PET and PET/CT system, it was just a matter of time until somatostatin analogues were labelled with positron emitting isotopes and further increased the sensitivity. Today most of the SRS scans in western European countries are PET-based, as this technique allows for higher spatial resolution, better visualization of small lesions (< 10mm), and thus increases the sensitivity (Ambrosini, Campana, Tomassetti, & Fanti, 2012).

Gallium- 68 became the preferred nuclide, mainly for technical reasons. The synthesis process is relatively easy and economical, no cyclotron is necessary as the nuclide is skimmed from a generator (Ambrosini et al., 2012), and it is possible to measure the standardised uptake value (SUV), a semi-quantitative measurement of the activity in a given region of interest, which correlates with the clinical and pathologic features and may be an accurate prognostic index (Ambrosini et al., 2012; Campana et al., 2010; Haug, Assmann, et al., 2010). In 1994 a preclinical study already used Ga^{67} and Ga^{68} octreotide (DFO-B-succinyl-(D)phe^{1}-octreotide) but experienced a low tumour-to-background ratio (Smith-Jones et al., 1994). In 1997 another research group labelled octreotide with ^{18}F (2-['8F]fluoropropionyl-(D)phe^{1})-octreotide) but detected an unfavourable fast tumour washout and a high hepatobiliary excretion which limited the use of this tracer in abdominal located tumours (Wester et al., 1997).

Finally, a research group from the University Hospital of Basel conjugated three new somatostatin analogues with the metal chelator DOTA (see Figure 8) and labelled those with ^{111}In, ^{90}Y and ^{67}Ga (Froidevaux et al., 1998). The preclinical results: ^{67}Ga- DOTATOC, ^{67}Ga- DOTATATE and, to a lesser extent ^{67}Ga- DOTAOC had an excellent tumour selectivity, with ^{67}Ga-DOTATOC being superior in the affinity to SSTR2, tumour uptake and the lower kidney uptake (Froidevaux et al., 1998). Up to now several studies engaged in biokinetics, clinical performance, SUV analyses and comparison to other radiopharmaceuticals and imaging modalities:

2.2.4.2.1 68Ga-DOTATOC (Gallium- 68-Edotreotide):

Even ^{68}Ga-DOTATATE showed a 10-fold higher in-vitro affinity to SSTR2 (0.2 ± 0.04 nM), compared to ^{68}Ga-DOTATOC (2.5 ± 0.5 nM), the difference may not seem to be clinically relevant in the visualisation of NETs mainly expressing SSTR2 (Pöppel et al., 2011; Reubi et al., 2000). ^{68}Ga – DOTATOC seems to have a higher affinity to SSTR5 compared to ^{68}Ga- DOTATATE, which may explain the higher tumour uptake of DOTATOC in some NET types (Pöppel et al., 2011; Reubi et al., 2000). Mentionable is the considerable discrepancy in SSTR expression in individual patients and between different tumour manifestations (Forrer et al., 2004; Pöppel et al., 2011). Further studies are analysing the biokinetics, SUVmax and compared ^{68}Ga-DOTATOC to ^{111}In-Octreoscan, ^{18}F-FDG, ^{18}F-DOPA, ^{68}Ga-DOTATATE, EUS, CT, MRI and histopathology (see Table 10).

In all studies ^{68}Ga- DOTATOC showed a higher sensitivity in the detection of NET lesions compared to ^{111}In-Octreotide

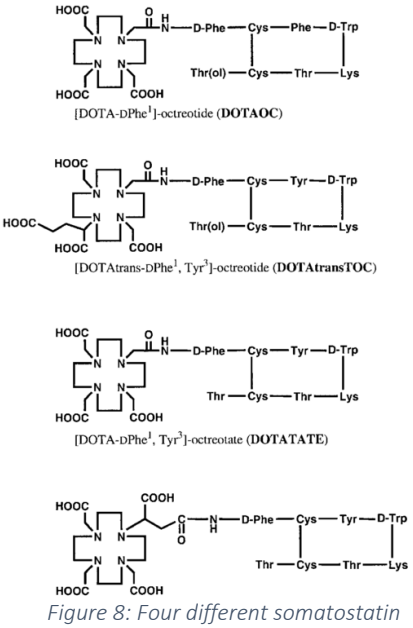


Figure 8: Four different somatostatin analogues conjugated with the metal chelator DOTA: DOTAOC, DOTAtransTOC, DOTATATE, DOTASATATE (Froidevaux et al., 1998)

(Buchmann et al., 2007; Hofmann et al., 2001; Kowalski, 2003; Müssig et al., 2010). Since December 2016 (SomKit TOC®) and November 2017 (TOCscan®) Gallium (^{68}Ga)-Edotreotide have received official marketing authorisation by the European Medicines Agency (EMA) with a 10-year orphan market exclusivity in the European territory.

Author	Topic	Year
Hofmann et al., 2001	Biokinetics and Comparison to ^{111}In- Octreoscan	2001
Buchmann et al., 2007	Comparison to ^{111}In- Octreoscan	2007
Kowalski, 2003	Comparison to ^{111}In- Octreoscan	2003
Koukouraki et al., 2006	Pharmacokinetics of ^{68}Ga-DOTATOC	2006
Miederer et al., 2009	SUVmax and SSTR correlation	2009
Poeppel et al., 2011	Comparison to ^{68}Ga DOTATATE	2011
Boy et al., 2011	SUVmax and SSTR correlation	2011
Poeppel et al., 2013	Comparison to ^{68}Ga-DOTATATE	2013
Müssig et al., 2010	Comparison to ^{111}In-Octreoscan	2010
Daniel Putzer et al., 2009	Comparison to CT	2009
Versari et al., 2010	Comparison to EUS and surgery	2010
Ruf et al., 2010	Comparison to CT and histopathology	2010
D Putzer et al., 2010	Comparison ^{18}F-DOPA	2010
Ruf et al., 2011	Comparison to CT and histopathology	2011
Alexander Kroiss et al., 2013	SUVmax Uptake	2013
Koukouraki et al., 2006	Comparison ^{18}F-FDG	2006
Van Binnebeek et al., 2016	Comparison to ^{111}In-Octreoscan	2016
Velikyan et al., 2014	Comparison to ^{68}Ga-DOTATATE	2014
Giesel et al., 2012	Comparison to CT and MRI	2012

Table 10: Further studies analysing Biokinetics, SUVmax, sensitivity, specificity of ^{68}Ga- DOTATOC

2.2.4.2.2 68Ga-DOTATATE (Gallium (68Ga) DOTA-(Tyr3)-Octreotate):

A recent systematic review and meta-analyses, comparing ^{68}Ga-DOTATATE with ^{111}In-DTPA-Octreotide and conventional imaging for pulmonary and gastroenteropancreatic NETs, showed a higher sensitivity of ^{68}Ga-DOTATATE compared to ^{111}In-DTPA- Octreotide and high sensitivity (90.9%) and specificity (90.6) compared to conventional imaging (Deppen, Blume, et al., 2016).

Besides the substantiated meta-analyses, many other studies have been conducted with 68Ga-DOTATATE (see Table 11 *shows a literature overview of imaging studies using Gallium- 68 in neuroendocrine tumours with a comparison to SRS, PET and conventional imaging.*) comparing its performance to other PET radiopharmaceuticals, SPECT and conventional imaging.

^{68}Ga- DOTATATE		
Author	**Topic**	**Year**
Haug et al., 2012 [a]	68Ga-DOTATATE compared to histopathology	2012
Haug et al., 2014 [a]	68Ga-DOTATATE compared to histopathology	2014
Goel et al., 2014	68Ga-DOTATATE compared to CT	2014
Armbruster et al., 2014	68Ga-DOTATATE compared to DCE-MRI, 18F-FDG	2014
Schmid-Tannwald et al., 2013	68Ga-DOTATATE compared to DW-MRI	2013
Maurice et al., 2012	68Ga-DOTATATE compared to 123I-MIBG SPECT	2012
Hofman et al., 2012 [a]	68Ga-DOTATATE compared to conventional imaging and 111In-Octreotide	2012
Łapińska et al., 2011	68Ga-DOTATATE compared to conventional imaging and histopathology	2011
Naji et al., 2011	68Ga-DOTATATE compared to 123I-MIBG SPECT	2011
Srirajaskanthan et al., 2010 [a]	68Ga-DOTATATE compared to CT, MRI, 111In-Octreotide and histopathology	2010
Conry et al., 2010	68Ga-DOTATATE compared to 18F-FDG	2010
Kayani et al., 2009	68Ga-DOTATATE compared to 18F-FDG	2009
Kayani et al., 2008 [a]	68Ga-DOTATATE compared to 18F-FDG	2008
Win et al., 2007	68Ga-DOTATATE compared to CT and 123I-MIBG SPECT	2007
Nickel et al., 2016	68Ga-DOTATATE compared to CT, MRI, US, IOUS and selective arterial secretagogue injection (SASI)	2016
Panagiotidis et al., 2016	68Ga-DOTATATE compared to 18F-FDG	2016
Kazmierczak et al., 2016	68Ga-DOTATATE compared to CT	2016

Janssen et al., 2016	68Ga-DOTATATE compared to CT, MRI, 18F-FDG (and partially 18F-FDOPA and 18F-FDA)	2016
Deppen et al., 2016 [a]	68Ga-DOTATATE compared 111In Octreotide	2016
Alonso et al., 2014 [a]	68Ga-DOTATATE compared to conventional imaging (CT)	2014
Etchebehere et al., 2014 [a]	68Ga-DOTATATE compared to SSRS SPECT and Whole Body MRI	2014
Haug et al., 2009 [a]	68Ga-DOTATATE compared to 18F-DOPA	2009
Lastoria et al., 2016 [a]	68Ga-DOTATATE compared to conventional imaging (CT, MRI, US, EUS)	2016
Poeppel et al., 2011 [a]	Comparison to 68-Ga DOTATOC	2011
Wild et al., 2013 [a]	Comparison to 68-Ga DOTANOC, conventional imaging (CT, partially MRI), partially 18F-FDG and histology	2013
a) Studies included in the meta-analyses by (Deppen, Blume, et al., 2016)		

Table 11 shows a literature overview of imaging studies using Gallium- 68 in neuroendocrine tumours with a comparison to SRS, PET and conventional imaging.

The study by Haug et al. (2012) from the Ludwig-Maximilians-University of Munich compared ^{68}Ga-DOTATATE to the gold standard pathology and should therefore be highlighted. The results showed that ^{68}Ga- DOTATATE had an overall sensitivity of 81%, correct identification of NETs in 29 of 36 cases, and a specificity of 90% with a correct exclusion of NET in 61 of 68. In a follow-up study in patients with metastatic NET, ^{68}Ga-DOTATATE identified a recurrence of disease in 26 of 29 patients (sensitivity 90%) and excluded the presence of recurrence in 28 of 34 patients (specificity 82%). The sensitivity (94%), specificity (89%) and accuracy (91%) were higher in patients with gastroenteropancreatic NETs (Haug et al., 2014a).

Hofman et al. (2012) suggested a high management (inter-modality change) impact of ^{68}Ga-DOTATATE, compared to ^{111}In-Octreotide in 28 (47%) of patients, moderate impact (intra-modality change) in 6 (10%) of patients, low impact in 24 (41%) of patients and the impact was not rateable in one patient (2%). Deppen et al. (2016) showed that ^{68}Ga-DOTATATE lead to an overall change of treatment in 36% (27 patients) of cases, in which 19 patients (24%) the significant change resulted in the cancellation of a surgery, a radical change in type of surgery or referring the patients for PRRT. Similarly Ilhan et al., 2015 demonstrated a change in surgical management in 20% of patients and provided additional information for surgical planning in more than 95% of cases.

Panagiotidis et al.(2016) demonstrated that ^{68}Ga-DOTATATE, as well as ^{18}F-FDG, affected the original treatment plan in 40 patients (38.4%). In 14 (27.4%) patients, the finding led to the initiation of PRRT and the commencement of somatostatin analogues in 12 (23.5%) of patients (Panagiotidis et al., 2016). One of the first papers, stating the impact of DOTATATE on the management of patients, was published in 2010 showing a change in 70.6% of patients, already undergoing ^{111}In-Octreotide imaging (Srirajaskanthan et al., 2010). After DOTATATE PET almost 39% of patients were considered for ^{90}Y-DOTATATE PRRT, in 13.7 patients with positive uptake, but without functional symptoms, an ant proliferative treatment with somatostatin analogues was conducted. In four patients (7.8%) a surgical approach was proposed (Srirajaskanthan et al., 2010).

With regard to the efficacy of ^{68}Ga-DOTATATE, based on the six-tiered model by Frynback & Thornbury, the results are comparable to study quality seen in the ^{111}In-Octreotide studies: the studies (refer to Table 11) were able to show diagnostic accuracy efficacy (level 1) and diagnostic thinking efficacy (level 2) in 96% of cases. Six studies (23%) focused on showing therapeutically efficacy (level 3), and succeeded in identifying an impact on patient management (Deppen, Liu, et al., 2016; Goel et al., 2014; M.S. Hofman et al., 2012; Kayani et al., 2008; Panagiotidis et al., 2016; Srirajaskanthan et al., 2010). Level 4 (improvement of patient outcome) and level 5 (improvement of societal efficacy) outcome was not shown in any study.

From the previously mentioned studies, it becomes evident that imaging plays an essential role in diagnosis, staging, treatment selection and follow-up of NETs. Currently, the clinically relevant

information is gathered in a multimodality approach: clinical manifestations, general anatomical-(radiological) and specialised functional (nuclear medicine) imaging techniques. In addition to the routine measurement of secretory products, imaging is indicated in different stages in the patient´s care such as screening, primary lesion detection, assessment of the disease extent and the follow-up/ treatment response (Modlin et al., 2008; Ramage et al., 2012). Imaging has essential influence on patient´s management and support the right therapy selection with cold or radiolabelled somatostatin analogues (PRRT) based in additional functional information (Bodei, Sundin, et al., 2014). Especially the positive results from the NETTER trial had substantial influence on current guidelines such as the practice guideline neuroendocrine tumours in Germany. Created under the leadership of the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS) and with participation of neighbouring scientific societies there is a strong recommendation and strong consensus among the societies that an initial PET/CT imaging procedure is recommended for every NET G1 or NET G2 besides stomach NET type I, rectum NET G1 (each <1 cm and no risk factors), and the incidental finding of an appendix NET (<1 cm) with no risk factors (Rinke et al., 2018).

2.2.5 Peptide Receptor Radionuclide Therapy (PRRT) with Somatostatin Analogues

With the ability to identify somatostatin receptor positive tumours with radiolabelled somatostatin analogues in the 1990s, it was the next logical step to use these analogues for therapy (especially) in patients with well-differentiated neuroendocrine tumours in stage IV disease, because chemotherapy does not seem to be so beneficial (Öberg, 2001; Rougier & Mitry, 2000). Already in 1987, Mörtel et al. evaluated the usefulness of different chemotherapeutical agents [Doxorubicin, 5-Fluorouracil (5FU), Dacarbazine (DTIC), Dactinomycin, Cisplatin, Streptozotocin, Mitomycin, Melphalan, Fluorometholone] in patients with advanced carcinoid tumours (significant symptoms; disabilities of malignant disease; poor prognostic signs) and concluded:

> *"The 33% response rate with the 5-FU combination has been our best experience, and this was duplicated by an ECOG study. Even with this, our most active regimen, the frequency of usually partial responses is too low, duration of response is too transient, and the price in often miserable toxicity is too high. We do not feel that any chemotherapy regimen for carcinoid tumours is of sufficient value to justify use in routine clinical practice* (Mörtel, 1987)."

The 2012 guidelines for GEP NETs (including carcinoids) considered a platinum-based regimen in poorly differentiated NETs (Level of evidence 2; grade of recommendation B), and a streptozotocin (STZ) based combination for moderately and well-differentiated tumours (Level of evidence 1; grade of recommendation A) (Ramage et al., 2012). A recently published meta-analysis by Wong et al., (2016) reviewed chemotherapies/systematic therapies in patients with advanced or metastatic NETs. Despite the poor quality of the studies they concluded that there is no difference between STZ/5-fluorouracil (5FU) to other chemotherapies in response rate (RR), progression-free survival (PFS) and overall survival (OS). Interferon (IF) may show a little higher response rate, but survival rates do not change (M. H. Wong et al., 2016).

Peptide Receptor Radionuclide Therapy (PRRT) was, therefore, a good alternative for patients with unrespectable NETs. Early radionuclide therapy used ^{111}In-DTPA-pentetreotide to treat patients with advanced disease stage, mainly with a high progressive tumour load. Symptoms decreased, but no consistent biochemical response could be shown (Valkema et al., 2002). Somatostatin analogues predominately had antisecretory (~70-80%) and ant proliferative (~50%) effects, but little cytoreductive capacity (Eriksson et al., 2007; Sabet, Biersack, & Ezziddin, 2016). In the next step radioisotopes with a wider particle range have been used to overcome the low tissue penetration such as Yttrium 90

(maximum energy $E_{\beta}max$ = 2.27 MeV, penetration range $R_{\beta}max$=11 mm, half-life T1/2 = 64 h) and Lutetium 177 ($E_{\beta}max$ = 0.49 MeV, $R_{\beta}max$ = 2 mm, T1/2 = 6-7 days) (Bergsma et al., 2013; Bodei, Kwekkeboom, Kidd, Modlin, & Krenning, 2016). At the moment nuclear medicine procedures such as PRRT are not recommended (recommendation with consensus among the societies) as first line therapy in patients with metastasised neuroendocrine tumours in the German practical guidelines (Rinke et al., 2018). But the guidelines states that PRRT may be considered in patients with exceptional high tumour burden of a small bowel tumour (Rinke et al., 2018).

2.2.5.1 Requirements

Prerequisite for a successful PRRT is a sufficient overexpression of somatostatin receptors on the tumour´s cell membrane surface, so the substance can sufficiently interacting with the tumour. Following the binding of the complex on the cell membrane, the radiolabelled somatostatin agonist complex is internalised and can subsequently release the radioactivity in the cell (Bodei et al., 2016). In a recent development a new SST analogue with receptor antagonistic properties showed a 5-times higher uptake of ^{177}Lu DOTA- JR11 (88% ± 1% membrane-bound) than of ^{177}Lu DOTA- octreotate (74% ± 3% internalised) and a higher DNA double-strand break in preclinical models (Dalm et al., 2016). The significant difference: contrary to the mechanism of action of agonists, the substance is not internalized, but recognises more binding sites and thus receives greater tumour irradiation (Wild et al., 2014).
Haug et al. (2010) from the University of Munich were first to assess the predictability of clinical outcome and progression-free survival after the first cycle of PRRT in NET patients using ^{68}Ga- DOTATATE PET/CT. Their findings suggest that the standardised uptake value maximum (SUV_{max}) is not a significant predictor of time-to-progression, because of the fluctuation of the value after several PRRT cycles (Gabriel et al., 2009; Haug, Auernhammer, et al., 2010). The standardised uptake value tumour-to-spleen ratio ($SUV_{T/S}$) was seen to be superior to baseline SUV_{max} ΔSUV_{max} in this study (Haug, Auernhammer, et al., 2010). Contrarily Kratochwil et al. (2014) suggested that a SUV_{max} cut-off > 16.4 (sensitivity 95 %) is a valid marker (95 % of the responding lesion being detected), but having a lower specificity of 60%. The research group concluded that tumour-to-lesion ratios are less robust, but may overcome the problem of comparability between different PET scanner hardware and reconstruction algorithm. A tumour-to-liver (T/L) ratio may be more reliable than a tumour-to-spleen (T/S) ratio (Kratochwil et al., 2014). The newest data from a multicentre trial with 141 patients undergoing radionuclide therapy suggests that the survival prediction is best estimated by eight independent heterogeneity parameters such as: entropy, skewness, correlation, short zone emphasis and homogeneity. Those textural characteristics have demonstrated superior diagnostic capability than standard PET parameters such as mean and maximum standardised uptake value (SUV_{max}/SUV_{mean}) (Werner et al., 2017).

2.2.5.2 Dosimetry

PRRT can be seen as a serious personalised therapy procedure by quantifying and delivering the necessary therapeutically dose based on the patient's individual disease status. The goal is to administer the maximal harmful radiation dose to a tumour and spare (healthy) organs and cells (Bodei, Cremonesi, & Paganelli, 2014). Due to the significant differences in patient´s individual organ dose limits, an individual patient dosimetry (IPD) before PRRT is suggested (Delker et al., 2015; Förster et al., 2001; Guerriero, Ferrari, & Botta, 2013; Helisch et al., 2004). Different dosimetry simulations (2D and 3D methods) (e.g.: Garkavij et al., 2010; Larsson et al., 2012; Sandström, Garske, Granberg, Sundin, & Lundqvist, 2010) are available and allow a more accurate estimation on the distribution and accumulation of the injected RP in different tissues (Celler, Grimes, Shcherbinin, Piwowarska-Bilska, &

Birkenfeld, 2013). IDP furthermore tries to establish a dose-response relation to predicting tumour response and organ toxicity by pre-therapy dosimetry, which in effect allows a comparison of the results of different radionuclide therapies and radiopharmaceuticals (Flux et al., 2006). IPD complies with the EU council directive 97/43/EURATOM (Rat der Europäischen Union, 1997), which tries to overcome the differences in patient treatment response by establishing a minimum effective and maximum tolerated absorbed dose per patient (Brans et al., 2007; Flux et al., 2006).

2.2.5.3 Administration

In the systemic administration protocol several cycles (usually four to five) every 6-10 weeks are scheduled until the cumulative activity has been reached (Bodei et al., 2016; Ramage et al., 2012). The recommended dose protocol based on the current guidelines (Ramage et al., 2012):

- ^{90}Y- DOTATATE and DOTATOC activity per interval is in the range of 3-6 GBq; 6-8 week cycles with a total cumulative dose of 12-18 GBq.
- ^{177}Lu- DOTATATE the activity ranges from 3.7- 7.4 GBq per cycle with intervals of 6-10 weeks and a total of 22-29.6 GBq

Intra-arterial administration of ^{90}Y and ^{177}Lu has been tested in NETs with mainly hepatic metastases, to overcome the first-pass effect and increase the radioligand concentration and binding in hepatic tumours (Bodei et al., 2016; Kratochwil et al., 2010; McStay et al., 2005). The results present a several-fold higher SUV and a partial and complete response in 60% of patients with G1/G2 GEP NETs (Kratochwil et al., 2010, 2011).

2.2.5.4 Side Effects

Generally PRRT with ^{90}Y and ^{177}Lu is well tolerated, acute side effects are usually mild and are related to the co-administration of nephron-protecting drugs, with nausea and occasional vomiting, or the radiopeptide itself with symptoms such as fatigue, weight loss, hematologic or renal toxicity, slight loss of hair, impairment of male fertility or, more rarely, an aggravation of a clinical syndrome (Bodei, Cremonesi, et al., 2014; Bodei et al., 2016; Geisler et al., 2012; Paganelli et al., 2014; Sabet et al., 2016; van der Zwan et al., 2015). Severe long-term adverse events such as kidney - and haematotoxicity have been reported, but are generally mild if precautions (amino acids, dosage fractioning, consider risk factors) are undertaken (Bodei et al., 2011, 2015; Hörsch et al., 2016; Imhof et al., 2011; Iten et al., 2007; Kwekkeboom et al., 2008; Sabet et al., 2013, 2014; Valkema et al., 2006). Kidney renal- protective agents, such as lysine and arginine or amifostine, are commonly used to reduce toxicity to the kidney through inhibition the proximal tubular reabsorption (Bodei et al., 2016; van Essen et al., 2009). The reabsorption can be inhibited by saturating the apical membrane megalin, which reduces the radioactivity in the kidney by 9-53% (Bernard et al., 1997). A reduction of renal function was more often associated with ^{90}Y peptides, likely to be based on the much larger particle penetration into the kidney and very high radioactivity doses (Bodei et al., 2016). One study detected the presence of two kidney clearance phases, which could hamper accurate dose estimation when using a single-phase dosimetry model (Delker et al., 2015).

Long-standing hypertension or poorly controlled diabetes or both have also been associated with a reduction of renal function (Bodei et al., 2003; Valkema et al., 2005). The latest multicentre study in Germany showed a meagre rate of nephrotoxicity (0.65%), which may be attributed to a high number of patients treated with both radiopeptides (^{90}Y and ^{177}Lu) and a short follow-up (Hörsch et al., 2016).

Study	Ligand	n	Nr. SAEs (% of pat.)	% of patients with … toxicities			
				Renal	Hematologic	Myelo-proliferative diseases	Liver
Iten et al., 2007	^{90}Yr- DOTATOC	31	11 (35.4)	19.4 Grade 3/4	12.9		
Imhof et al., 2011	^{90}Yr- DOTATOC	1109	142 (22.1)	9.3 Grade 4/5	12.8	0.2	
Kwekkeboom et al., 2008	[^{177}Lu-DOTA0,Tyr3]octreotate	504	9 (1.8)	0.4 Grade 4[a]		0.8	0.6
Lisa Bodei et al., 2011	[^{177}Lu-DOTA0,Tyr3]octreotate n	51	11 (21.7)	21.7 Grade I	0	0	0
Hörsch et al., 2016	^{90}Yr & ^{177}Lu with DOTATATE and DOTATOC[b]	450	13 (2.89)[c]	0.22 Grade III (no data for Grade I-II) [c]	2.67 [c]		
Lisa Bodei et al., 2015	^{90}Yr- octreotide (44.4%) & ^{177}Lu - ocetreotate (34.4%); ^{90}Yr & ^{177}Lu combined (19.5%)	807	88 (9.17)	33.1 Grade I/II 1.5 Grade III/IV	82.2 Grade I/II 9.5 Grade III/IV	2.35	0
Valkema et al., 2006	[^{90}Y- DOTA^{0}, Tyr^{3}]Octreotide	58	5 (8.62)	3.45 Grade IV	1.7	1.7	1.7
Sabet et al., 2013, 2014	^{177}Lu- DOTATATE	74/203	27 (13.3)	1.3 Grade III/IV	11.3 Grade III/IV	1.4	
Nr. SAEs, Number of severe adverse events in per cent of patients							

Table 12 Long-term toxicity in patients treated with Yttrium-90 and Lutetium-177 somatostatin analogues.

2.2.5.5 Results and Efficacy of Yttrium-90

After the insignificant success of [^{111}In-DTPA^{0}], -octreotide as a therapeutic agent, a new somatostatin analogue ([Tyr3]-octreotide) and chelator (DOTA) were developed to safely bind the β- emitting radionuclide Yttrium- 90. This new stable β- emitting radionuclide compound (^{90}Y-DOTA-tyr^{3}-octreotide = ^{90}Y-DOTATOC) showed a higher affinity to somatostatin receptors 2 (and 3) and could deliver a cytotoxic dose of radiation to somatostatin receptor–positive tumour cells (de Jong, Breeman, Bernard, Bakker, Visser, et al., 2001).

Several studies (Table 13) have investigated the usefulness of ^{90}Y- DOTATOC and indicated great safety and tolerability (De Jong et al., 2002; Paganelli et al., 2001; Valkema et al., 2002; Waldherr, Pless, Maecke, Haldemann, & Mueller-Brand, 2001) as well as clinical efficiency in the sense of morphological, biochemical and clinically response in progressive metastasized neuroendocrine tumours (Iten et al., 2007; Waldherr, Pless, et al., 2002; Waldherr et al., 2001). The objective response ranges from four to thirty-three per cent, however, a direct comparison is not valid as the studies included different cycle doses, tumour subtypes and patient characteristics. Nevertheless, the results were encouraging, especially as there are few alternatives for patients at this stage of the disease. For this reasin ^{90}Y became the most widely used radiopeptide in the first decade of PRRT (Bodei et al., 2016).

In some subtypes of NETs the response rate to ^{90}Y was remarkable, such as gastrinomas with a high rate of complete remission. This may be mainly based on the high somatostatin receptor status and radiosensitivity of these tumours (Imhof et al., 2011). In the same large phase II study with 1,109 patients with a broad spectrum of neuroendocrine tumours, 34.1% of patients experienced a morphologic response, 15.5% a biochemical response and 29.7% a clinical response with a significant correlation to longer survival (Imhof et al., 2011). Another single-arm, multicentre study investigated the effect of ^{90}Y-DOTA-tyr^{3}-octreotide in 90 patients with biopsy-proven malignant carcinoid tumours. A total of 74.4% patients were objectively stable or responded (0% complete remission, 4.4% partial remission and 70% stable disease). The number of adverse events (nausea, vomiting, and abdominal pain) was high (87.6%), but severe adverse events with induced nephrotoxicity of grade 3/4 were only observed in 3.3% of patients (Bushnell et al., 2010).

> "*The overall median survival of 26.9 months was better than historical controls (12.0 and 18.0 months) (Anthony et al., 2002; Perez et al., 2007) and then to the most promising combination chemotherapy results for metastatic carcinoid (11.9, 15.7, 24.3 months) (Sun, Lipsitz, Catalano, Mailliard, & Haller, 2005).*"(Bushnell et al., 2010)

Data on efficacy in specific tumour subtypes such as paraganglioma, pheochromocytoma and meningioma are rare.

Study	Ligand	N	CR (%)	PR (%)	SD (%)	PD (%)	CR+PR (%)
90Yr- labelled somatostatin analogues							
Bodei et al., 2003 [3]	[90Yr-DOTA^0,Tyr^3]- octreotide	21	0	29	52	19	29
Waldherr, Pless, et al., 2002; Waldherr, Schumacher, et al., 2002; Waldherr et al., 2001,[3]	[90Yr-DOTA^0,Tyr^3]- octreotide	74	4	20	65	11	24
Valkema et al., 2006 [1]	[90Yr-DOTA^0,Tyr^3]- octreotide	58	0	9	61	19	9
Bushnell et al., 2010 [1]	[90Yr-DOTA^0,Tyr^3]- octreotide	90	0	4.4	70	12	4.4
Pfeifer et al., 2011 [2]	[90Yr-DOTA^0,Tyr^3]- octreotide	53	4	19	64	13	23
Forrer, Waldherr, Maecke, & Mueller-Brand, 2006 [3]	[90Yr-DOTA^0,Tyr^3]- octreotide	58	4	22	62	11	26
Imhof et al., 2011 [2]	[90Yr-DOTA^0,Tyr^3]- octreotide	1109	0.6	33.5	5.2	60.7	34.1
Cwikla et al., 2010 [2]	[90Yr-DOTA^0,Tyr^3]- octreotate	58	0	23	73	5	23
^{177}Lu- labelled somatostatin analogues							
Kwekkeboom et al., 2003 [4]	[177Lu-DOTA^0,Tyr^3] -octreotate	35	3	35	41	21	38
Kwekkeboom et al., 2008 [1]	[177Lu-DOTA^0,Tyr^3] -octreotate	310	2	28	35	20	30
Garkavij et al., 2010 [2]	[177Lu-DOTA^0,Tyr^3] -octreotate	12	0	17	40	17	17
Swärd et al., 2010 [2]	[177Lu-DOTA^0,Tyr^3] -octreotate	26	0	38	50	13	38
Bodei et al., 2011 [2]	[177Lu-DOTA^0,Tyr^3] -octreotate	42	2	29	26	21	31
Sansovini et al., 2013 [1]	[177Lu-DOTA^0,Tyr^3] -octreotate	52	8	21	52	19	29
van Vliet et al., 2013 [1]	[177Lu-DOTA^0,Tyr^3] -octreotate	268	1	24	49	26	25
Ezziddin et al., 2014 [1]	[177Lu-DOTA^0,Tyr^3] -octreotate	68	0	60	12	15	60
Paganelli et al., 2014 [1]	[177Lu-DOTA^0,Tyr^3] -octreotate	43	7	0	77	16	7
Delpassand et al., 2014 [2]	[177Lu-DOTA^0,Tyr^3] -octreotate	32	0	31	41	28	31
Sabet et al., 2015 [1]	[177Lu-DOTA^0,Tyr^3] -octreotate	61	0	13.1	47.5	8.2	13.1
Ianniello et al., 2016 [1]	[177Lu-DOTA^0,Tyr^3] -octreotate	34	3	12	16	69	15
Baum et al., 2016 [2]	[177Lu-DOTA^0,Tyr^3] -octreotide	56	16.1	17.9	32.1	33.9	34
Combination therapy with ^{90}Y & ^{177}Lu SSA							
Kunikowska et al., 2011 [2,A]	^{90}Y/^{177}Lu-DOTATATE	25	0	0	62	8	0
Pfeifer et al., 2011 [2]	^{90}Y/^{177}Lu-DOTATOC	69	7.4	16.2	61.8	14.7	23
Villard et al., 2012 [2]	^{90}Y/^{177}Lu-DOTATOC	249	Na	Na	Na	Na	Na
Seregni et al., 2014 [2]	^{90}Y/^{177}Lu-DOTATATE	26	7.7	34.6	42.3	15.4	42.3
Hörsch et al., 2016 [2]	^{90}Y and ^{177}Lu-DOTATOC & ^{90}Y and ^{177}Lu DOTATATE[5]	357	7	28	59	5	35
Kong et al., 2016 [2]	^{90}Y/^{177}Lu-DOTATATE	26	0	21	5	0	21

CR, complete remission; MR, minor remission; PD, progressive disease; PR, partial response; SD, stable disease; NA, not available;
[1] SWOG, Southwest Oncology Group: PR ≥ 30% reduction of tumour size; MR, 30% reduction or an increase of SD, < 30% reduction or an increase of < 20% of tumour size; PD, ≥ 20% increase of tumour size or new lesion(s), measurement bi-dimensional;
[2] RECIST, Response Criteria in Solid Tumours: PR, ≥ 50% reduction of tumour size; SD, <25% reduction or an increase of tumour size; PD, >50% increase of tumour size. Unidimensional.
[3] WHO, World Health Organisation: PR, ≥ 50% reduction of tumour size; SD, <50% reduction or an increase of <25% of tumour size; PD, ≥ 25% increase of tumour size or new lesion(s). measurement bi-dimensional
[Four] not mentioned
[5] Patients treated with 90-Y only: 76; ^{177}Lu only: 243; combined: 130;
A.) Data from 36 months' follow-up

Table 13 Efficacy of somatostatin analogues labelled with Yttrium-90 and Lutetium-177 for the therapeutically purpose. Studies using different criteria to evaluate the therapy response such as SWOG, RECIST or WHO.

2.2.5.6 Results and Efficacy of Lutetium- 177

Compared to Yttrium-90, Lutetium-177 is a medium energy β- emitter with a maximum tissue penetration of 2mm and also emits low energy γ- rays, which can be used for imaging purpose. The replacement of threoninol with threonine in the C-terminal of the Somatostatin complex also induced in a six- to nine-fold higher affinity with SSTR 2 compared to [DOTA^0, Tyr^3] octreotide (Kwekkeboom et al., 2001; Reubi et al., 2000). This new radioligand ([177Lu-DOTA^0, Tyr^3]- octreotate (^{177}Lu DOTATATE)) indicated an objective response rate ranging from 7 to 60 per cent, with a favourable low radioactive burden to the kidney (Table 13).

The first study reporting the efficacy of ^{177}Lu- DOTATATE was published by the research group from Rotterdam, showing an objective response in 38% of patients treated with three fixed cycles of ^{177}Lu-DOTATAE (1st cycle 100mCi, 2nd cycle 150mCi, 3rd cycle 200mCI with intervals of 6-9 weeks) (Kwekkeboom et al., 2003). The same group published a follow-up study with 310 patients (504 patients included, but at the time of the study data on objective response and survival was only available for 310 patients) showing a reduction in tumours size in 46% of patients, a median overall survival of > 48 months and a PFS of 33 months (Kwekkeboom et al., 2008). The quality of life (mainly fatigue, insomnia and pain) also improved significantly in patients with objective response, but interestingly also in those with progressive disease (Khan et al., 2011; Teunissen, Kwekkeboom, & Krenning, 2004).

A recent meta-analyses by Kim, S. J. et al. (2015) analysed six studies (Bodei et al., 2011; Delpassand et al., 2014; Ezziddin et al., 2014; Paganelli et al., 2014; Romer et al., 2014; van Vliet et al., 2013) with a total of 473 patients with inoperable or metastatic NETs. All patients have been treated with ^{177}Lu-labelled somatostatin analogues. The disease response rate, defined as the percentages of patients with CR and PR, in the RECIST group (four studies with 256 patients) showed a pooled effect of 29% and a disease control rate, defined as CR, PR and SD, of 81%. In the SWOG group (three studies with 374 patients) the disease response rate was 23% and the disease control rate 82% (Kim et al., 2015).

With high expectation, the nuclear medicine community was looking for the first results from the Phase III multicentre, stratified, open, randomised, controlled trial evaluating ^{177}Lu-DOTATATE (Lutathera®) in patients with inoperable, progressive, somatostatin receptor positive midgut NETs (Strosberg et al., 2016).

> "*230 patients with Grade 1-2 metastatic midgut NETs were randomised to receive Lutathera 7.4 GBq every eight weeks (x4 administrations) with renal protection (amino acid solution infusion) versus Octreotide LAR 60 mg every 4-weeks. The primary endpoint was PFS per RECIST 1.1 criteria, with objective tumour assessment performed by an independent reading centre every 12 weeks until tumour progression. Secondary objectives included objective response rate, overall survival, TTP, safety, tolerability and health-related quality of life. An independent Data Safety Monitoring Board regularly assessed the safety outcome.*" (Strosberg et al., 2017)

The results confirmed previous academic clinical studies and showed a superiority of ^{177}Lu- DOTATATE and 30mg Sandostatin –LAR compared to 30mg Sandostatin-LAR alone. Estimated PFS at month 20 was 65.2% in the ^{177}Lu- Dotatate group and 10.8% in the control group. The response rate was 18% in the ^{177}Lu-Dotatate group versus 3% in the control group (P<0.001). The overall survival in the planned interim analysis revealed 14 deaths in the ^{177}Lu-Dotatate group and 26 in the control group (P = 0.004) (Strosberg et al., 2017).

2.2.5.7 Combination Therapy with Yttrium-90 and Lutetium-177 Somatostatin Analogues

Theoretically, simultaneous treatment of large- (high energy and penetration range of ^{90}Y) and small lesions such as metastases (low energy and penetration range of ^{177}Lu) should be beneficial due to the different physical properties of both radionuclides (Bodei et al., 2016). In 2005 the research group from Rotterdam conducted an animal tumour model, investigating the antitumor effect of a combination of 50 percent ^{177}Lu and 50 percent ^{90}Y- analogues. The results suggested a superiority of the combinational treatment compared to ^{90}Y- or ^{177}Lu analogue alone (de Jong, Breeman, Valkema, Bernard, & Krenning, 2005).

In humans, Villard et al. (2012) showed a significantly longer median survival (66.1 vs. 47.5 months) and median survival from diagnoses (123.6 vs. 82.6 months) in 86 patients treated with a combination of

^{90}Y-DOTATOC and ^{177}Lu-DOTATOC compared to the group which has only been treated with ^{90}Y-DOTATOC. Similar results have been shown in a study with 50 patients with disseminated NETs being randomised to either ^{90}Y-DOTATATE (n=25) or ^{90}Y/^{177}Lu-DOTATATE (n=25). The patients in the ^{90}Yr/^{177}Lu-DOTATATE group showed a longer overall survival with a calculated probability of 24-month survival of 89% vs 62% in the ^{90}Y- group (Kunikowska et al., 2011). In another phase II clinical study by Seregni et al. (2014) 26 patients with NETs have been treated with ^{90}Y- and ^{177}Lu- DOTATATE and showed an objective response of 42.3% and a median PFS longer than 24 months.

In a sizeable multi-institutional registry study in Germany the data from 450 patients with progressive, locally advanced or metastatic low to intermediate grade neuroendocrine neoplasms with overexpression of somatostatin receptors had been evaluated (Hörsch et al., 2016). These results suggest that patients exclusively treated with ^{90}Y had a significant decreased OS and PFS compared to patients treated with ^{177}Lu alone or in combination with ^{90}Y (median OS and PFS shown in Table 14) (Hörsch et al., 2016).

Radionuclide	Patients	median OS	median PFS
Lutetium-177	241	Not reached	40
Yttrium-90	76	38	27
Combined	130	58	50

Table 14 Median Overall survival (OS) and progression-free survival (PFS) in a multi-institutional registry study in Germany. The study population included 450 patients with progressive, locally advanced or metastatic low to intermediate grade NETs (Hörsch et al., 2016)

2.3 Case II- Radionuclide Imaging and Therapy in Prostate carcinoma

Prostate cancer (PC) is the fourth most common cancer in both sexes combined and the most common malignancy in men worldwide, with a death rate of ~ 1-2% in men (Attard et al., 2016; Ferlay et al., 2014). The incidence rate varies worldwide more than 25- fold, mainly due to the implementation of the screening programs (prostate-specific antigen –PSA) and routinely biopsies (Ferlay et al., 2014).

The risk factors for PC can be classified as endogenous and exogenous. In the group of endogenous risk factors age, race and family history are the most established. During ageing, cellular oxidants (free radicals and reactive oxygen species) are continuously produced in the metabolic process and lead to damage of macromolecules and organelle functions in the cells (Minelli, Bellezza, Conte, & Culig, 2009). The race-related differences in risk may reflect multiple factors, including differences in genetic factors, exposures, dietary and detection. African- American men have the highest incidence rates for PC in the world (Bostwick et al., 2004). Family history also seems to play an important role: the risk for first-degree relatives of men with PC is about twice that for men in the general population (Schaid, 2004), and about four times higher in first- degree relatives of men with cancer diagnosed younger than 60 years (Johns & Houlston, 2003). Genetic predisposition seems to have a high impact on PC: around 77 single nucleotide polymorphisms (SNPs) have been identified to be associated with PC (Attard et al., 2016). Diet and nutrition may be an exogenous risk factor contributing to PC, but the overall inhomogeneity of prospective epidemiological studies showed considerable inconsistency (Markozannes et al., 2016). An umbrella review of existing meta-analyses indicates that the associations between food, body size, physical activity and PC remain uncertain (without substantial evidence), except the factor “height” which seems to have a positive correlation to PC risk (Markozannes et al., 2016).

2.3.1.1 Pathology of the Prostate:

The healthy prostate is composed of glands and stroma, and with normal ageing of the prostate, small clotting within the glandular lumina happens. Benign prostatic hyperplasia is a progressive enlargement from a non-malignant proliferative process of epithelial and stromal elements of the prostate gland and is present in more than 50% of men aged over 60 years (Bushman, 2009; Thorpe & Neal, 2003). In up to 25% of cases, the benign prostatic hyperplasia needs surgical and medical therapy because of lower urinary tract symptoms, which can have serious medical complications (Thorpe & Neal, 2003). Prostatic Intraepithelial Neoplasia (PIN) is described as a deformity of the epithelium lining of the prostate glands with the high-grade PIN being a precursor lesion to prostate cancer (Singh et al., 2009).

Nearly all prostate cancers are prostatic adenocarcinoma, very common in aged men, but often small and clinically insignificant (Mercer University School of Medicine, 2016). The use of a serum prostate-specific antigen (PSA) test has improved the percentage of pathologically organ-confined PC (Catalona, Smith, Ratliff, & Basler, 1993), but many false positive results remain, if only PSA measurement was used (Partin et al., 1997). PSA is a glycoprotein, which is almost exclusively produced in the epithelium of the prostate gland with subtypes of a complexed PSA (cPSA) or free PSA (fPSA). The total PSA (cPSA + fPSA) level usually does not exceed 4 ng/ml; a level less than 10.0 ng/ml indicates early-stage disease, whereas a PSA level greater 10.0 ng/ml is a reference of advanced disease in more than 50% of the patients (Catalona et al., 1994). Unfortunately, the PSA level in the range of 4.0 – 10.0 ng/ml shows a lack of specificity and thus leads to many unnecessary biopsies (Catalona et al., 1998). The measurement of the specific PSA types and their ratios (fPSA, cPSA, fPSA/tPSA, cPSA/tPSA, fPSA/cPSA) has shown promise to discriminate between prostate cancer and benign prostatic disease, especially in the grey

zone of 4.0 – 10.0 ng/ml total PSA (Brawer et al., 1998; Catalona et al., 1998; Jung et al., 2000; Luderer et al., 1995; Polascik, Oesterling, & Partin, 1999)

2.3.1.2 Staging:

Autopsy studies have shown that in men over 50 the prevalence of prostate cancer is about 30% (Dhom, 1983; Mcneal et al., 1986; Montie, Wood, Pontes, Boyett, & Levin, 1989; Scardino, Weaver, & Hudson, 1992), although not every cancer is clinically relevant. PC shows a wide range of biological behaviour with around 80% being clinically unimportant and 20% possessing a threat to the patient's life or well-being (Scardino et al., 1992). PC are usually graded according to the Gleason grading system, developed by Dr Donald F Gleason, a pathologist in Minnesota, and members of the Veterans Administration Cooperative Urological Research Group (VACURG). The score differentiates between five grades (see Figure 9), which are based upon the architectural patterns of the carcinoma.

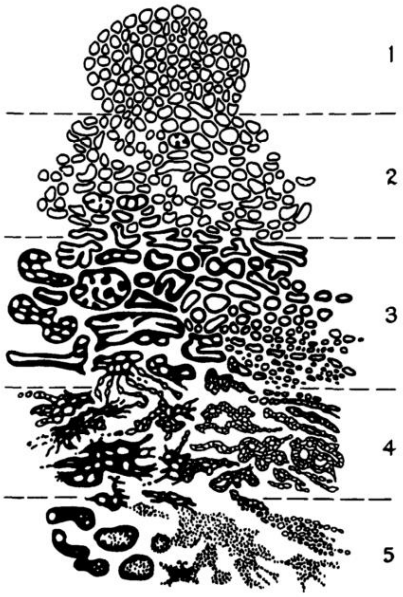


Figure 9 Prostatic adenocarcinoma (histologic patterns). Standardized drawing for grading system on the left (Gleason, 1992)

	Original Gleason system	Modified system*
Gleason grade 1	Very well differentiated, small, closely packed, uniform glands in essentially circumscribed masses	Circumscribed nodule of closely packed but separate, uniform, rounded-to-oval, medium-sized acini (larger glands than pattern 3)
Gleason grade 2	Similar to pattern 1, but with moderate variation in size and shape of glands and more atypia in individual cells; cribriform pattern might be present—still essentially circumscribed, but more loosely arranged	Similar to pattern 1, fairly circumscribed, although a little infiltration might be seen at the edge of the tumour nodule; glands are more loosely arranged and not quite as uniform as pattern 1
Gleason grade 3	Similar to pattern 2, but substantial irregularity in size and shape of glands, with tiny glands or individual cells invading stroma away from circumscribed masses, or solid cords and masses with easily identifiable glandular differentiation within most of them	Discrete glandular units; typically smaller glands than seen in pattern 1 or 2; infiltrates in and among non-neoplastic prostate acini; substantial variation in size and shape; smoothly circumscribed, small cribriform nodules of tumour
Gleason grade 4	Large, clear cells growing in a diffuse pattern that resembles hypernephroma; might show gland formation	Fused microacinar glands; ill defined glands with poorly formed glandular lumina; large cribriform glands; cribriform glands with an irregular border; hypernephromatoid variant
Gleason grade 5	Very poorly differentiated tumours; usually solid masses or diffuse growth with little or no differentiation into glands	Essentially no glandular differentiation—composed of solid sheets, cords, or single cells; comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

Table 15 Original Gleason scoring system and the 2005 modified system (defined by the International Society of Urological Pathology) (Ahmed, Arya, Freeman, & Emberton, 2012)

The challenge in adenocarcinoma is that roughly half of the tumours could not be fitted in one grade and typically showed more than one histologic grade. For this reason, two grades are added together

to a final grade of 2 to 10, in which the first grade represents the most common- and the second grade the second most common architectural patterns. The stage is determined by the size and location of cancer, whether it has invaded the prostatic capsule or seminal vesicle, and whether it has metastasised (Gleason, 1992). Adenocarcinomas with a Gleason grade of four and five typically show adverse pathologic findings and disease progression. Gleason score two to four describe well- differentiated, five to seven moderately differentiated, and a score of eight to ten as poorly differentiated (Epstein, Partin, Sauvageot, & Walsh, 1996; Humphrey, 2004).

In the current guidelines from the European Association of Urology (EAU), European Society for Radiotherapy & Oncology (ESTRO) and the International Society of Geriatric Oncology (SIOG) the 2009 TNM classification for staging, and the EAU risk group classification was recommended for patients with curative prostate cancer (Mottet et al., 2016). Currently, the recommended PCa grading system is the modified Gleason score (GS) introduced from the International Society of Urological Pathology (ISUP) in 2005 the (see Table 15).

2.3.1.3 Diagnosis

Prostate cancer may be diagnosed either by digital rectal examination (DRE), transrectal ultrasound (TRUS) or screening for rising PSA levels. The current EAU, ESTRO and SIOG Guidelines for patients with curative intent value PSA as a better predictor of cancer than DRE and TRUS. However, definitive diagnosis is still based on histopathologic verification via TRUS- guided biopsy (Mottet et al., 2016).

Epidemiological data from the SEER database show a dramatically decrease of patients with PC and distant metastases at the time of diagnosis from around 20% (1975-1984) to 5% (1995-2000), as well as a significant increase in five-year survival rates in all races in the period from 1980-2000 (1980: 83%; 1990: 93% and 99% since 2000) (Jemal et al., 2005; Siegel, Miller, & Jemal, 2016). These data also highlight a spike in incidence rates of PC in the late 1980s and early 1990s, which reflects the increased use of PSA testing and prostate needle biopsy to detect asymptomatic PC forms (Potosky, Miller, Albertsen, & Kramer, 1995). However, absolute PSA serum levels must be interpreted with care as there is a high proportion of cancers, which may not develop symptoms during their lifetime (Bangma, Roemeling, & Schröder, 2007). The right treatment selection requires a more profound characterisation of a tumour, to maximise cancer control and to minimise the risk of complications (Hricak, Choyke, Eberhardt, Leibel, & Scardino, 2007).

Moreover, while imaging plays a significant role in many malignant cancer diseases, the value of prostate cancer imaging is controversially discussed. It is often argued that the majority of men are diagnosed with the low-risk disease (T1c or T2a; Gleason score ≤ 6; and a PSA serum level < 10 ng/m) and a low risk of metastasis (D'Amico et al., 1997). Nonetheless, this patient group has a high use of imaging for staging purpose, whereby this is not indicated and recommended (Choi et al., 2011; Cooperberg, Broering, Kantoff, & Carroll, 2007; Mottet et al., 2016). In the period from 1995 to 2002 a shift towards fewer staging imaging studies before treatment in patients with low-risk (63%), intermediate-risk (25.9%) and high-risk patients (11.4%) has been observed (Cooperberg, Lubeck, Grossfeld, Mehta, & Carroll, 2002). But an overuse in low- risk patients still seems to persist (Choi et al., 2011; Dinan et al., 2010; Lavery et al., 2011; Palvolgyi, Daskivich, Chamie, Kwan, & Litwin, 2011; Porten et al., 2014; Prasad, Gu, Lipsitz, Nguyen, & Hu, 2012). A Swedish national registry study confirmed the more appropriated use of imaging in Europe with a dramatic decrease in low-risk patients in the period from 1998 to 2009, and a small but still significant reduction of imaging procedures in high-risk patients (Makarov et al., 2013). With the ongoing debate about the usefulness of imaging the following question

remains: “What is the optimal role of imaging in prostate cancer detection, staging, treatment planning and follow- up?”

The current interdisciplinary German S3- guideline for early diagnosis, diagnosis and therapy of the prostate carcinoma recommends the use of DRE and TRUS for primary staging, and in cases of a negative biopsy MRI (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, 2016). For patients with low-risk (cT1) no imaging test is recommended, for patients with intermediate-risk a recommendation is not possible because of lacking evidence and for patients with Gleason score ≥ 8 or cT3/4 tumours a CT or MRI study of the pelvis is recommended. PET/CT is not recommended in staging, scintigraphy in patients with histologically confirmed prostate carcinoma and a serum PSA level > 10 ng/ml or a Gleason score ≥ 8 (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, 2016).

Also the current EAU, ESTRO, SIOG guidelines (see Figure 10) do not recommend imaging for patients with low risk of localised PC, but suggest at least cross-sectional abdominopelvic imaging and a bone scan for patients with intermediate- and high risk PC (Mottet et al., 2016).

Risk group	LE	GR
Any risk group staging		
Do not use CT and TRUS for local staging	2a	A
Low-risk localised PCa		
Do not use additional imaging for staging purposes	2a	A
Intermediate-risk PCa		
In predominantly Gleason pattern 4, metastatic screening, include at least cross-sectional abdominopelvic imaging (s.a. CT/MRI) and a bone scan for staging purposes	2a	A*
In predominantly Gleason pattern 4, use prostate mpMRI for local staging	2b	A
High-risk localised PCa or high-risk locally advanced PCa		
Use prostate mpMRI for local staging	2b	A
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan	2a	A

CT = computed tomography; GR = grade of recommendation; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PCa = prostate cancer; TRUS = transrectal ultrasound.

Figure 10: EAU, ESTRO and SOIG Guidelines for staging of prostate cancer (Mottet et al., 2016).

In case of relapsing, metastatic, and castration-resistant prostate cancer the early diagnosis of local recurrence is necessary, but imaging was said to be poor in asymptomatic patients (Rouviére, Vitry, & Lyonnet, 2010). A recurrence after treatment with curative intent is defined as a rising PSA level after a specific post-treatment nadir and is called a biochemical failure or biochemical recurrence.

> “*Following radical prostatectomy (RP), biochemical recurrence (BCR) is defined by two consecutive rising PSA values > 0.2 ng/ml (Amling, Bergstralh, Blute, Slezak, & Zincke, 2001). After primary radiation therapy (RT), the Radiation Therapy Oncology Group (RTOG) and American Society for Radiation Oncology Phoenix Consensus Conference definition of PSA failure is any PSA increase > 2 ng/ml higher than the PSA nadir value, regardless of the serum concentration of the nadir* (M. Roach et al., 2006)*”* (Cornford et al., 2016).

Not every rise in PSA is due to a recurrence of prostate cancer. Hence it is crucial to accurately detect the possible local or distant recurrence to continue with the right treatment choice (Rouviére et al., 2010). The standard imaging modality for detection of distant metastases usually includes abdominopelvic CT and skeletal scintigraphy, but in this case especially PET/CT using the radiopharmaceutical PSMA shows promising results.

In the following pages, we briefly review essential imaging modalities and their benefit in local and distant tumour staging and monitoring.

2.3.1.3.1 Transrectal ultrasound (TRUS)

Transrectal ultrasound (TRUS) is currently the most widely used imaging modality in the staging process of PC. TRUS enables a good measurement of the volume of the prostate gland and the tumour, predicts nomograms, and helps to calculate the PSA density (PSAD) (Benson et al., 1992; Terris & Stamey, 1991). Secondly, TRUS is essential for the ultrasound-guided needle biopsy to systemically sample (usually from six areas of the prostate peripheral zone). A TRUS examination without a biopsy is considered to be of little value in the detection of cancer and is as useful as a DRE (Hricak et al., 2007).

In general, TRUS has significant higher sensitivity (77.2% vs 57.9%) and a similar specificity (96.3% vs 89.4%) compared to DRE (Mettlin, Lee, Drago, & Murphy, 1991).

Today, with the better awareness and the use of PSA testing, the tumours tend to be smaller, and TRUS alone does not seem to be sufficient for PCs detection alone (Kuru et al., 2015). Also, the use of Doppler sonography with and without contrast does not significantly change the detection rate (Taverna et al., 2011). Nevertheless, ultrasound will remain an essential instrument for therapeutically applications such as the guidance for the placement of brachytherapy seeds, cryotherapy, and high-intensity focused ultrasound (HIFU)

2.3.1.3.2 Computer Tomography (CT)

CT is not the first choice in PC detection or staging, because of a low resolution of the prostate anatomy and poor delimitation to surrounding tissue (Hricak et al., 2007). It is still used to detect or rule out lymph-node metastases, but with low sensitivity and specificity (Heesakkers et al., 2008; Hoevels et al., 2008; Wolf et al., 1995). With the rise in PSA testing, the majority of patients with newly diagnosed localised prostate cancer have a low risk of metastases, and thus the diagnostic yield of CT is low (Albertsen et al., 2000). The current EAU/ESTRO/SIOG guidelines recommend the use of at least a cross-sectional abdominopelvic imaging with CT or MRI, and a bone scan for metastatic screening (staging in curative intent) in patients with predominantly Gleason pattern 4 (Mottet et al., 2016)

2.3.1.3.3 Magnetic Resonance Imaging (MRI)

MRI is said to be the best available imaging technique for the identification of PC to date. It is especially recommended in cases of a suspected cancer but with negative TRUS and biopsy (Barentsz et al., 2012; Mottet et al., 2016). However, signals in MRI can also be associated with prostatitis, scarring, or hyperplasia (Schuster, Nanni, & Fanti, 2016) and there is a considerable variation in sensitivity in unenhanced MRI ranging from 37% to 96%, depending on the observer and study's inclusion and exclusion criteria (Kirkham, Emberton, & Allen, 2006; Rifkin et al., 1990). Additionally, the sensitivity for tumours smaller than 5mm is low (5%), but increases up to 89% detection rate in tumours with a size greater than 10mm (Ikonen et al., 1998; Nakashima et al., 2004).

To overcome the shortcomings of one or the other single MRI technique, a multiparametric MRI (mp-MRI) protocol was developed to improve accuracy (Hoeks et al., 2011). The mp- MRI includes the anatomic T2 weighted MR imaging protocol (T2WI) and at least two functional MRI techniques such as a dynamic contrast–enhanced (DCE-MRI) protocol, diffusion-weighted imaging (DWI) or MR spectroscopic imaging (MRSI) (Barentsz et al., 2012). The ESUR guideline recommends a fast mp-MRI protocol without an endorectal coil and a pelvic phased array coil. The entire prostate should be covered, and T2WI, DWI and DCE-MRI should be included. For staging purpose, the use of an endorectal coil is recommended (Barentsz et al., 2012).

Many single- centre studies suggest a negative predictive value of 63% to 98% and positive predictive value of 34% to 68% in the detection of aggressive tumours with mpMRI (Fuetterer et al., 2015). In tumours with Gleason score > 7 several studies acknowledged a high sensitivity for the mp-MRI protocol (Bratan et al., 2013; Selnæs et al., 2012; Turkbey et al., 2010, 2011), and the identification of anterior tumours missed in the systematic biopsy (Hoeks et al., 2011; Kim et al., 2016; Lemaitre et al., 2009). Furthermore, MRI can better evaluate the aggressiveness of the tumour based on biopsies targeted on MR abnormalities (Hambrock et al., 2012; Komai et al., 2013).

However, the variance of accuracy data (54% to 93%) of staging prostate cancer with MRI raised questions on inter-observer variability and the heterogeneity of definition of NPV and PPV (Hricak et al., 2007; Mottet et al., 2015, 2016).

2.3.1.3.4 Positron Emission Tomography (PET)

Current guidelines do not recommend PET as the first choice in the detection and staging of localised prostate cancer. The guidelines recommend DRE and PSA evaluation, and a histological verification. CT or MRI of the lower abdomen. Bone scintigraphy is recommended in patients with intermediate- to high-risk prostate cancer, and patients with recurrence disease to detect new sites and evaluate treatment response (European Association of Urology, 2016). However, the current results suggest that some lesions, especially in advanced disease status, might still be missed with these diagnostic modalities (Dianat, Carter, & Macura, 2014; Hoeks et al., 2013; Reisæter et al., 2014; Schimmöller et al., 2014).

The efficacy of PET in diagnosis and staging of PC was initially evaluated in connection to the radiopharmaceuticals [^{11}C]- and [^{18}F]-labelled choline derivate and fluorodeoxyglucose (FDG). Unfortunately these specific tracers showed some limitations in the reliable identification of local recurrence, lymph node involvement, or visceral metastases and PET as a complete method was consequently evaluated to be not beneficial (Bangma et al., 2007; Beresford, Gillatt, Benson, & Ajithkumar, 2010; Brogsitter, Zöphel, & Kotzerke, 2013; Evangelista, Guttilla, Zattoni, Muzzio, & Zattoni, 2013; Graute et al., 2012; Krause et al., 2008; Souvatzoglou et al., 2011; Tilki et al., 2013; Yu, Desai, Ji, Groshen, & Jadvar, 2014). The main restriction of ^{11}C- or ^{18}F- choline tracers was the low sensitivity (10 to 73%) in the detection of lymph node metastases (Brogsitter et al., 2013; Poulsen et al., 2012). Also, the relatively high rate of false negative results of ^{11}C-choline narrowed the use of intraprostatic tumour identification (Farsad et al., 2005).

More recently, a promising tracer selectively binds to the type II transmembrane protein “PSMA”, which is also known as glutamate carboxypeptidase 2. It consists of a small intracellular segment, a transmembrane domain, and an extracellular domain (Afshar-Oromieh, Avtzi, et al., 2015). PSMA is a cell surface protein which is expressed with a thousand-fold greater level on the prostate compared to other tissues such as kidney, small intestine, salivary gland (Ghosh & Heston, 2004). PSMA expressions were also reported in blood vessels of some other solid tumours such as breast, renal- and subtypes of bladder cancer and colon (Chang, 2001; Chang et al., 1999; Samplaski, Heston, Elson, Magi-Galluzzi, & Hansel, 2011) and in astrocytes of the central nervous system (Marmiroli, Slusher, & Cavaletti, 2012). In the past there have been several reports of a high uptake of the tracer in several non-prostatic lesions, which may have been considered pathological, but have in fact been physiological (Krohn et al., 2014; St. P Rowe et al., 2016; Verburg, Krohn, Heinzel, Mottaghy, & Behrendt, 2015).

Very quickly it became clear that PSMA is an ideal target for molecular imaging in prostate cancer. The protein is overexpressed in 90-100% of local PC lesions, cancerous lymph node metastases and bone lesions with higher expressions in high-grade, metastatic and castration resistant PCs (Bostwick, Pacelli, Blute, Roche, & Murphy, 1998; Chang, 2004; Silver, Pellicer, Fair, Heston, & Cordon-Cardo, 1997; Wright, Haley, Beckett, & Schellhammer, 1995). In addition to the large binding properties of PSMA, the ligand is also rapidly internalised via clathrin-coated pits and prolonged retained in lysosomal compartments or the cytoplasm (Ghosh & Heston, 2004; Kratochwil, Giesel, et al., 2016b).

Up to now numerous studies have shown the benefit of radiolabelled PSMA targeted agents in identifying local PCa lesions and metastases (Afshar-Oromieh, Avtzi, et al., 2015; Babich et al., 2013;

Budäus et al., 2015; Milowsky et al., 2004; Pandit-Taskar et al., 2015). One of the first RPs targeting PSMA was ^{111}Indium capromab pendetide (Prostacint®), which consists of a monoclonal antibody targeting the cytoplasmic domain (Kahn et al., 1998). The second generation had an improved tumour uptake by binding to the extracellular domain such as the antibody J591 (Chang et al., 1999). This monoclonal anti- PSMA antibody has also been labelled with ^{131}I, ^{177}Lu and ^{90}Y and has shown proper tumour targeting, acceptable toxicity and therapeutically efficiency (Milowsky et al., 2004, 2007; Tagawa et al., 2013).

However, antibodies have some disadvantages: increased size of the protein and consequently a longer plasma half-life and limited diagnostic value (Warram et al., 2014). Small- molecule RPs such as PSMA inhibitors are advantageous because they are typically cleared quickly from the bloodstream and have a low background activity. ^{68}Ga-PSMA-11 (Glu-NH-CO-NH-Lys-(Ahx)) also known as ^{68}Ga- PSMA-HBED-CC is an already clinically investigated urea-based inhibitor (Afshar-Oromieh, Avtzi, et al., 2015; Budäus et al., 2015). The high affinity to PSMA, the favourable biodistribution and half-life, as well as excellent contrast as early as one hour after injection makes ^{68}Ga- PSMA-11 an excellent imaging ligand, even in PCs with low PSA levels (Afshar-Oromieh et al., 2013; M. Eder et al., 2012; Matthias Eder et al., 2014). Unfortunately, ^{68}Ga- PSMA-11 cannot be labelled with ^{177}Lu or ^{90}Y, so it cannot be used for PRRT (Weineisen, Simecek, Schottelius, Schwaiger, & Wester, 2014). Consequently, some modifications have been made to PSMA-11 resulting in a new ligand called PSMA-617. This ligand even shows a significantly higher affinity to PSMA, a better internalisation into the PCa cells compared to PSMA-11 and can be labelled to ^{68}Ga, ^{177}Lu, ^{111}In and ^{90}Y (Afshar-Oromieh, Hetzheim, et al., 2015; Benešová et al., 2015).

Another chelator is DOTAGA-FFK (Sub-KuE), a radiometalated analogue with natural labelling properties, quick internalisation and a favourable pharmacokinetic profile (Weineisen et al., 2014). The same research group further optimised DOTAGA-FFK by increasing the lipophilic interaction of the tracer with the PSMA enzyme, creating the new ligand called PSMA I&T (for imaging and therapy) (Weineisen et al., 2015). This ligand showed favourable dosimetry, comparable to other PET RPs, a good bio distribution and desirable image quality (see Table 16) (Herrmann et al., 2015). A direct comparison to ^{68}Ga PSMA HBED-CC showed comparable results in the detection of recurrent prostate cancer, and increased sensitivity in patients with rising PSA levels (Berliner et al., 2016). Another benefit for the PSMA I&T tracer is the easy labelling with ^{111}In, thus an option for centres currently relying on SPECT imaging.

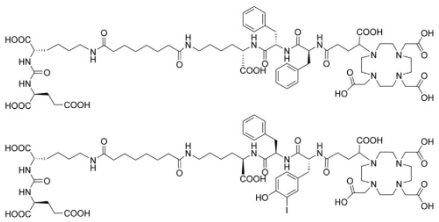


Figure 11 Chemical structures of DOTAGA-FFK (Sub-KuE) (top) and PSMA I&T (below) (Weineisen et al., 2015).

Target organ	Unit	PSMA-IT[1]	DOTATOC[2]	DOTATATE[2]	^{18}F-FDG[3]	^{123}I-MIP-1072[4]	^{123}I-MIP-1095[4]	^{124}I-PSMA[7]
Kidneys	mSv/ MBq	2.20E-01	8.20E-02	9.30E-02	1.70E-02	5.4E-02	1.10E-2	1.39E+00
Liver	mSv/ MBq	4.31E-02	4.10E-02	5.00E-02	2.10E-02	2.4E-02	5.8E-2	1.66E-00
Spleen	mSv/ MBq	6.34E-02	1.08E-01	1.09E-01	1.10E-02	2.3E-2	4.7E-2	7.7E-01
Urinary bladder wall	mSv/ MBq	6.74E-02	1.19E01	9.80E-02	1.30E-01	9.2E-2	2.1E-2	5.7E-01
Effective dose coefficient	mSv/ MBq	1.99E-02	2.10E-02	2.10E-02	1.90E-02	2.5E-2	3.2E-2	5.9E-01
Typical injected activity	MBq	150	185	150	370	370	370	67
Effective dose	mSv	3.0	3.9	3.2	7.0	9.3	11.8	38.9

Data source: (1) Herrmann et al., 2015; (2) Sandstroem et al., 2013; (3) International Commission on Radiological Protection (ICRP), 2013 (4) Barrett et al., 2013; (5) Zechmann et al., 2014

Table 16 Doses for each target organ using different prostate specific compounds. Table adapted from (Herrmann et al., 2015)

Recently a PMSA inhibitor (DCFPyL) has also been labelled with ^{18}F for imaging purpose. In comparison to ^{68}Ga-PSMA-HBED-CC, ^{18}F-DCFPyL showed an excellent image quality and detected the same suspicious lesions in patients with biochemical relapsed PCa as ^{68}Ga-PSMA-HBED-CC. The mean SUV_{max} of ^{18}F-DCFPyL (14.5 vs 12.2; p=0.028) and the tumour to background ratios (referring to kidney, spleen and parotid) were significantly higher compared to ^{68}Ga-PMSA-HBED-CC (Dietlein et al., 2015). The advantage of ^{18}F labelled RPs would be the better spatial resolution, higher positron yield, shorter positron range in tissues and a longer half-life (Sanchez-Crespo, 2013).

2.3.1.3.4.1 PSMA PET in Staging:

Morphological imaging (CT and MRI) alone missed almost 80% of metastatic lymph nodes since the threshold size of 8mm is mostly not reached (Heesakkers et al., 2008; Hoevels et al., 2008). DWI MRI improved sensitivity and specificity, but CT and MRI may still not reliably identify lymphatic spread (Maurer et al., 2015). However, current guidelines recommend the use of mpMRI in patients with suspected PCa, but negative biopsy findings, as well as for clarification of capsule penetration and seminal vesicle involvement.

Lately, several study groups compared the sensitivity and specificity of ^{68}Ga- PSMA PET/CT (or PET/MRI) to mpMRI (see table 18) in primary and secondary staging. Equal or even superiority results for PET/CT has been demonstrated (Fendler et al., 2016; Rhee et al., 2016).

Author	N	Design	Purpose	Ligand	Inclusion criteria	Comparison modality	The result of Comparison Imaging Modality	PET/CT or PET/MRI results
Giesel et al., 2016	10	RS	Primary staging (Tumour size/ Origin)	68Ga PSMA-11 PET/CT	Confirmed PCa, high risk, before radiotherapy	mp-MRI	96.8% of PET/CT lesions detected	89.4% of mp-MRI lesions detected
Zamboglou et al., 2016	22	RS	Primary staging (Tumour size/ Origin)	68Ga PSMA-11 PET/CT	Confirmed Pca	mp-MRI	Gross tumour volume in accordance in 47 % of patients (40%–54%of lesions)	Gross tumour volume significantly larger in PET/CT
Budäus et al., 2015	30	RS	Primary staging (lymph node assess.)	68Ga PSMA	Confirmed PCa w intermediate/ high risk, before RP	Histopathology	n.a.	Sensitivity 33.3% , Specificity 100%, PPV 100%, NPV 69.2%,
S. P. Rowe et al., 2015	12	RS	Primary staging (Tumour size/Origin)	18F-DCFBC	Confirmed PCa with high risk, before RP	mp-MRI/ histopathology	Sensitivity 39%, Specificity 89%; PPV 73%, NPV 58%	Sensitivity 17%, Specificity 96%; PPV 81%, NPV 53%
Rhee et al., 2016	20	PS	Primary staging (Tumour size/ Origin)	68Ga PSMA-11 PET/CT	Suspected Pca, before RP	mp-MRI/ histopathology	Sensitivity 44%, Specificity 94%; PPV 81%, NPV 76%	Sensitivity 49%, Specificity 95%; PPV 85%, NPV 78%
W. P. Fendler et al., 2016	21	PS	Primary staging (Tumour size/ Origin)	68Ga PSMA-11 PET/CT	Confirmed PCa with high risk, before RP	Histopathology	n.a.	Sensitivity 67%, Specificity 92%; PPV 97%, NPV 42%
Sahlmann et al., 2016	35	RS	Primary & Secondary staging (lymph node staging)	68Ga PSMA-11 PET/CT	Confirmed Pca, high risk; for staging and BCR	CT and histopathology	n.a.	Sensitivity 94%, Specificity 99%; PPV 89%, NPV 99.5%
Sterzing et al., 2016	57	RS	Primary & Secondary staging	68Ga PSMA-11 PET/CT	Confirmed Pca, high risk; for staging and BCR	Conv.l Imaging (MRI, CT, bone scan)	CT: In 21.1 % patients at least 1 lesion detected	85 lesions detected in 34 patients
Matthias Eiber et al., 2016	53	RS	Primary staging (Tumour size/ Origin)	68Ga PSMA-11 PET/MRI	Confirmed Pca, intermediate and high risk	PET & MRI only	Sensitivity 43%, Specificity 98%	Sensitivity 76%, Specificity 97%
Maurer et al., 2015	130	RS	Primary staging (lymph node involv.)	68Ga PSMA-11 PET/CT & PET/MRI	Confirmed Pca, high risk, before RP + LND	CT/MRI and histopathology	Sensitivity 44%, Specificity 85%, PPV 58%, NPV 77%	Sensitivity 66%, Specificity 99%, PPV 96%, NPV 86%
Herlemann et al., 2016	34	PS	Primary & Secondary staging	68Ga PSMA-11 PET/CT	Confirmed PCa with high risk, before RP + LND	CT and histopathology	Sensitivity 65%, Specificity 76%,	Sensitivity 84%, Specificity 84%, PPV 82%, NPV 84%

			(lymph node staging)				PPV 75%, NPV 67%	
van Leeuwen et al., 2016	30	PS	Primary staging (lymph node involv.)	68Ga PSMA-11 PET/CT	Confirmed Pca, intermediate and high risk, before RP	Histopathology	n.a.	Sensitivity 64%, Specificity 95%, PPV 88%, NPV 82%
Steven P Rowe et al., 2016	17	PS	Primary staging (metastases)	18F-DCFBC PET/CT	Confirmed PCa, intermediate and high risk	CT and bone scan	73%	83%
Levent Kabasakal et al., 2015	28	RS	Primary & Secondary staging (metastases)	68Ga PSMA-11 PET/CT	Confirmed PCa, intermediate and high risk	Bone scan, CT, MRI	n.a.	primary tumour 77%; lymph nodes 36%, Bone lesions 25% (per patient)
Pyka et al., 2016	126	RS	Primary & Secondary staging (metastases)	68Ga PSMA-11 PET/CT	Confirmed PCa, high risk	Bone scan	Sensitivity 87%, Specificity 61%	Sensitivity 99%, Specificity 88%
A. Afshar-Oromieh et al., 2015	319	RS	Mainly Secondary staging, but also primary staging (27)	68Ga PSMA-11 PET/CT	Mixed: 292 with BCR, 27 primary staging	n.a.	n.a.	Sensitivity 76.6%, Specificity 100%, PPV 100%, NPV 91.4% (all lesion based)
Van Leeuwen et al., 2016	70	PS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	Confirmed PCa, BCR after RP; scheduled RT	CT	n.a.	positive lesions in 54% of patients
Verburg et al., 2016	155	RS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	n.a.	CT	n.a.	68Ga PSMA positive in 44 % (PSA level ≤1 ng/ml), 79 % (PSA 1-2 ng/ml), 89 % (PSA ≥2 ng/ml)
Eiber et al., 2015	248	RS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	BCR after RP	CT	n.a.	PSA 0.2 - 0.5 ng/mL (57.9%), PSA 0.5 - 1 ng/mL (72.7%), PSA 1 -2 ng/mL (93%) and PSA ≥ 2 ng/mL (96.8%)
Ceci et al., 2015	70	RS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	BCR after definitive primary treatment	MR/CT and partially histopathology, 18F-choline	n.a.	74.4% positive findings with low PSA value
Morigi et al., 2015	38	PS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	Disease progression before salvage LND	18F-fluoromethylcholine PET/CT; diagnostic CT; histopathology	n.a.	54% positive with 68Ga PSMA; 68% with 18F-fluoromethylcholine and 68Ga-PSMA; 4% with 18F-fluoromethylcholine alone
Ali Afshar-Oromieh et al., 2014	37	RS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	Confirmed PCa, progressive disease; prior treatment (RP, RT)	18F-fluoromethylcholine PET/CT.	n.a.	SUVmax higher in 79.1 % of lesions, Tumour to background ratio higher in 94.9 % of lesions (compare to 18F choline)
David Pfister et al., 2016	28	RS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	Disease progression before salvage LND	18FEC PET/CT	Sensitivity 71.2%, Specificity 86.9%; PPV 67.3%, NPV 88.8%	Sensitivity 86.9%, Specificity 93.1%; PPV 75.7%, NPV 96.6%
Dietlein et al., 2015	14	RS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	BCR after primary treatment	18F-DCFPyL PET/CT	mean SUVmax = 14.5 (PSMA-positive lesions) - 18F	mean SUVmax = 12.2 (PSMA-positive lesions) - 68Ga
Sachpekidis et al., 2016	31	RS	Secondary staging (BCR)	68Ga PSMA-11 PET/CT	BCR after primary treatment	dynamic PET	SUVaverage = 12.6 SUVmax = 20.2	SUVaverage = 16.3 SUVmax = 23.5 Overall detection rate 71%
Zang et al., 2017	40	PS	Primary & Secondary staging	68Ga PSMA-11 PET/CT	Consecutive patients; staging and risk stratification Pca and mCRPC	MRI, bone scan	n.a.	Sensitivity 97.3%, Specificity 100%, Accuracy 97.5%,
RS, Retrospective study design; PS, Prospective study design; SUV, Standard Uptake Value; SUVmax, maximum standard uptake value; PCa, Prostate carcinoma; PET, Positron Emission Tomography; BCR, Biochemical Recurrence; MRI, Magnetic Resonance Imaging; mp-MRI, multiparametric Magnet Resonance Imaging; CT, Computer Tomography								

Table 17: Study overview for PSMA ligands being used in imaging studies of prostate cancer in primary and secondary staging. Data includes PET/CT results and those from the comparisons modality

A study group from the Ludwig Maximilian University in Munich investigated the ^{68}Ga- PSMA-11 accuracy in localising primary tumour lesions in patients with proven histopathological PCa. The results showed a significant higher SUV_{max} in histopathological affirmative than in negative regions, a high accuracy (72%), sensitivity (67%) and specificity (92%). Furthermore, PET/CT correctly detected invasion of seminal vesicles (86% accuracy) and tumour spread through the capsule (71% accuracy) (Fendler, Schmidt, et al., 2016). The same research group also evaluated the accuracy of ^{68}Ga-PMSA-11 PET/CT for nodal staging before lymph node dissection (LND) in PCa patients. The results showed a higher accuracy of ^{68}Ga PSMA -11 PET/CT for primary LND (88% vs 75%) and secondary LND (77% vs 65%) detection compared to conventional imaging with CT. A possible explanation: around 40% of lymph nodes metastases were smaller than 5mm and thus undetectable by size criteria in conventional CT (Herlemann et al., 2016). Other studies confirmed the high accuracy in lymph node staging (see Table 17) (Maurer et al., 2015; van Leeuwen et al., 2016). However, it should also be mentioned that PSMA-PET missed tumour-positive lymph nodes in PSMA negative primary tumours and cases of micro metastases (Maurer, Eiber, Schwaiger, & Gschwend, 2016).

PSMA PET Imaging is also more accurate in the detection of bone and visceral metastases compared to conventional imaging such as CT or bone scan (Chakraborty, Kumar, Tripathi, Das, & Bal, 2015; Levent Kabasakal et al., 2015; Pyka et al., 2016; Steven P Rowe et al., 2016). The reason: ^{99m}Tc-MDP has a low specificity and the uptake in many benign bone lesions could lead to false-positive results. Additional imaging with CT or MRI is very often requested. In a retrospective comparison between PSMA PET/CT and bone scan in 126 patients, PSMA PET/CT showed a higher sensitivity (98.7%- 100%) and specificity (88.2%-100%) compared to bone scan (sensitivity: 86.7-89.3%; specificity: 60.6%-96.1%) (Pyka et al., 2016).

2.3.1.3.4.2 PSMA PET in Biochemical Recurrence

Biochemical recurrence (BCR) is quite frequent in patients with prostate cancer following radical prostatectomy and occurs in approximately 35% of patients within a ten year period (Han, Partin, Pound, Epstein, & Walsh, 2001; Ward, Blute, Slezak, Bergstralh, & Zincke, 2003). Other studies suggest an even higher number of biochemical recurrence with 26-68% of patients within five to six years after treatment (Bolla et al., 2012; Stephenson et al., 2007; Wiegel et al., 2014)

Salvage radiotherapy is known to be most effective in patients with PSA values > 0.2ng/ml and < 0.5ng/ml and should therefore be started as early as possible (Briganti et al., 2012; D Pfister et al., 2014; Taguchi et al., 2016). Especially in patients with low PSA values, a differentiation between localised disease and metastatic spread is essential for further therapeutically strategies. For this reason it is very important to have an accurate marker that helps to identify candidates for early salvage therapy before the clinical progression begins (Cookson et al., 2007).

The 2016 EAU–ESTRO–SIOG Guidelines on Prostate Cancer recommend a bone scan, abdominal CT, mpMRI, or choline PET/CT for patients suspicions for biochemical recurrence (Cornford et al., 2016). Unfortunately the probability of a positive bone scan is <5% if the PSA level is < 7ng/ml, thus bone scan and abdominal-pelvic CT are recommended to be used in patients with BCR after RP and a high baseline PSA > 10ng/ml, high PSA kinetics (PSA DT < 6mo) or in patients with symptoms of bone disease (Beresford et al., 2010). Also, CT may have a significant disadvantage in the detection of small-sized metastasis, as it was proven to miss almost 2/3 of nodal size metastases since they fall below the detectable size criteria (F. L. Giesel, Fiedler, Stefanova, Sterzing, & Rius, 2015)

Recently, several studies have been published investigating the clinical relevance of PSMA PET/CT and PET/MRI in patients with biochemical recurrence (see Table 17). Afshar-Oromieh, Avtzi et al. (2015), members from a research group at the University Hospital in Heidelberg, retrospectively analysed results from 319 patients, of whom 292 patients showed progression after local therapy. The lesion based sensitivity was 76.6%, specificity 100%, PPV 91.4% and an NPV of 100%. On a patient based breakdown the detection rate increase to 88.1%, independent from the PSA value. However, it became apparent that the detection rate increased with rising PSA levels, showing the lowest rate (50%) between 0.2 – 0.5ng/ml and the highest (86%) in PSA levels > 2 ng/ml (Afshar-Oromieh, Avtzi, et al., 2015). These detections rates have also been confirmed in two additional retrospective studies by Eiber et al. (2015) and Verburg et al. (2016).

Van Leeuwen et al. (2016) published results from a prospective study with 70 patients, which had a prostatectomy but a BCR and where therefore planned to receive salvage radiotherapy. The study population had a median PSA of 0.2 ng/ml and were inconspicuous in conventional imaging. After the ^{68}Ga-PSMA-11 PET/CT scan 38 patients (54%) had a pathological uptake of the tracer, with 24 patients (34%) having verified positive lesions. This high detection rate in patients with low PSA levels (0.2– 0.29 ng/mL) is especially beneficial as this patient- group benefits the most from early salvage treatment (Cornford et al., 2016). Consequently a significant change in patient management in 35% of patients due to the results of the ^{68}Ga-PSMA PET/CT (Van Leeuwen et al., 2016). Another prospective study compared the detection rate of ^{18}F-fluoromethylcholine and ^{68}Ga-PSMA-11 in thirty-eight (83) PC patients with a rising PSA level after radical prostatectomy, radiotherapy (external beam or other), or both (Morigi et al., 2015). The results indicate a rising detection rate with rising PSA levels as suggested by other studies (Afshar-Oromieh, Avtzi, et al., 2015; Eiber et al., 2015; Morigi et al., 2015), but also a significant higher detection rate for ^{68}Ga-PSMA-11 compared to ^{18}F- fluoromethylcholine (Morigi et al., 2015). The habit between detection rate and PSA levels was also established with other tracers such as ^{11}C-Acetate PET/CT: In a retrospective study with 721 men with histologically proven PCa and PSA biochemical recurrence the detection rate in patients with PSA levels <1 ng/ml was 74%, and the optimal PSA cut-off was 1.09 ng/ml (Almeida et al., 2017). The dependency of the PSA value was in accordance with other studies (27-74%) using ^{18}F-fluorocholine (Graute et al., 2012; Kwee, Coel, & Lim, 2012; Morigi et al., 2015; Tilki et al., 2013; Vees et al., 2007) and ^{11}C- choline PET/CT (Krause et al., 2008; Mitchell et al., 2013).

2.3.1.3.4.2.1 68Ga PSMA versus choline PET/CT

In a direct comparison between ^{68}Ga-PSMA PET/CT and choline PET/CT, the Gallium-PSMA tracer is way ahead in staging of recurrent disease in patients with PCa (Table 17). This is true for accuracy and tumour to background ratios on a patient and lesion based analyses (Afshar-Oromieh, Avtzi, et al., 2015; Bluemel et al., 2016; Giesel et al., 2016; Morigi et al., 2015; David Pfister et al., 2016). In a study by Morigi et al. (2015) 38 patients with BCR suspicious findings were detected in 26 patients (68%) using ^{68}Ga-PSMA PET/CT and ^{18}F- Fluorethylcholine. Of these 26 positive scans, 14 (54%) were positive with ^{68}Ga-PSMA alone and 11 (42%) with both ^{18}F-fluoromethylcholine and ^{68}Ga-PSMA. Only one (4%) scan was positive using ^{18}F fluoromethyl- choline alone (Morigi et al., 2015). Bluemel et al. (2016) showed that ^{68}Ga- PSMA I&T identified lesions in 43.8% of the choline-negative patients and improved the overall recurrence detection rate from 74.4% to 86.6%.

2.3.1.3.4.3 PSMA PET/CT Impact on Patient Management

An early detection of lesions at low PSA values (< 1.0 ng/ml) is of particular clinical interest, as salvage radiotherapy, especially for cancers with aggressive features, is most effective at this stage (D'Amico,

Chen, Roehl, & Catalona, 2005; Fossati et al., 2016; Karlin et al., 2013; Pfister et al., 2014; Valicenti et al., 2013). Findings suggest that patients with salvage therapies and a PSA level smaller 2.0ng/ml have a significantly improved disease-free survival (Briganti et al., 2014; Stephenson et al., 2004)

Currently there is excellent scientific evidence that ^{68}Ga-PSMA PET/CT has a clinical impact, but unfortunately, the proof in prospective randomised clinical studies is limited. Two retrospective studies demonstrated a change in management after ^{68}Ga PSMA PET/CT in patients with biochemically recurrent prostate cancer in 50.8% and 29% of patients (Sterzing et al., 2016; Van Leeuwen et al., 2016). In the first study, the PMSA scan changed the management of 29 patients (50.8%), compared to the initial plan based upon conventional staging. In 89.6% (26 patients) the radiation dose and field was adjusted, and four patients (10.4%) moved from radiotherapy to systemic therapy (Sterzing et al., 2016). The second study demonstrated a significant management change in 20 patients (28.9%), which were also directly attributed to the 68Ga-PSMA findings (Van Leeuwen et al., 2016). In a further study, examining a sequential imaging approach with 18F-choline (initial imaging approach) and ^{68}Ga-PSMA-PET/CT (secondary approach, if 18F-choline PET/CT was negative), 14 (43.8%) additional lesions have been detected in patients with a previously negative 18F-choline scan. These results are highly likely to impact patient management, but have not been further investigated (Bluemel et al., 2016). But other retrospective (Albisinni et al., 2017; Eiber et al., 2015; Giesel et al., 2015) and some prospective studies (Roach et al., 2018) have looked into the influence of Ga-PSMA PET/CT on the clinical management and have a very positive view.

2.3.1.3.4.4 The conclusion of PSMA imaging

PSMA- based imaging has the potential to influence the future management of patients with prostate cancer, whether for primary staging or staging recurrent disease. Currently, there are some limitations in the use of PSMA- based tracers, especially about regulatory approval (Maurer et al., 2016). Several clinical trials still evaluate PSMA imaging in patients with the prostatic disease, no agent has reached phase III stage so far (clinicaltrials.gov). Because of national regulations, some countries in Europe, South American and Asia are also allowed to use these novel tracers other than clinical trials and expand knowledge on efficacy and safe usage. However a widespread of this new imaging technique may not be observed shortly, seeing obstacles with regulatory approval, reimbursement and the limiting number of prospective trials (Maurer et al., 2016).

2.3.1.3.5 Theranostics Approach with PSMA

The therapeutic management of prostate cancer has become extremely complex, depending on the patient's characteristics, actual TNM staging level and available treatment options. Current treatment ranges from active surveillance and watchful waiting for men patients with very low-risk PCa, prostatectomy for localised PCa and more radical therapies for intermediate to high-risk PCa patients (Mottet et al., 2016).

Improvements in radical prostatectomy and radiation therapy have led to decreasing morbidity and improved outcome in localised PCa (Metcalfe, Smaldone, Lin, Aparicio, & Chapin, 2017), but the overall survival and cancer-specific survival with metastatic PCa has not significantly changed in the past 20 years (Mohler, 2014). Especially patients with metastatic castration-resistant prostate cancer (mCRPC) represent a significant clinical hurdle with poor prognosis and a predicted survival rate of less than two years (Frieling, Basanta, & Lynch, 2015; Huang, Chau, & Figg, 2012). Salvage Radiotherapy (SRT) is usually introduced in patients with BCR after RP and can cure patients with an increasing PSA after RP (Cornford et al., 2016). Androgen deprivation therapy (ADT) with or without chemotherapy is added to SRT and

has shown to increase the PFS after five years in retrospective series (Goenka et al., 2012) and in high-risk tumours (Soto, Passarelli, Daignault, & Sandler, 2012).

For mCRPC, the first line therapy is the use of life-prolonging agents such as docetaxel and cabazitaxel or using the immunotherapeutic pathway with sipuleucel-T or newer antihormonal drugs such as abiraterone and enzalutamide (Cornford et al., 2016). The EAU-ESTRO-SIOG Guidelines also recommend treating painful metastases early on with external beam therapy, RT, radionuclides (SM-153 EDTMP, Strontium, Alpharadin, Lu-177 labelled bisphosphonates), and adequate use of analgesics (Cornford et al., 2016). Radium-223 is a bone-seeking radiopharmaceutical based on the alpha- (α-) particle emitter Radium-223 dichloride and can relief pain, but also showed a significant increase in survival in a phase-III study (Parker et al., 2013).

Current chemotherapeutical drugs such as Abiraterone and Enzalutamide, which provide an average survival benefit of 3.9 and 4.9 months, tend to prolong overall survival (Morris et al., 2015; Ramadan, Kabbara, & Al Bassiouni Al Masri, 2015), ^{223} Radium chloride increases average survival by 3.6 months in patients with skeletal metastases (Parker et al., 2013) and immunotherapy with Sipuleucel-T also adds a few months but shows some immunological side effects (Kantoff et al., 2010). The real challenge for clinicians is to determine the optimum treatment pathway by combining different strategies (Asselah & Sperlich, 2013).

Another option for patients with mCRPC has emerged with the alternative to label the PSMA ligand with Lutetium- 177 or Yttrium- 90. The first PSMA ligand used in humans for mCRPC treatment was a small molecule inhibitor of PSMA (MIP-1095) labelled with Iodine -131. A second generation inhibitor was J591, which has been labelled with ^{90}Yr and ^{177}Lu and tested in several preclinical trials focusing on toxicity and dosimetry. In a trial with ^{90}Yr- J591 the patients (2) experienced thrombocytopenia in the highest dose of 20mCi/m², but also an 85% and 70% decline in PSA and objective, measurable disease response (Milowsky et al., 2004). Using the radionuclide Lutetium-177 allowed a much higher maximum tolerated dose (MTD) of 70mCi/m² compared to Yttrium-90, and even multi-dose with 30mCI/m² are well tolerated (Bander et al., 2005).

Actually, Lutetium seems to be better suited for this Theranostic approach because of its preferred physical properties: (1) The longer half-life allows the delivery of high activity to the tumour cell, (2) the shorter ß -range (< 2mm) fits best for small tumours and protects healthy tissue around and (3) allows a higher proportion of its energy to a tumour/metastases (O'Donoghue, Bardies, & Wheldon, 1995). Indeed the most significant advantage for Lutetium is the dual usage for imaging and therapeutically use, and the lower share of gamma radiation, which reduces the mandatory hospital stay.

2.3.1.3.5.1 Regulatory Requirements

To date, no PSMA ligand has received an official market authorisation for therapeutically use from any regulatory agency worldwide. Several clinical trials currently test the radioligand, some centres administered the ligands outside of clinical trials based on current legal exceptions. For example in Germany, the Medicinal Products Act (Arzneimittelgesetz- AMG) explicitly deals with RPs and prohibits the placement of RPs on the market unless the authorisation has been given by ordinance. There are some exemptions, which are very strict, but allow the in-house production of some RPs under strict rules and guidance (AMRadV; §13 (2) AMG; §§ 7 and 8 ApBetrO).

For the application of an RP in an investigational trial, the rules in Germany are in line with the Directive 2001/20/EC by the European Union and require a manufacturing license according to Good manufacturing practice (GMP), approval by the local ethics committee, the BfArM and the Federal Office

for Radiation Protection). Thus studies being currently performed are very restrictive and focusing on a very narrow patient population. For example, several characteristics need to be fulfilled when the patient applies via an individual treatment attempt ("Heilversuch"- GER). Histologically proven adenocarcinoma of the prostate, already treated with hormone deprivation therapy, asymptomatic or mildly symptomatic progression course; unsuitable for taxane-based chemotherapy (age, not tolerated because of comorbidity et cetera) and/or alpharadin therapy, tumour progression and current treatment options are exploited (§ 41 AMG).

From a medical point of view, the radioligand therapy can be successful, if there is adequate binding of the PSMA- ligand to the tumour cells and its metastases. Currently, ^{177}Lu- PSMA therapy is mainly offered to patients with advanced mCRPC and verifiable progressions such as a PSA level rise or tumour expansion based on a radiology scan. The therapy is contraindicated in patients with high renal insufficiency, bone marrow depression, and haematological changes. Treatment schedules are ordinarily 4-6 cycles at intervals of 6-8 weeks with average 5– 7 Giga Becquerel (GBq) dose per cycle (Heck et al., 2017). The number of cycles depends on the tumour burden, tolerance, and therapy response.

2.3.1.3.5.2 Dosimetry

Patient-specific dosimetry does not only improve the efficacy of the therapy, but also the safety in already profoundly ill persons. The goal is to deliver the highest possible tumour dose and spare normal organs (such as the kidneys). This individual dosimetry can be very challenging since there is considerable tumour and organ uptake variability in individuals and an in-depth knowledge on biodistribution and biokinetics is necessary (Thierens, Monsieurs, & Bacher, 2005).

The pre-therapy biodistribution tests, the dosimetry study and overall therapy cycles became simpler when the ß- and γ emitting radionuclide Lutetium-177 had been used. Furthermore, the linear quadratic model, made it easier to assess dose rates and organ-dose delivery, as well as the repair potential (Erbas & Tuncel, 2016). A comparison between different models (MIRDOSE3, MIRD Pamphlet 19 and BED) showed that the effective biologic dose (BED) model was the most accurate reliable predictor of renal toxicity, being based on the linear quadratic model (Barone et al., 2005). At the Ludwig-Maximilian University Munich the dosimetry is based on quantitative SPECT images and a quantitative 3D SPECT OSEM reconstruction. The data from the images is used to calculate the absorbed dose for various organs using a combination of linear approximation, exponential fit, and target-specific S-values, according to MIRD (Delker et al., 2016). This quantitative SPECT dosimetry calculation enables a reduction of 20 to 30% of radiation to the salivary gland compared to planar scintigraphy; and approximately a six to twelve-fold higher radiation to a tumour than to critical organs (Delker et al., 2016; L. Kabasakal et al., 2015; Kratochwil, Giesel, et al., 2016a).

The kidneys are the main dose-limiting organ because of the effective glomerular filtration, tubular reabsorption by the proximal tubules, and interstitial retention of the tracers (Erbas & Tuncel, 2016). The recommended dose limit should not exceed 27 Gy (Kwekkeboom et al., 2005), a valued which derives from conventionally fractionated external beam therapy and was associated with a 5% probability of developing severe late kidney damage within five years (Cassady, 1995). Current studies show that with exact dosimetry tests the dose to the kidney is well below the 23Gy dose limit and that the parotid gland receives higher doses than the kidney (Baum, Kulkarni, et al., 2016; Delker et al., 2016).

2.3.1.3.5.3 Side Effects

The side effects of PRRT with PSMA are generally low (see Table 18). Some grade 3 and 4 toxicities (mainly haemoglobin toxicities) have been mentioned, but are mostly limited to individual cases. A third (30%) of all patients reported xerostomia, 25% felt fatigue and 10% reported nausea up to 48 hours after injections (Emmett et al., 2017). Whereas a dry mouth is mostly reversible using the beta-emitting radionuclide Lutetium-177, it seems to be persistent with Actinium-225 (Ahmadzadehfar, Eppard, Kurpig, et al., 2016; Fendler, Reinhardt, et al., 2016; Heck et al., 2016; Kratochwil, Bruchertseifer, et al., 2016; Rahbar et al., 2017).

Due to the currently mainly retrospective study designs, the side effects can hardly be assigned to effects caused by the therapy and those due to the progression of the disease. Especially haematological toxicity may predominantly occur because of advanced skeletal metastases and borderline marrow function, rather than radiation effect on the bone marrow (Emmett et al., 2017). To date, the most significant retrospective study was initiated in multiple centres in Germany and analysed the data from 145 patients. Overall the toxicity profile was favourable, with some of the reported adverse events may also be connected to prior therapies and/or advanced disease (Rahbar et al., 2017).

> *"In the current study grade, 3-4 hematologic adverse events occurred in 12% of the patients: thrombocytopenia and anaemia occurred in 4% and 10%, respectively. The reported rate of adverse events is slightly lower or comparable to the rate in other mCRPC cohorts. Patients undergoing placebo or ^{223}Ra within the ALSYMPCA trial (Parker et al., 2013) demonstrated grade ≥3 anaemia in 13 to 14% and grade ≥3 thrombocytopenia in 3% to 7%. The present study shows significantly lower haematotoxicity when compared to results of second-line chemotherapy or radiolabelled antibody therapy: The TROPIC study (De Bono et al., 2010) revealed a grade ≥ three leukopenia in 68% of patients receiving cabazitaxel and in 42% of patients receiving mitoxantrone vs 3% in our study. Application of ^{177}Lu labelled J591 monoclonal antibody was associated with grade 4 thrombocytopenia in 47% of patients (Tagawa et al., 2013). In the present study, only 4% of the patients experienced a grade ≥ three thrombocytopenia."* (Rahbar et al., 2017)

			Adverse Events	
Author	**Ligand**	**Number of Patients**	**Grade 3**	**Grade 4**
Ahmadzadehfar et al., 2015	177Lu-DKFZ-617 PSMA	10	10% Haematotoxicity	
Ahmadzadehfar, Eppard, Kürpig, et al., 2016	177Lu-DKFZ-617 PSMA	24	8% Anaemia	-
Kambiz Rahbar et al., 2016	177Lu-DKFZ-617 PSMA	74	1.4% haemoglobin 1.4% platelets	-
C. Kratochwil, Giesel, et al., 2016a	177Lu-DKFZ-617 PSMA	30	3.3% Anaemia 3.3% Thrombocytopenia	-
Ferdinandus et al., 2016	177Lu-DKFZ-617 PSMA	40	Toxicity data published in (Kambiz Rahbar et al., 2016)	
W.P. Fendler et al., 2016	177Lu-DKFZ-617 PSMA	15	7% Leukocytes 7% Nausea	-
K. Rahbar et al., 2017	177Lu-DKFZ-PSMA-617	145/121 (Toxicity) 99 (BCR)	3% Leukopenia (n=121) 10% Anaemia (n=145) 4% Thrombocytopenia (n=121) 1% Biliary obstruction (n=145) 1% Fatigue (n=145) 2% Lung embolism (n=145) 1% Stroke (n=145) 2% Bone fracture (n=145)	
Yadav et al., 2016	177Lu-DKFZ-PSMA-617	31	3.2% haemoglobin toxicities	-
M. Weineisen et al., 2015	177Lu- PSMA I&T	2	-	-
Richard P Baum et al., 2016	177Lu-PSMA I&T	56	-	-
Matthias M. Heck et al., 2016	177Lu-PSMA I&T	19	-	-
Tagawa et al., 2013	177Lu-J591	47	10.6% Haemoglobin 46.8% Leukocytes 36.2% Neutrophils 2.1% Febrile neutropenia 21.3% Thrombocytopenia	46.8% Thrombocytopenia 25.5% Febrile neutropenia 8.5% Leukocytes

C. Kratochwil, Bruchertseifer, et al., 2016	225Ac-PSMA-617	2	50% Xerostomia	-

Table 18 Overview of Grade 3 and Grade 4 adverse events after several cycles of ^{177}Lu- PSMA PRRT

2.3.1.3.5.4 Response and Efficacy

Up to date, few randomised controlled trial investigated the efficacy of ^{177}Lu-PSMA in patients with mCRPC in a controlled manner. Recently, a single arm, single centre Phase II study investigated the response and efficacy in men with mCRPC with progressive disease and after standard treatment regime with chemotherapy. Their results indicate a high response rate in this population, with 17 patients (57%) experiencing a PSA decline of 50% or more, an objective response in nodal or visceral disease in 14 (82%) of 17 patients and 11 patients (37%) experienced a ten point or more improvement in global health score by the second cycle of treatment. (Hofman et al., 2018).

The bulk of knowledge, however, relies on retrospective studies, mostly single- arm with a high variance in the treatment regime (dose and number of cycles). Nevertheless, these studies showed a clear benefit for most patients, who have already completed every treatment option available and are running out of alternatives. In these studies, around 30-100% of patients experienced a more than 50% reduction in serum PSA, and > 58% of patients experienced any PSA decline (see Table 19). Compared to currently available chemotherapy agents (Mitoxantrone and Cabazitaxel) the change in PSA (>50%) is similar to the therapy with Lutetium-177 PSMA (Mitoxantrone: 17.8%; Cabazitaxel: 39.2%), but having a significantly lower rate of adverse events (Rahbar et al., 2017).

Germany is taking the lead in the research and clinical testing with radiolabelled therapeutic agents, mainly because of favourable regulations and intense university research. In 2014 Zechmann et al., from the research group of Haberkorn from the University Hospital of Heidelberg, reported about their experience with one cycle (dose 4.8 GBq) of ^{131}I-MIP-1095 in 28 mCRPC patients. 61% of patients showed a decrease of PSA serum level of >50% and 85% reported a reduction in pain, but also an intense accumulation in the salivary and parotid glands with some adverse events (Zechmann et al., 2014).

Soon after the research group from the University Hospital of Bonn published first results of the novel agent ^{177}Lu-DKFZ-617 PSMA in ten hormone- and/or chemo-refractory patients with distant metastases (seven patients with serious metastatic disease in bone and lymph nodes) and progressive disease. A mean dose of 5.6 GBq was administrated and eight weeks after the therapy 50% of patients had a PSA decline >50% and three had progressive disease (Ahmadzadehfar et al., 2015). In a follow-up study, 30 patients with mCRPC resistant to or with contraindications to other conventional therapies received up to three cycles repeated every second month. The initial dose was 3.7 – 4.0 GBq but was increased to 6GBq after the first ligand-specific dosimetry data was available. 21 patients (70%) showed any PSA response and 13 (43.3%) a decrease >50%. After three cycles, 8 of 11 patients had an ongoing PSA response of >50% for over 24 weeks, which was also verified via radiologic imaging (Kratochwil, Giesel, et al., 2016a).

The research group at the Ludwig Maximilian University in Munich investigated 15 patients with mCRPC, who received two cycles of 3.7 GBq (n = 5) or 6.0 GBq (n =10) ^{177}Lu-PSMA-617 at an eight to ten weeks' interval. Their primary endpoint was radiological response rate based on RECIST (PR 27%; SD 40%; PD 33%), and secondary endpoints were PSA change (80% any PSA decline; 60% PSA decline >50%), quality of life (improvement in 60%) and pain- relief (70% significant improvement) (Fendler, Reinhardt, et al., 2016).

Results from a second generation Lutetium analogue (^{177}Lu- PSMA I&T), with higher affinity to PSMA and better internalisation into the cells, showed high absorbed tumour doses and a PSA decrease in 80.4% of patients. These 56 patients with progressive mCRPC (median Gleason score 8) had a rising PSA level and received several cycles of ^{177}Lu-PSMA (1 cycle for 16 patients, 2 cycles for 15 patients, 3 cycles

for 17 patients, 4 cycles for 6 patients, and 5 cycles for 2 patients) with a dose/ cycle of 5.76GBq. Remarkable also in this study that 45% of patients already had systemic chemotherapy (Docetaxel), bone metastases were present in 77%, liver metastases in 9% and lung metastases in 13% of patients. This study suggested a possible survival benefit with a survival rate after 28 months of 78.6%, median progression-free survival of 13.7 months and median overall survival was not reached. Imaging results from 15 patients minimum after six months showed partial remission in 20%, stable disease in 52% and progressive disease in 28% of patients (Baum, Kulkarni, et al., 2016).

In the currently most significant retrospective multicentre study worldwide, 12 centres in Germany analysed results from 145 patients (median age 73 years, range: 43-88) with mCRPC treated with 248 cycles of 177Lu-PSMA-617 between February 2014 and end of July 2015. The patients had an advanced mCRPC stage with 87% having bone -, 77% lymph node- and 36% either liver-, lung- or other metastases. All patients had previous androgen deprivation therapy, 64% received Abiraterone, 54% chemotherapy and some Enzalutamide (52%), ^{223}Ra (17%) and EBRT to bone (35%).

Results from 99 patients with PSA levels over the whole treatment cycle were available: After the first cycle 40% of patients showed a PSA decline > 50%; after the second therapy cycle 57% had PSA decline > 50%; after the third (65%) and the fourth (100%) of patients had a PSA decline > 50%. Visceral metastases and alkaline phosphatase ≥ 220 U/L hurt biochemical response, whereas more therapy cycles had a positive effect on the biochemical response (Rahbar et al., 2017).

In general therapy with 177-Lu PSMA seems to be promising, but the different retrospective results and treatment regimens need to be verified with prospective trials in future. In Germany, the treatment with Lutetium PSMA expanded rapidly but is still categorised as a treatment attempt (“Heilversuch”) with the palliative purpose to treat patients with mCRPC.

Author	Ligand	Number of Patients	Median Serum PSA level (ng/ml)	PSA decline	PSA decline >50%	Response CT (RECIST)	Response PSMA PET[a]/ PSA rise[b]	Symptomatic Response	PFS	OS
Ahmadzadehfar et al., 2015	177Lu-DKFZ-617 PSMA	10	298.5	70%	50%		PD 30%[b]	-	-	-
Ahmadzadehfar, Eppard, Kürpig, et al., 2016	177Lu-DKFZ-617 PSMA	24	522	79.1%	41.6%	PR 40% SD 55% PD 5%	PR 80% SD 0% PD 20%	-	-	-
Kambiz Rahbar et al., 2016	177Lu-DKFZ-617 PSMA	74	342	64%	31%	-	PD 23%[b]	-	-	-
C. Kratochwil, Giesel, et al., 2016a	177Lu-DKFZ-617 PSMA	30	n.a.	70%	43.3%	-	PD 27%[b]	-		-
Ferdinandus et al., 2016	177Lu-DKFZ-617 PSMA	40	325.5	67.5%	32.5%	-	PD 32.5%[b]	-		-
Fendler et al., 2016	177Lu-DKFZ-617 PSMA	15	388	80%	60%	PR 27% SD 40% PD 33%	-	Pain: CR 20%; PR 27%; PD 20% QoL: 53% improvement; 20% a 30% Improvement		-
Rahbar et al., 2017	177Lu-DKFZ-PSMA-617	145/121 (Toxicity) 99 (BCR)	214	60%	45%	CR 2%[1] PR 45%[1] SD 28%[1] PD 25%[1]	-	-		-
Yadav et al., 2016	177Lu-DKFZ-PSMA-617	31	275 (mean)	Pre- and post 275/141 (mean)		-	CR 6.4% PR 9.6% SD 3.2% PD 0%	CR 6.4%[2] PR 64.5%[2] SD 9.6%[2] PD 19.3%[2]	12 mo	16 mo
Weineisen et al., 2015	177Lu- PSMA I&T	2	47.2		100% (1 patient)	-	PR 50%	symptomatic pain relief	-	-
Baum et al., 2016	177Lu-PSMA I&T	56	43.2	58.3%	58.9%	PR 20% SD 52% PD 28%	PR 56% SD 8% PD 36%	33% PR	13.7 mo (median)	median not reached
Heck et al., 2016	177Lu-PSMA I&T	19	349	89.4%	26.3%	PR 11% SD 56%	CR 5% SD 63%	CR 14% PR 42%	175 days	-

						PD 33%	PD 32%		(median)	
Tagawa et al., 2013	177Lu-J591	47	74.4	59.6%	10.6%	PR 8.3%[3] SD 66%[3] PD 16.6%[3]	-	-	-	17.6 mo (median)
Kratochwil, Bruchertseifer, et al., 2016	225Ac-PSMA-617	2	>3000 & 294	100%	100%	-	CR 100%	-	-	-

[1] data from 47 patients; [2] Data based on PSA values; [3] Data from 12 patients
OS, Overall Survival; PFS, Progression Free Survival; mo, months;

Table 19 Currently published trials showing the efficacy of PSMA ligands in the treatment of patients with metastatic castration-resistant prostate carcinoma (mCRPC)

3 Current Challenges in the Radiopharmaceutical Industry – A Case Story of DOTATATE

Probably the best example of successful clinical implementation of a peptide-based radiopharmaceutical for diagnoses and therapy was in the field of neuroendocrine tumours.

The case started with the discovery of an extract from the rat´s hypothalamus in 1968, which stimulated or inhibited the release of pituitary growth hormone and was thus named growth hormone- inhibiting factor (GIF) (Krulich et al., 1968). In further research Roger C L Guillemin and colleagues isolated, sequenced and synthesised the 14- amino-acid peptide structure and confirmed the inhibiting properties in in-vivo and in-vitro experiments (Brazeau et al., 1973). This discovery led to the patent application (US 3904594 A) and was described as a "*novel peptide compositions having an inhibitory influence on the growth-promoting function of the pituitary gland in humans and animals. More particularly the present invention is directed to novel peptide compositions which influence the release of growth hormone by the pituitary gland*." (Guillemin et al., 1975). Roger Guillemin and Andrew Schally were honoured with the Nobel Prize in Medicine 1977 for their work with somatostatin and other hormones.

Early on it has already been suggested that this novel peptide could have pathological and potential therapeutic use. Based on the preliminary work of Rivier, Vale and Veber (Rivier, Brazeau, Vale, & Guillemin, 1975; Veber et al., 1979, 1981) the preclinical research group from Sandoz Ltd. developed a highly potent and active somatostatin analogue that would also be therapeutically effective. The compound was well tolerated in laboratory animals and in human and active by several routes of administration (Bauer et al., 1982). The substance was named Sandostatin LAR (octreotide acetate, EQ 0.05 mg base/ml injection, Sandoz AG) and was the first therapeutically somatostatin analogue granted marketing authorisation by the US Food and Drug Administration (FDA) in October 1988 and registered in Germany under the tradename Octreotide s.c.D in 1990. The authorisation granted the indications acromegaly, severe diarrhoea/flushing episodes associated with metastatic carcinoid tumours and profuse watery diarrhoea associated with VIP- secreting tumours (Novartis Pharmaceuticals Corporation, 2002).
Parallel to the therapeutic use of somatostatin, J.C. Reubi, a professor of pathology and cell biology at the University of Bern, researched with his team the affinity binding sites of the somatostatin complex (Reubi, Perrin, Rivier, & Vale, 1981). Their discovery of the over-expression of these somatostatin receptors on some tumour cell´s surface led to the development of the first diagnostic compound labelled with Iodine-125 (Krenning et al., 1989; Reubi, Häckl, & Lamberts, 1987), which was later replaced by the radionuclide Indium-111 and Technetium-99m. The preclinical research group from Sandoz Ag published first preclinical imaging studies with the ^{111}In-labelled SRIF analogue SDZ 215-811 in 1993 and showed a high affinity to somatostatin receptors (Bruns, Stolz, Albert, Marbach, & Pless, 1993). A final product (Indium-111 Pentetreotide kit, tradename: "Octreoscan") was submitted to the FDA in October 1992 by Mallinckrodt and was approved as a medicinal product to be used in the diagnosis of gastroenteropancreatic neuroendocrine (GEP) tumours and carcinoid tumours in February 1994. Octreoscan was developed by Mallinckrodt and Sandoz, with Sandoz providing the synthetic somatostatin analogue octreotide known as Pentetreotide (Sandostatin).

In connection with the successful development of Octreoscan, several other patents had been filled by Mallinckrodt Medical, Inc. including US 5,382,654 registered in February 1992 for a *"radiolabelled peptide compound, methods of preparing these compounds, pharmaceutical compositions comprising*

these compounds and use of these compounds in kits for therapeutic treatment of tumours and for diagnostic imaging of tumours" (Lyle, Rajagopalan, & Deutsch, 1995) and WO 1993004702 A1 a stabilizer for radiolabelled peptides and proteins (Deutsch, Goedemans, Maria De, Miller, & Brodack, 1993).

In the 1990s also the research of Gallium- 68 radiochemistry improved and led to the development of new chelate conjugates, suitable for PET imaging. PET is said to be a method with higher diagnostic yield, compared to SPECT, due to higher sensitivity, absolute quantification, shorter scanning time and a reduction in radiation absorbed dose by the patient (Rahmim & Zaidi, 2008). Also from a radiochemistry point of view, RPs labelled with Gallium-68 have some desirable features like the general availability, the inexpensiveness of the nuclide and the easy access via an in-house generator (Ambrosini et al., 2012).

In 1993, Mäcke et al. synthesised a new modification to octreotide designed to be linked to Gallium 67 and Gallium 68 and showed a high binding affinity and fast tumour localisation in rats. The trivalent metal radionuclides had to be conjugated to a suitable chelator to complex with Indium, Yttrium, Gallium, and Lutetium in order to get a stable radiolabelled somatostatin analogue. Two chelators have been widely used: DTPA (diethylenetriameinepentaacetic acid) and DOTA (1,4,7,10-tetraazacyclododecanetetraacetic acid), at which DOTA complexes have a higher thermodynamic and kinetic stability compared to DTPA complexes (Sosabowski & Mather, 2006). The DOTA complex is also tetra acid and thus has four sites for conjugation, which makes it the preferred application for peptide conjugation.

DOTATATE

DOTA – [Tyr3] octreotate also known as DOTATATE proved to be a diagnostically and therapeutically very useful compound (see Chapter 2.2.4 and 2.2.5) and is currently the clinically most widely used analogue for diagnosis and therapy in neuroendocrine tumours. The substance has been used without marketing authorisation for a long time (Leugs, 2013) and just recently granted official approval by the FDA and EMA as a diagnostic (^{68}Ga- DOTATATE) and therapeutic (^{177}Lu-DOTATATE) compound (European Medicines Agency, 2017c; U.S. Food and Drug Administration, 2018b).

This was preceded by extensive researched of academic research facilities in Europe, in cooperation with employees from Mallinckrodt Medical Inc. in the late 90s and beginning of 2000. The preclinical and clinical investigational work was mainly focused on toxicity and dosimetry (Lewis et al., 2001; Lewis, Laforest, Lewis, & Anderson, 2000; Lewis et al., 1999), the use of the substance as an PET imaging biomarker (De Jong et al., 1998), and labelled with Lutetium-177 and Yttrium-90 to be used in the PRRT approach (Bernard et al., 2004; de Jong, Breeman, Bernard, Bakker, Schaar, et al., 2001; Kwekkeboom et al., 2001). On the basis of the published literature one can assume that the support from Mallinckrodt, acquired by Tyco International in 2000, decreased in the years after 2003 and academic research institutions (notably the Erasmus Medical Centre in Rotterdam) resume research efforts.

Mallinckrodt Medical Inc. filled the intellectual property rights (later Covidien- Mallinckrodt and later sold to IBA Molecular) in June 1996, and the patent expired in June 2016. Even the compound could not be used in daily routine, Mallinckrodt allowed some licensed manufacturers to supply the product to research groups, who conducted registered clinical trials approved by health authorities (Leugs, 2013). Two of these licensed manufactures where ABX GmbH, a German company manufacturing chemicals for nuclear medicine based in Leipzig, and the Swiss-based biochemical and pharmaceutical drug products producer Bachem AG with its affiliates in Europe and the US. Those were able to provide

DOTATATE for clinical trials registered in the EudraCT registry for diagnostic use with Gallium-68 or therapeutic use with Yttrium-90. Currently, Advanced Accelerator Applications (AAA) exclusively holds the rights for a special labelling method for DOTATATE (in context to Lutetium-177 and Gallium-68) and has presented encouraging results from a randomised, controlled phase III trial in 2017 (Chiti, 2013; Strosberg et al., 2017).

DOTATOC

The other compound used for the diagnostic purpose in NETs is DOTATOC, a somatostatin peptide analogue (Tyr3-octreotide) coupled with (DOTA). Even ^{68}Ga-DOTATATE showed a 10-fold higher in-vitro affinity to SSTR2 compared to ^{68}Ga-DOTATOC, the difference may not seem to be clinically relevant in the visualisation of NETs mainly expressing SSTR2 (Pöppel et al., 2011; Reubi et al., 2000). Until 2007, Novartis held the intellectual property rights to DOTATOC (commercial name OctreoTher) and conducted Phase I and Phase II trials to demonstrate the safety and therapeutic effectiveness (disappearance or significant shrinkage) of somatostatin receptor positive solid tumours (e.g. neuroendocrine, breast or small cell lung tumours) (Smith et al., 2000). Phase II multicentre clinical trials have were performed in cooperation with Mallinckrodt Medical Inc. in Australia, Europe and the United States. It was also announced that the compound's efficacy should be tested in breast and small cell lung cancer. In 2007 also a phase II study tested the therapeutic compound [90-Yttrium-DOTA]-TOC in metastasised medullary thyroid cancer with grant support by the Swiss National Science Foundation.

Also in 2007, Novartis Pharma AG licensed Onalta (previously OctreoTher, Y-90 SMT 487) to Molecular Insight Pharmaceuticals Inc., which sublicensed the intellectual property rights and know-how to BioMedica Life Sciences in September 2009. Novartis still allowed the distribution of the diagnostic compound by licensed manufactures, if producers could state that the peptide is going to be used under the local radiopharmaceutical rules. The patent has already expired, and the compound is available at ABX, piCHEM, Bachem, JPT, IBD and BioMedica.

DOTANOC

DOTANOC is the third compound used for neuroendocrine tumours and is somewhat different to DOTATATE and DOTATOC due to its higher affinity to the somatostatin receptors subtypes 2 and 5 (Wild et al., 2003). The patent (US7122622 B2) for DOTANOC was filled in 2002 by Biosynthema Inc. with the inventors Helmut Robert Mäcke, Jean-Claude Reubi, Jörg Simon Schmitt, Mihaela Ginj and was transferred to Advanced Accelerator Applications (AAA) on May 1st 2015. The patent will expire in April 2022 in the United States.

3.1 The long Way to Market Authorisation

At the moment thousands of radiolabelled molecules have been researched, several hundred tested in human, but only a few dozen received an international market authorisation for a diagnostic and therapeutic purpose (Zimmermann, 2013). Over the years, 122 new molecular entities for all imaging modalities have been approved by the FDA till the end of 2015: Thirty-three were approved for anatomic imaging and sixty-seven for functional or molecular based imaging. This clearly shows that cardiovascular, oncology and neurology applications now lead the way of imaging, whereas the area of urology decreased over the century (Kinch & Woodard, 2017).

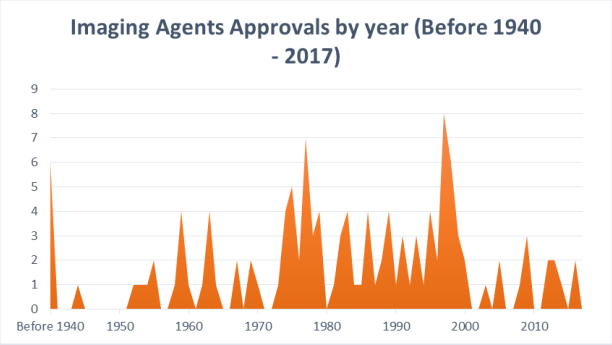


Figure 12 Overview of imaging new molecular entities (NMEs) approved from (before) 1940 to 2017 (Kinch & Woodard, 2017; U.S. Food and Drug Administration, 2017b).

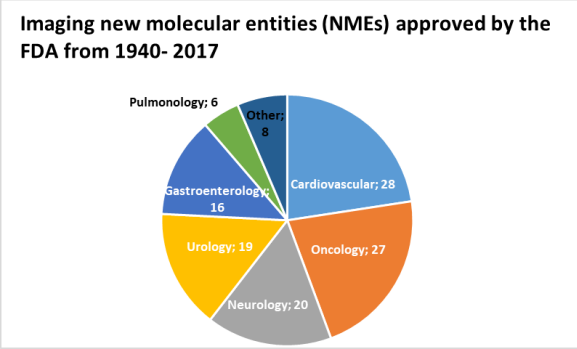


Figure 13 Approved indications of the 124 NME imaging agents until September 2017 (Kinch & Woodard, 2017; U.S. Food and Drug Administration, 2017b)

Historically, the private sector has been responsible for research and development of these imaging agents, mainly driven by five companies: Mallinckrodt, Squibb (now in Bristol-Myers Squibb), Roche Medic Physics (now in GE Healthcare), DuPont (now in Lantheus) and Schering AG (now in Bayer AG). However, their investment decreased substantially and R&D efforts have been replaced by public sector organisations (Kinch & Woodard, 2017). In the case of somatostatin analogues, it is well shown that several companies still registered new compounds suitable for imaging and therapy, but very few tried to receive a marketing authorisation. There are many reasons for this low approval rate, ranging from economic-, scientific-, regulatory-, manufacturing, and other non-medical related issues. The development process, including the approval of new RPs, is very complex and linked to a sustainable development period and high costs, also because RPs are regulated under the same rules as therapeutic drugs (Schwaiger & Wester, 2011). Newer radiopharmaceuticals in oncology (for imaging and therapy purpose) also tend to be more specific, which has a negative effect on the sales volume, the return on investment (ROI) and thus the investor´s market attractiveness (Henderson et al., 2005; Nunn, 2007a; Zimmermann, 2013). Also, the reimbursement values for diagnostic RPs have dropped in the past, which has brought significant uncertainty to the market (Zimmermann, 2013).

The pharmaceutical industry, as a fundamental investor for RPs, is currently struggling with several challenges: less revenue due to expiration of patented blockbusters (≥ 1 billion of annual sales); low productivity in new drug development (Khanna, 2012) and pressure on the reimbursement of new products (Kaitin & DiMasi, 2011). Several of the larger pharmaceutical companies adjusted their business strategies, their risk-reward ratios and may as a result not invest in products with low or moderate market size (< 300 million dollars) (Khanna, 2012). Furthermore, especially in the imaging sector there was a substantial decline in private companies involved in imaging R&D, mainly because of industry consolidation (Kinch & Woodard, 2017). The declining R&D budgets (for products with higher commercial risk) are also leading to falling investor´s interest in nuclear medicine products and, as a result, subsequently prevents the market authorisation of new RPs.

Several barriers, connected with the development of RPs, have been described in literature and can be summarised in five subordinated topics:

I. Economic and Market-related Challenges
   i. The market is small because imaging agents are undervalued and current prices will not support an investment in a new drug unless the agent is used in high volume (Nunn, 2007b).
   ii. RPs have limited profitability even if they are proprietary (Zimmermann, 2013).
   iii. There is a limited possibility for commercial exploitation of academic discoveries (Mather,

1998).

II. Research and Development Challenges

i. High development costs for radiopharmaceuticals, ranging from 100-200 million dollars for an RP imaging agent and around 800 million dollars for a new therapeutic drug (e.g. Dimasi, Grabowski, & Hansen, 2016; DiMasi, Hansen, & Grabowski, 2003; Henderson et al., 2005; Nunn, 2006)

ii. Some biological imaging markers are clinically not validated and adopted, because they do not measure a relevant biological feature nor enable disease diagnosis or outcome prediction (O´Connor et al., 2017).

iii. Experimental RPs are used in the drug development process to investigate pharmacokinetic and dosing, but are not intended to be developed further (Nunn, 2007a).

iv. Intellectual property right (IPR) issues between public research groups and potential investors. Sharing IPRs may limit exclusive commercial rights and discourage commercial development for investors (Schelbert, 2011).

III. Regulation and Marketing Authorisation Challenges

i. National authorities request several validation steps to receive regulatory and safety approval either in the development but also in production (Henderson et al., 2005; Nunn, 2007a; O´Connor et al., 2017; Zimmermann, 2013).

ii. Regulatory approval requirements by FDA and EMA are the same for imaging agents as for therapeutic drugs (Agdeppa & Spilker, 2009).

iii. Imaging biomarkers are evaluated based on the same patient-related benefits indicators (mortality, morbidity and health-related quality of life) as pharmaceutical drugs (Institute for Quality and Efficiency in Health Care - IQWIG, 2017a).

IV. Reimbursement and Revenue Planning Challenges

i. Shrinking revenue for investors based on the low or even decreasing reimbursement rates for diagnostic imaging tests (Nunn, 2007a; Zimmermann, 2013).

ii. Health Technology is often assessed in advance by government-related organisations demanding evidence of the value of the technology (Ciani & Jommi, 2014). The results of this assessment will subsequently affect reimbursement negotiations between the industry and healthcare provider.

V. Different goals between the Scientific Community and Investors/Industry

i. There is a fundamental difference in industrial- and academic research: The questions asked in academia most of the time generates data, which may not be helpful in the market authorisation process (Buscombe, 2015).

ii. Limited knowledge in the scientific community (outside of the nuclear medicine field) on the benefits of radiopharmaceuticals in diagnosis and therapy of cancer (Zimmermann, 2013);

VI. Special Manufacturing, Distribution and Handling of Radiopharmaceuticals

i. Special manufacturing and distribution of RPs due to the utilization of radioactive components (Bundesministerium für Justiz und Verbraucherschutz, 2017; Bundesministerium für Erwelt Naturschutz und Reaktorsicherheit, Bundesministerium für Gesundheit, & Bundesministerium für Verkehr Bau und Wohnungswesen, 2017; European Commission, 2017; International Atomic Energy Agency, 2008; Zimmermann, 2013).

To date, just a handful of imaging biomarkers received market authorisation in the US and Europe, and many of these biological imaging agents are still under evaluation and tested in clinical trials (European Medicines Agency, 2017b; U.S. National Institute of Health, 2017). The history of DOTATATE, DOTATOC and DOTANOC indicates that the interest from potential investors is low and that big pharmaceutical companies have intentionally avoided the nuclear medicine business. To overcome the issue of lacking marketing approval for many new RPs the U.S. National Institute of Health (NIH) and the U.S. National

Cancer Institute (NCI) for example try to promote the entry of new investors into the segment. Lately, several small and medium-sized enterprises (SME) have entered the market and facilitated the translation of clinically successful markers into final products. However, SMEs may lack the structure and experience in performing the tasks of identification, validation, translation and qualification of biomarkers. Understanding the biology of biomarkers, the relevance to the disease, the technological features and of course the regulatory requirements is demanding (Asadullah, Busch, Gottwald, Reinke, & Landeck, 2015). Especially the regulatory requirements, to provide the same level of empirical evidence for an imaging marker as for a therapeutic drug, are a significant cost and time contributor and a real obstacle for SME (Gazelle, McMahon, Siebert, & Beinfeld, 2005). This statement is confirmed by an evaluation by the FDA, which highlighted that SMEs ask more questions during the approval process than large companies and that quality documentation seems to be a particular bottleneck in SMEs (Putzeist, Mantel-teeuwisse, & Leufkens, 2011).

Furthermore, SMEs have a substantially longer preclinical phase, which higher stage related out-of-pocket cost and therefore overall costs (DiMasi, Grabowski, & Vernon, 1995). In Europe, EMA also addressed these challenges and started an initiative to support SMEs in the fields of administration, regulatory and offer them a financial incentive (European Medicines Agency, 2017d). Also, the concept of public-private partnerships (PPP) was promoted, to invite different players to actively participate in clinical trials and share the financial risk (Mercanoglu & Ozer, 2015).

With the further push towards personalised therapy, including the measurement of early therapy- and drug response, the use of specific biomarkers in the drug development process and clinical routine will become increasingly more important (Asadullah et al., 2015). Thus, it will be crucial to identify the barriers and challenges in the current authorisation process of RPs, determine the success factors in new R&D processes (e.g. public-private partnerships) and clear the way for new biological imaging markers to enter clinical routine. In the following, we will analyse the challenges described in the literature, and then put them in context with our empirical results.

3.2 Market Size and Potential

In the current economic environment, privately held companies follow the path of maximising the value of the company. They have to make decisions based on investment, financing and dividends with the objective to generate revenue for themselves or shareholders. This is of course also true for the pharmaceutical industry, which focuses on attrition rates to balance costs of R&D, explore cost containment and thus generate shareholder value (Kola & Landis, 2004). Moreover, when it comes to investment decisions the principles states, that the return must be higher than the minimum acceptable hurdle rate (Damodaran, 2012). The hurdle rate is the personal riskiness indicator and reflects the mix of debt and equity financing the investment, with the return to defined as the magnitude and timing of the cash flows and all side effects (Damodaran, 2012). The return, therefore, can be a gain or a loss relative on investment, with greater potential of wins and losses the more risk is associated with the investment. These opportunity costs are by a magnitude higher in the pharmaceutical industry than interest rates on other safe investments and compensates the funders' higher risks and attract them to further invest into the business (Chit et al., 2015).

Consequently, new discoveries in the medicinal product market are often not solely shaped by the autonomous progress of scientific breakthroughs, but rather by the extent of the market (Schmookler, 1966). This market is often influenced by three factors: (1) demographic and socioeconomic changes; (2) degree of competition and (3) public policies (Dubois, de Mouzon, Scott-Morton, & Seabright, 2015). Substantial literature investigates the external and internal factors influencing investment decisions in new drug development, and how the size of the market affects R&D decisions. One study showed that a 10% increase in real drug prices increases the future R&D spending by approximately six per cent (Giaccotto, Santerre, & Vernon, 2005). An increase in the U.S. pharmaceutical market size by one per cent increases the total market of new drugs by six per cent (Acemoglu & Linn, 2004). Also, several studies showed a dramatic change in private-sector R&D investment after federal policies changed, which substantially affected the market size (Blere-Kohout & Sood, 2013; Finkelstein, 2004; Yin, 2008). It is the task of economic models to assess the elasticity of innovation and thus to show how R&D investments react to a change in market size. Dubois et al. (2015) calculated an elasticity of innovation of 23.1%, which means that a company needs to have another $ 2.5 billion in revenue growth to support one new drug development.

With the shareholders in mind, the pharmaceutical industry prioritise projects with high net present value, adjusted for the future risk (risk-adjusted net present value -rNPV) (Stewart, Allison, & Johnson, 2001). This rNPV describes the current value of a drug by summarising all future cash flows (discounted to today's money), integrate the risk and costs associated with the development, and the time it takes to go to market. The intimate goal is to choose those projects, which "*maximise expected financial returns at an acceptable level of risk for a given level of corporate resources*" (Blau, Pekny, Varma, & Bunch, 2004). Moreover, a minimum expected financial return is more than $ 600 million per year in peak sales (Tollman, Morieux, Murphy, & Schulze, 2011). However, a report indicates a 11.4 percent year-on-year decline in average peak sales per asset since 2010 and a lower return on the R&D investment (Deloitte Centre for Health Solutions, 2016). It seems that companies with a clear focus on a specific therapy areas outperform those, who are changing the focus of their R&D program. Thus, any R&D

Project therapeutic class	Risk adjusted NPV x $1,000,000
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable Antibiotic (Gm+)	100
MS- Psoriasis	60
Liver Transplant	20
Oral Contraceptive	10

Table 20 shows the risk-adjusted Present Net Value (rNPV) of drugs in different therapeutic classes. Data from 2003. (Projan, 2003)

investment decision is never seen as a singular event but always in connection to other competing R&D investment decisions. Mcgrath & Nerkar (2004) analysed more than 7.000 patent filings from pharmaceutical companies between 1979 and 1995 and assessed the factors influencing decision making in the R&D process. It seems that the scope of opportunity, prior experience, and competitive effects are the main drivers. Investments, which relate to the same scope of previous research, seem to be more positive valued because they also do not increase investor´s risk premiers (Mcgrath & Nerkar, 2004). Companies with distinctive focus and expertise on specific therapy areas built a robust target product profile and target the population with maximised value. They appear to be more successful and achieve a higher commercial value (Deloitte Centre for Health Solutions, 2016).

Strategic focus on therapy areas seems to be of high value for every pharmaceutical company. It is said that they can make better decisions, leverage existing relationships to critical stakeholders (opinion leaders, researchers, clinical investigators, et cetera), have more focused portfolio and business development efforts, efficiently use internal and external resources, and can further improve research execution based on prior development expertise (Deloitte Centre for Health Solutions, 2016). With the pressure from shareholders, and their preference to have lower R&D investments and greater dividends (Scannell, Blanckley, Boldon, & Warrington, 2012), pharmaceutical companies seem to become more focused and efficient in their area of expertise. Excursions in new therapy areas, such as orphan diseases, show a higher average gross margin (85.9%) compared to non-orphan drug companies (74.8%) but also need a double R&D investment (as a percentage of sales; 33.9% vs 17.3% of sales) (Morel, Popa, & Simoens, 2013). So profitability for an investor, measured in return on equity (ROE), is 33% lower in the field of orphan drug companies, compared to non-orphan drug companies (Morel et al., 2013). In the last century a lower profit may not have stopped pharmaceutical companies from investing, because *"[…] that the mission of Merck and other pharmaceutical companies at the time was to take care of patients and profits would follow"* reported by Prof. J. Hay from the University of Southern California (Bobkoff, 2016). However, today many shareholders are capable of putting pressure on the company´s management and influence the strategic orientation. It is in the shareholder´s interest since wrong decisions in new product development efforts strongly influence the market valuations and news about a candidate's failure can create high financial losses on the market (Sharma & Lacey, 2004).

3.2.1 The Radiopharmaceutical Market Potential and Investors Interest

Market research institutes estimate the global nuclear/radiopharmaceutical market to be around $ 4.67 billion, rising to $ 7.27 billion in 2021 with a share gain for the therapeutic radioisotopes (Markets and Markets, 2016). Others see the market to rise to $ 8.2 billion in 2022 (Allied Market Research, 2014) or $ 8.5 billion in 2026 (Future Market Insights, 2017). Outstanding are the expectations by the Radiopharmaceutical company Advanced Accelerator Applications (AAA), which expects a global radiopharmaceutical market of $ 25 billion by 2030, with an annual growth rate of 7% for diagnostic RPs and 27% for therapeutic RPs. Their main argument: therapeutic products, now 10% of the global nuclear medicine market, will represent 60% of the total market in 2030 and have a much higher reimbursement rate of up to 100 times the costs of diagnostic products (Advanced Accelerator Applications SA, 2016).

However, the market is very fragmented: SPECT (SPECT/CT) procedures still lead in the cardiology segment, PET (PET/CT) procedure dominate the oncology segment. The growth of the market is expected to be driven by increased use of SPECT (SPECT/CT), PET (PET/CT), advances in radiotracers and targeted cancer treatment (Markets and Markets, 2016). So the market could to be attractive for newcomers, but new companies may not be able to enter the market quickly since the development, handling and production of RPs is somewhat special and challenging.

The Case of Somatostatin Analogues Imaging and Therapy:

Since newer RPs tend to have a more specific targeting, the markets may be significantly smaller than products in the conventional pharmaceutical market. A good example are the imaging somatostatin analogues Octreotide (OctreoScan, Mallinckrodt) and DOTA- TOC/NOC/TATE (NETSPOT® (U.S.A) or SomaKit TOC™ (European Union)), which are currently labelled with Indium-111, Gallium-68 or Fluor-18. But the same compounds can also be used in a theranostic approach and linked to β– radionuclides (e.g. Lutetium-177, Yttrium-90) to treat patients (DOTA- TOC/NOC/TATE (Lutathera®)) (see Chapter 2.2.5).

The evaluation of the imaging market showed that the return on investment of ^{111}In-Octreotide is very low compared to an average product in the conventional pharmaceutical market. Mallinckrodt Inc. introduced ^{111}In Octreotide in 1994 with the indication to use the imaging agent for an adjunct in the diagnosis and management of receptor-bearing gastroenteropancreatic neuroendocrine (GEP) tumours and carcinoid tumours (Mallinckrodt Inc., 1994). The very straightforward market potential calculation for ^{111}In- Octreotide (without taking into account the costs of the radionuclide and in-house preparation costs) at the time of market entry was approximately $ 18.8 to 37.6 million (depending on the incidence rate) in the U.S.A and Western Europe[1]. With a participated price drop of ~ 50% since the introduction of the product in 1994 (Schreiter et al., 2012), the market has shrunk even further. For the new product DOTATATE the current mean pharmaceutical price for NETSPOT® in the U.S. is around $ 3.550, without taking into account any discounts. The same product is registered in the EU under the name SomaKit TOC™, but no retail prices are available and due to the different market structure a much lower price can be anticipated. The cost for Lutathera® intravenous solution (370 MBq/mL) is around $49,598 for the supply of 1 solution in the U.S., prices in Europe are commercial in confidence (National Institute for Health and Care Excellence, 2017). The indication for NETSPOT®/ SomaKit TOC™ is very similar to OctreoScan but since the incidence of NET has risen over the years and the diagnostic agent is also more often used in the tandem theranostic approach we can anticipate a higher sales volume. A current limitation is the low number of PET scanners in Europe and the U.S.A. (Europe: SPECT 3,309 vs PET 724; U.S.A.: SPECT 14,825 vs PET ~2,380) (Eurostat, 2014; Imaging Technology News, 2013; IMV, 2015). Troublesome could also be that many countries already have fixed reimbursement rates for the scintigraphy with ^{111}In-Octreotide or even radio-targeted therapy, which could limit pricing negotiations. With the currently approved indication Lutathera® will apply to a very narrow patient population, but with an expected higher price compared to diagnostic DOTATATE products.

Due to the low market potential, compared to other drugs in the oncological business, big pharmaceutical companies have decreasing interest in their molecular imaging portfolio. Merck discontinued their joint venture with DuPont on their radiopharmaceuticals division in 1997, since it was not a significant contributor to their earnings growth objectives (Diagnostig Imaging, 1998). Bristol-Myers Squibb bought DuPont in 2001, but sold the business to a New York City investment firm already in 2008. The investment firm founded Lantheus Medical Imaging in March 2018. Another smaller radiopharmaceutical company Avid Radiopharmaceutical founded in 2004 as a spinoff from the University of Philadelphia, received venture capital from Pfizer and Lilly in 2006 and was fully acquired

[1] Calculation Input: Incidence rate of GEP-NETs as stated in the literature 2.5 to 5/100,000 population p.a. (Massironi et al., 2008)); Estimated average price for the U.S.A and Western Europe of $ 1,600/ dose OctreoScan ($ 1,850 for 6.6 mCi; $ 1,500 for 3.3 mCi) (The Medicare Services Advisory Committee, 1999); Population (1996): 269 million in the USA, 181 million in Western Europe; Assumption that every patient just needs one scan as SPECT has higher radiation doses and a PRRT approach was not often used in 90s; Higher Values in case OctreoScan is used for differential diagnosis outside of indication.

by Eli Lilly in 2010. Bayer Healthcare AG sold their PET tracer assets to Piramal Imaging SA in April 2012, focusing solely on RPs with therapeutic applications such as Xofgio (Radium 223 Dichloride). Today, several SMEs are participating in the development of diagnostic and therapeutic RPs and even some bigger pharmaceutical companies have shown interest in the development of new therapeutic RPs such as PSMA (U.S. National Library of Medicine, 2018).

3.3 Barriers and Challenges associated with Research and Development (R&D):

3.3.1 High Development Costs and Low Chances of Success – Conventional Drugs

When talking about market potential we also have to take the costs of development into account, which are said to be very high in the pharmaceutical industry. R&D expenses are all costs associated with research, development and final regulatory approval (Mestre-Ferrandiz, Sussex, & Towse, 2012). There have been several publications on the costs of drug development (see Table 21), systematic reviews, publications by pharmaceutical associations, and calculations by consultancies. Notable is the differentiation between the actual R&D costs directly spent for a successful candidate – "cash or out-of-pocket costs" and "capitalised costs", which are the full out-of-pocket costs capitalised over a specific period (mostly until the date of marketing approval) (DiMasi et al., 2016; S. Morgan, Grootendorst, Lexchin, Cunningham, & Greyson, 2011). Studies estimate R&D costs for the successful registration of a new molecular entity (NME) from $ 965 million ($ 860 million in 2000 USD) to $ 2.2 billion (C. P. Adams & Brantner, 2006; DiMasi et al., 2016, 2003; Gilbert, 2003; Mestre-Ferrandiz et al., 2012; O´Hagan & Farkas, 2009; Paul et al., 2010). However, these numbers should be evaluated with caution since there are significant differences in the study designs, the quantity of analysed drug candidates, the area of indication and the limited access to private databases. Furthermore, the R&D process is susceptible to changes in science, technology and regulatory requirements (U.S. Congress, 1993) and thus it is tough to compare the available data.

The most active research group is from the *Tufts Center for the study of drug development* at the Tufts University in Boston, USA. Joseph DiMasi and colleagues have continuously published the latest R&D expenditures and the change of costs and success rates in the development process of a new molecular drug. Their calculation of the overall clinical approval rate, estimated distribution of failures and total costs in each phase is based on data from the top fifty pharmaceutical companies (DiMasi et al., 2016). Since their methodological approach has not changed over the years, they believe that the data is comparable and this data indicates that costs are rising and the success rate is decreasing. In the 1991 publication (data from new drugs between 1970 and 1982) mean R&D out-of-pocket costs per successful NME were $ 114 million in 1987 USD ($ 245 million in 2017 USD). In 2003 (data from new drugs between 1983 to 1994) these costs already increased to $ 403 million in 2000 Dollars ($ 572 million in 2017 Dollars), and in the latest publication from 2016 (data from new drugs between 1990–2010) the mean R&D out-of-pocket costs have risen to $ 1.395 million in 2013 Dollars ($ 1.464 million in 2017 USD) (DiMasi et al., 2016, 2003).

Other researchers (see Table 21) estimate different out-of-pocket costs, ranging from $ 235 million to $ 1.395 million (both in 2017 USD) and a success rate of 9.0% to 21.5%. The wide variety of costs results from different indications, different economic analyses and - models (C. P. Adams & Brantner, 2010; DiMasi et al., 2016; Young & Surrusco, 2001). Mestre- Ferrandiz and colleagues from the Office of Health Economics in London analysed unpublished data (via confidential surveys) for new drugs in any phase

of clinical development from 1997 to 2002 and calculated out-of-pocket costs of $ 977 million (in 2017 USD) (Mestre-Ferrandiz et al., 2012).

					Out-of-pocket costs (in million Dollar 2017 $)			
Study	**Period**	**Primary data**	**Study Design**	**Out-of-pocket Costs***	**Pre-clinical**	**Clinical**	**Total**	**Success rate estimate (in %)**
(Young & Surrusco, 2001)	1990-2000	published data	Retrospective	166	n.a.	n.a.	235	9.0 %
(DiMasi et al., 2003)	1983-1994	Confidential surveys	Retrospective	224	169	397	567	21.5 %
(C. P. Adams & Brantner, 2006)	1989-2002	private database	Retrospective	459	186	436	624	11.0 %
(DiMasi & Grabowski, 2007)	1990-2003	Confidential surveys	Retrospective	525	247	451	698	21.5 %
(C. P. Adams & Brantner, 2010)	1989-2001	private database	Retrospective	n.a.	n.a.	577	n.a.	11.0 %
(Paul et al., 2010)	1995-2010	Confidential surveys	Retrospective	897	323	682	1.006	11.7 %
(Mestre-Ferrandiz et al., 2012)	1997-2002	Confidential surveys	Retrospective	899	82	897	977	10.7 %
(DiMasi et al., 2016)	1995-2013	Confidential surveys	Retrospective	1.395	430	965	1,395	11.83 %
(Prasad & Mailankody, 2017)	2006-2015	SEC10-K filings	Retrospective	648	n.a.	n.a.	n.a.	n.a.

***average, no capitalised costs**

Table 21. Overview of published literature analysing costs associated with the development of new pharmaceutical drugs (New Molecular Entities -NMEs).

It is liable to assume that capitalised costs are higher than out-of-pocket costs, ranging from $ 458 million (Young & Surrusco, 2001) to more than $ 2 billion, depending on the indication area and the data used (C. P. Adams & Brantner, 2006; DiMasi et al., 2016; Mayerhoefer et al., 2013; Paul et al., 2010). Not all studies calculated the out-of-pocket costs (Gilbert, 2003; O´Hagan & Farkas, 2009), some just focused on capitalised costs. Gilbert (2003) for example identified declining productivity and increased phase III costs an estimated total cost of $ 2.259 billion, including launch costs of $ 250 million. The study from O´Hagan & Farkas (2009) estimated total costs of $ 2.2 billion, but it is difficult to validate their results since they have not specified their methodological approach or given access to their data set. Another research group created a specific model with industry-appropriate R&D assumptions for success rate, cycle time and costs. They calculated capitalised costs of $ 1.778 billion per NME, excluding costs for exploratory discovery research, post-launch expenses and overhead (Paul et al., 2010). Finally, Dimasi et al. (2016) calculated capitalised costs of $ 2.558 billion.

A very new study from Prasad & Mailankody (2017) has a slightly different approach. They have used the publicly accessible data from SEK-10 fillings from pharmaceutical manufacturers which had, at the time of the FDA approval, no other drugs on the market. The reported R&D costs are therefore directly linked to the single successful drug candidate, plus the failing “sibling- candidates”. The results show median costs of development of $ 648 million (in 2017 USD) and $ 757.4 million in capitalised costs (discount rate of 7% p.a.). A few interesting details within this study: drugs being authorised via the “accelerated approval process” cost less than those in the regular approval process (median $ 328.1 million vs $ 817.6 million; p = .08). Drugs being classified as novel drugs (New Molecular Entity; not previously approved by the FDA) were higher than next-in-class drugs (variation of previously existing product) (median, $899.2 million vs $473.3 million; p = .047). Drugs being developed by the company itself had a significantly higher R&D spending than drugs acquired by a third party (median $899.2million vs $ 328.1million; p= .02) (Prasad & Mailankody, 2017).

Unfortunately, all published studies have a retrospective study design and almost all data cannot be validated due to confidentiality (C. P. Adams & Brantner, 2006, 2010; DiMasi & Grabowski, 2007; DiMasi

et al., 2016, 2003; Gilbert, 2003; Mestre-Ferrandiz et al., 2012; O´Hagan & Farkas, 2009; Paul et al., 2010; Prasad & Mailankody, 2017).

In line with the rising costs and challenging success rate is the reduction of R&D returns over time, which were reduced from 10.1% in 2010 to 3.7% in 2016 (Deloitte Centre for Health Solutions, 2016). A consulting group linked the R&D spending in the period of 1998 to 2004 of the 25 leading pharmaceutical companies to the successfully launched NMEs (peak sales per year exceeded $ 600 million) in the year 2002-2008 (see Figure 3). The figure shows big differences in total R&D expenditures and the number of successful introduced drugs (Tollman et al., 2011).

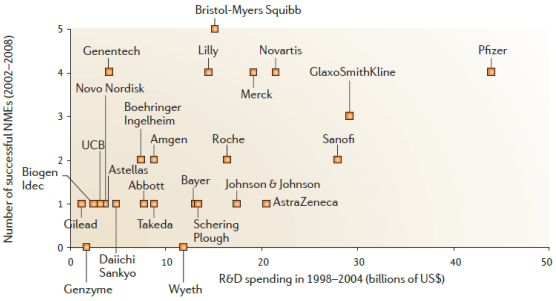


Figure 14 compares the R&D expenditures of the leading 25 pharmaceutical companies from 1998 to 2004 and the number of successful new molecular entities (NME) in the year 2002 to 2008. Visible is that some companies achieve a high number of NMEs with substantial less R&D investment (Tollman et al., 2011).

In Europe, we can look at the numbers published by the European Federation of Pharmaceutical Industries and Associations (EFPIA). They have reported that their member´s annual R&D expenditures increased from 7.766 million in 1990 to 31.500 million in 2015 (European Federation of Pharmaceutical Industries and Associates, 2017). The US counterpart PhRMA published a likely rise in R&D spending from $ 8,420 million in 1990 to $ 58,820 million in 2015 (PhRMA, 2016). One has to bear in mind that under the US and European law investments are deductible from tax, and that research is often supported by government/ taxpayer-funded research institutions or grants (Young & Surrusco, 2001). Nevertheless, the data from these lobby groups indicate an increase in R&D spending and a constant decline in R&D efficiency. Also Munos (2009) reported that the annual number of drugs approved in the USA per billion USD dropped from around ten drugs per one billion USD in the 1960s to less than one drug in the years after 2000. The reasons for the decrease in efficiency are manifold: the FDA believe that applied sciences have not kept pace with advances in basic science and that the current development process works with tools from the last century and have failed to introduce new tools for safety and effectiveness measurement (U.S. Department of Health and Human Services - Food and Drug Administration, 2004). Others blame regulatory and organisational obstacles (Ruffolo, 2006; Weatherall, 1982), organisational challenges (Gassmann & Reepmeyer, 2005), the “cautions regulator” problem (Scannell et al., 2012), overestimation of basic research in genomics and molecular biology in general (Scannell et al., 2012), and many more.

3.3.2 High Development Costs and Low Chances of Success – RP Imaging Markers

The number of studies investigating the R&D expenses in the field of radiopharmaceuticals is very low. As there are no publicly available figures, Adrian D. Nunn, an employee of Bracco Research USA Ltd., estimated costs for the development for an imaging agent to be around $100 to $150 million in 2006 Dollar ($ 121- $ 181 million in 2017 USD). This number is not specifically for RPs, but an evaluation for any imaging agent used in CT, MRI, Ultrasound or molecular imaging. His assumption was accurate in the context of a new magnetic resonance imaging agent developed by the company Epix Pharmaceuticals in the U.S.A (Epix Pharmaceuticals Inc., 2004; Nunn, 2006). For radiopharmaceuticals there is no in-depth study or calculation available, except for some estimations by Zimmermann (2008, 2012). In the 2008 paper he guessed that total R&D costs (in a ten year research period) should be around 22 to 30 million € ($ 26 to 35 million in 2017 USD) for a diagnostic - and 44 to 69 million € ($ 52 to 82 million in 2017 USD) for a therapeutic compound. He specified that for the therapeutic compound

an existing vector has been used and thus substantial costs for preclinical and Phase III R&D could be saved. The expenses break down: 500 k€ ($ 595.000 in 2017 US) for formulation and manufacturing (without equipment), 900k€ ($ 1.07 million in 2017 US) for Regulatory Affairs and the rest for clinical testing (Zimmermann, 2008). In the 2012 publication, he focused on therapeutic RPs and estimated total development costs of less than € 100 million ($ 119 million in 2017 USD) for a new therapeutic RP being registered worldwide (Zimmermann, 2012a). Unfortunately, he did not specify whether these expenses are out-of-pocket- or capitalise costs.

The Case of DOTATATE - R&D Costs and Timeline for Lutathera:

> *Lutathera is a somatostatin analogue which is linked to Lutetium-177 and is used for therapy of patients with inoperable progressive midgut carcinoid. The vector is octreotate, a synthetic somatostatin analogue initially developed to treat symptoms in patients with neuroendocrine tumours, linked to a DOTA complex to allow dynamic marking with a radioisotope (DOTA-octreotate also known as DOTATATE). In 2012 Advanced Accelerator Applications (AAA) started their commercial development process on the existing preclinical results and Phase II studies from Sandoz and other, mainly academic institutions. A phase III study was initiated in September 2012 and lasted until mid-January 2016, enrolling 229 patients in 41 sites (27 sites in Europe and 14 in the United States). Based on the public available company reports and SEK-10 documents the expenses for R&D were rising from 7.2 million € ($ 8.5 million in 2017 USD) in 2013, to 10.4 million € ($ 12.4 million in 2017 USD) in 2014, 14.7 million € ($ 17.4 million in 2017 USD) in 2015 and 13.8 million € ($ 16.4 million in 2017 USD) in 2016. In total € 46.1 million ($ 54.7 million in 2017 USD), which have been predominantly related to the Phase III trial of Lutathera as stated by AAA in their 2016 report (Advanced Accelerator Applications S.A., 2016). Some of the 2013-2016 R&D expenses may also be related to the development of the imaging agent NETSPOT, and the new therapeutic and diagnostic candidates such as ^{177}Lu-PSMA-R2 and ^{68}Ga-PSMA-R2, and ^{177}Lu-NeoBOMB1 and ^{68}Ga-NeoBOMB1. From a time perspective, one can see that a single Phase III study already needed five years till final publication.*

As already mentioned in the chapter market potential (chapter 3.2), R&D costs are very much dependant on the success rate of new molecule entities in the development process. In the conventional drug discovery process the success rate, defined as the cumulative probability of success from preclinical to phase III, ranges from 12.9% (Paul et al., 2010) to 34% (C. P. Adams & Brantner, 2006). Since RPs are commonly considered to be less toxic than conventional drugs, the success rates are somewhat higher (see Table 22). Only ~ 20% of the molecules drop out in the toxicological phase, and chances of success in the first human trial are about 30% (Zimmermann, 2008).

		Preclinical Phase (Proof of Concept)	Toxicology	Clinical Phase I/II	Clinical Phase III
Diagnosis (Oncology)	Estimated chances of success	40%	80%	33%	80%
	Number of molecules[1]	12	5	4	1
Therapy (Oncology)	Estimated chances of success	33%	80%	33%[2]	50%[2]
	Number of molecules[1]	24	8	6	2

(1) Number of molecules investigated to reach a minimum number of molecules for the next phase
(2) Assumption that imaging biomarker is developed in parallel.

Table 22: Estimated minimum number of molecules investigated to achieve marketing authorization for at least one diagnostic or one therapeutic radiopharmaceutical (Zimmermann, 2008)

When the diagnostic compounds show enough sensitivity and specificity in Phase I/II, *"Phase III is usually only a confirmation of the potential of the drug and has a very high level of success."* (Zimmermann, 2008).

3.4 Intellectual Property Right Issues

Another hurdle that complicates the introduction of new RPs according to the literature is the issue of Intellectual Property Rights (IPRs). The pharmaceutical- and chemical industry is highly dependent on IPRs and patent applications since the production of their products does not rely on complex and expensive manufacturing infrastructure like in other industries. Their products can easily be replicated by a 3rd party, without investing much in the production facilities (Lehman, 2003). Pharmaceutical companies therefore secure the investment and block potential competitors via IPRs on potential new chemical entities (NMEs) years ahead of the final product. However, this early application has a negative effect by significantly shortening the period of market exclusivity since the development of these products is time consuming (Lehman, 2003).

> *Definition of a patent:*
>
> *"A patent is an exclusive right to exploit (make, use, sell, or import) an invention over a limited period (20 years from filing) within the country where the application is made. Patents are granted for inventions which are novel, inventive (non-obvious) and have an industrial application (useful). There are other types of exclusive rights over intangible assets, notably copyright, design protection and trademarks, but patents provide broader protection that extends beyond the specific expression of an invention to the invention itself. [..]."* (Organisation for Economic Cooperation and Development (OECD), 2004).

Protecting the product and thus the investment via patents is a definite advantage for the company. On the one hand, competitors are blocked for a specific period to introduce a generic product and patent holders can also set a higher-than-competitive price over the patent period. However, even IPRs and other incentives such as direct R&D tax incentives, non-profit tax exemptions for research institutions, public financing of R&D activity are in place (Lichtenberg & Philipson, 2002), R&D efforts in medicines for tropical diseases (in developing countries) and for rare diseases (also known as orphan disease) are minor (H. Grabowski, 2002). From an industry perspective, the investment may not be economically feasible since R&D expenditures on rare diseases are also very high (see Chapter 3.3.1) and return of investment is low. The FDA in the U.S.A. and EMA in Europe have therefore, among other things, introduced another incentive: additional time of market exclusivity for the drug´s market application holder (The Congress of the United States of America, 1997; The European Parliament and the Council of the European Union, 2000). In the USA these exclusivity is granted for drugs treating diseases or conditions affecting fewer than 200,000 people (or more than 200,000 and no hope of recovering costs) over a period of seven years (CDER Small Business and Industry Assistance & Issues, 2015). In Europe, the European Commission grants market exclusivity for orphan drugs for maximum ten years (reduction to six years under certain conditions) for diseases or conditions with a prevalence of fewer than five in 10,000 people. The European Commission (EC) and the member states declare that they will not accept, grant and approve a marketing application for the same therapeutic indication, in respect of a similar medicinal product (The European Parliament and the Council of the European Union, 2000).

In the US the Orphan Drug Act is regarded as a domestic success story (M. E. Haffner, 1998) and also in Europe the positive tenor predominate: "*The response in the EU has far exceeded initial expectations, more than 450 applications for orphan designation have been submitted in the period between April 2000 and April 2005. Of those, more than 260 have been designated (April 2005), and 22 have gone on to receive a marketing authorisation*" (European Medicines Agency, 2006). Of course, this exclusivity also has some disadvantages: high drug prices and subsequently a burden for health insurances with

the consequences that the access for patients gets restricted. This is not satisfactory for all parties, and so it was suggested that incentives go beyond market exclusivity and also integrate patient access and reimbursement (Drermond, Wilson, Kanavos, Ubel, & Rovira, 2007).

3.4.1 Academic Institutions and Intellectual Property Rights

A look at the history of Nuclear Medicine shows that especially universities- and other public (and few private) research centres all over the world have set the groundwork for new imaging products, tests and radiopharmaceuticals. In the past there was also a strong link between governmental investment and the development of nuclear medicine technology, with public investments exceeding the financial support of the industry (Committee on State of the Science of Nuclear Medicine, 2007). In the onset of nuclear medicine activities in the 1950s to 1960s mainly long-lived radiopharmaceuticals have been produced in primarily state-controlled facilities, further products were then supported by big enterprise companies (Feld, de Roo, & Schicha, 2003). Especially medical imaging instrument companies knew that the RP is as important as the equipment technology itself. As a result, big medical technology companies have acquired or partnered with RP producing companies and invested in R&D of new RPs, until recently. Now the big medical imaging equipment companies (such as GE Healthcare or Siemens) and some well-known companies in the radiopharmaceutical business (e.g. Mallinckrodt) downsized, outsourced, sold or discontinued their R&D projects for radiopharmaceuticals.

One could say that the nuclear medicine business was kept alive by the academic sector, who continued their research in the oncology and neurology area and extended their knowledge in the development and testing of RPs. However, when it comes to setting the research objectives, the goals of academics and industry are very different. Academic, medical scientists are encouraged to research new scientific findings, conduct experiments, analyse their results and timely publish those in peer-reviewed scientific or medical journals. The value for the scientist is manifold and desirable:

> *"For individual investigators, the publication is a way of receiving intellectual credit and recognition from one's peers (and perhaps the broader public) for the genesis of new knowledge and the prospect of its conversion into beneficial goods and services. The publication also enhances a researcher's job prospects, ability to be promoted or gain tenure, and prospects for research support."* (Committee on Responsibilities of Authorship in the Biological Sciences, 2003).

However, even if a quick publication of research findings may be advantageous in some cases (e.g. growth in interest from investors, the effect on share prices, recognition, et cetera) the private "for-profit" investors generally do not have the desire to quickly publish research findings since the publication of these valuable data may negatively affect the development and IPRs (Committee on Responsibilities of Authorship in the Biological Sciences, 2003). Current evidence already indicates a decrease in unrestricted sharing of publication-related data, which could be based on a rise in research collaborations between the pharmaceutical industry, academia and other third-party research institutes. (Committee on Responsibilities of Authorship in the Biological Sciences, 2003). For many big pharmaceutical companies (GSK, Merck, Pfizer, Bayer et cetera), as well as companies in the imaging sector (Philips, Siemens, GE Healthcare, etc.), these partnerships are great to get access to new ideas, skills, technologies (Schuhmacher, Gassmann, & Hinder, 2016). In detail, the industry gains access to new research, new product development, obtain new patents, solve technical problems and can additionally tighten the relationship with the Universities (Lee, 1996). From an university perspective this partnership can also be beneficial as they can obtain further funds for research assistance, lab equipment and test their theory empirically (Lee, 1996). Moreover, universities recognised that they

could benefit by securing their innovations through patents and licensing, especially in the Anglo-Saxon region (Mowery & Sampat, 2005). In the USA the government introduced the Bayh-Dole Act of 1980 and encouraged universities and other public funded non-commercial research institutions to protect their inventions, and get economic returns in case it was federally funded (Committee on Responsibilities of Authorship in the Biological Sciences, 2003).

The Case of Somatostatin Imaging and DOTATATE:

The groundwork for the successful use of somatostatin analogues in imaging was to a certain extent laid by Jean Claude Reubi, a pathologist emeritus from the University of Berne (Switzerland). In 1987 Reubi published a study showing the somatostatin receptor density in neuroendocrine tumours and suggested that the chronically applied somatostatin receptors analogues, used to treat the symptoms in NET disease, are likely to bind to the tumour itself (Reubi, 1987). At the time of the discovery, J.C. Reubi was employed at the Sandoz Research Institute in Berne and the IPRs thus belonged to Sandoz Ltd.

Today, many of the interesting RPs or at least molecular pathways have been developed or co-developed by academic institutions or other non-for-profit research institution, which thereby gain rights on intellectual property and royalties for the cession of exclusive commercial rights (Schelbert, 2011). An excellent example is Pittsburgh Compound B, an RP developed by the University of Pittsburgh to image amyloid plaques in the brain of Alzheimer patients. Pittsburgh Compound B never got marketed, but it was the basis of a new Fluor based Amyloid tracer receiving marketing authorisation in 2014.

Academic scientists need to decide in an early stage, if they want to share the findings with the scientific community, which may stop further industrial supported development. Or decide whether they want to find a potential investor to continue development with the intention to receive a marketing authorisation in the end. The second strategy would lead to broad use within the nuclear medicine community and access of patients (Zimmermann, 2008).

3.5 Experimental RPs are not Evolving

The pharmaceutical industry is challenged by a very complex, costly and time-consuming R&D process (DiMasi, Seibring, & Lasagna, 1994; Hughes, Rees, Kalindjian, & Philpott, 2011; Janero, 2012). Overall costs are rising substantially with every drug failure that´s why the industry is feverish looking for new tools to separate the possible failure candidates from the best drug targets in early stage (DiMasi, 2001; Hughes et al., 2011). It has been mentioned that 72% of overall spending is attributed to failing candidates, mainly because there is poor predictability of preclinical models and insufficient learning before entering Phase III (Bergström, Grahnén, & Langström, 2003).

With vigorous exploration of new biological processes and the influence of gene modification on the molecular level (Phelps, 2000b) molecular imaging (PET and SPECT) has the potential to visualize the distribution of potential drugs and evaluate their effectiveness on disease tissue and organ systems in early phases (Bergström et al., 2003). PET or SPECT radionuclides linked to a potential biological target in very low levels (100 µg) enable the exploration of in-vivo pharmacokinetic (PK) and pharmacodynamics (PD) properties in Phase O and at the same time a very small chance of adverse events (Bergström et al., 2003; Burt et al., 2016). These studies are commonly called micro-dosing trails (also named Phase- O trails) and there is an excellent hope that promising drug candidates can be detected before the expensive, time- consuming pre-clinical trials start (U.S. Department of Health and Human Services - Food and Drug Administration Center for Drug Evaluation and Research (CDER), 2006).

Regulatory authorities in Europe and the USA have supported this initiative and drafted clear regulations for such exploratory clinical trials (European Medicines Agency, 2009; U.S. Department of Health and Human Services - Food and Drug Administration Center for Drug Evaluation and Research (CDER), 2006). For example, EMA has described two different approaches to micro-dosing studies:

> "*The first approach would involve not more than a total dose of 100 µg that can be divided among up to five doses in any subject. This could be useful to investigate target receptor binding or tissue distribution in a PET study. A second use could be to assess pharmacokinetics with or without the use of an isotopically labelled agent. These uses could be supported by an extended single dose toxicity study in one species, usually rodent, by the clinical route of administration, together with the appropriate characterisation of pharmacology.*
>
> *The second microdose approach is one that involves < five administrations of a maximum of 100 µg per administration (a total of 500 µg per subject). This can be useful for similar applications as for the first microdose approach described above, but with less active PET ligands. This approach could be supported by a seven-day toxicity study in one species, usually rodent, by the clinical route of administration, together with SAR assessment of the genotoxic potential of the unlabelled compound and appropriate characterisation of pharmacology.*" (European Medicines Agency, 2009)

There are commonly three main techniques to assess PD and PK in (pre-) clinical trials: liquid chromatography-tandem mass spectrometry (LC-MS/MS), positron emission tomography (PET), and accelerator mass spectrometry (AMS) (see Table 23).

Sensitivity			
Sample Types	Mostly plasma but any sample may be used (e.g. biopsies, bronchial lavage, VSF, urine, faeces, blister samples	Real-time imaging, dynamic, contemporaneous information from multiple tissues/ targets	Mostly plasma but any sample may be used (e.g. biopsies, bronchial lavage, VSF, urine, faeces, blister samples
Sample frequency/ duration	6-10h duration limited	Continuous/ dynamic; duration limited by radioisotope half-life	6-10h duration limited
Plasma sample volume	Typically 50 µl, but as little as two µl	n/a; continuous/ dynamic "counting" of drug molecules per unit space	Typically 100 µl- 2ml, but as little as 25 µl
Radiolabelling	14C	^{11}C, ^{13}N, ^{15}O, ^{18}F, and ^{124}I	None
Radiation exposure	Very low	low	none
Parent compound and metabolites	Discriminating parent compound from metabolites possible	No discrimination	Discriminating parent compound from metabolites possible
Administration	PO and IV	IV	PO and IV
Site of analysis	Can be outsourced	On-site only	Can be outsourced
Costs per Study	~ $ 400-600k	~ $ 500-700k	$ 80-140k
Availability	Limited availability; ~six facilities dedicated to biomedical research worldwide	Available in specialised centres (e.g., tertiary- care facilities)	Commonly available
AMS, accelerator mass spectrometry; PET, positron emission tomography, LC-MS/MS, liquid chromatography-tandem mass spectrometry; CSF, cerebrospinal fluid; N/A, not applicable			

Table 23 Comparison of the three most commonly used techniques for pharmacodynamics and pharmacokinetic assessment (original table from M. Bauer et al., 2008; adapted by Burt et al., 2016)

All methods have some advantages and disadvantages in terms of their sensitivity, sample frequency, availability and costs per study (Bauer et al., 2008; Svendsen et al., 2015; Yamane et al., 2013). AMS is seen to be the most sensitive method, compared to PET; but cannot sample the distribution and PK in all organs over time (Bauer et al., 2008). PET has the ability to identify very important drug properties at an early stage such as: (1) exposure at the target site to measure the pharmacological effect over a certain period, (2) efficient binding to the pharmacological target (binding kinetics- desirable and unwanted binding) and (3) expression of primary pharmacology at the site of action (sufficient levels) (Morgan et al., 2012).

To date, many of the newer biomedical drugs already have a fitting companion diagnostic assay or imaging diagnostic agent co-developed with success (Naylor & Cole, 2010; Van Heerter, Scarimbolo, Ford, Berdougo, & Neal, 2015), which reduced the clinical trial costs due to picking the right patients (fewer, but the right patients) for Phase III trials and speed up the development process (Agarwal, Ressler, & Snyder, 2015). Unfortunately, 97% of all FDA approved companion diagnostics (counting 40 in September 2017) are in-vitro diagnostic devices/assays (total 39) with currently only one imaging companion diagnostic (Ferriscan) registered (U.S. Food and Drug Administration, 2017c). Those in-vitro assays typically have some limitations in terms of locating the drug target, showing overall distribution, which in the end narrows the scope and sensitivity (Van Heerter et al., 2015). In contrast, PET is able to provide a more objective assessment~~,~~ but so far micro-dosing studies with RPs are infrequently used by the pharmaceutical industry. Svendsen et al. (2015) showed in his recent review that only 33 studies have used RP micro-dosing in the drug development process. PET was generally used less often in pharmacokinetic -, never in biodistribution -, but most often in distribution studies and some occasions in combination with other methods. Even if imaging biomarkers are potentially better suited to assess the phenotype of the disease and to offer continuous structural and functional assessment of the therapy (planning and monitoring), their clinical evaluation, in regard to primary effectiveness measurement, is extensive (M. Bauer et al., 2008; Burt et al., 2016; Katz, 2004; Pien, Fischman, Thrall, Sorensen, et al., 2005; Willmann, Bruggen, & Dinkelborg, 2008). This assessment (the correlation between the imaging biomarker and the clinical outcome) requires large, costly and time-consuming

trials, which are currently rarely performed by the pharmaceutical industry (Willmann et al., 2008). Consequently, RPs used in the development process have no clinical role after drug approval (Nunn, 2007a). However, this could change quickly if the imaging- and biomarker community can verify that their data is robust, quantitative and easy to implement across multiple centres (Willmann et al., 2008). This is achieved by having the imaging biomarkers validated.

3.5.1 Imaging Markers are not Validated

In the past, especially academic curiosity was a driver for academic and other non-profit research organisations research purposes. That is why we have some beneficial radiolabelled compounds for diagnostic and therapeutic today, but few of them have been developed due to a clear clinical need (Mather, 1998).

> *"A good example is the use of radiolabelled monoclonal antibodies for tumour imaging. Over the last fifteen years, an enormous amount of work has gone into development programmes based on these materials, and this has resulted in radiopharmaceuticals which can effectively image cancer with sensitivities and specificities comparable or superior to other imaging modalities. But, however successful the particular imaging technique developed, unless it influences the management of a particular group of patients, it will not find routine application in clinical practice, and so far at least, this seems to be the situation for these new radiopharmaceuticals."*(Mather, 1998).

Molecular imaging biomarkers, as well as therapeutic RPs, need to be extensively validated on their pathophysiological effects and clinical endpoints, otherwise they will not be successfully implemented in clinical routine and/ or the personalised medicine approach. So far, regulatory agencies have demanded evidence that shows benefits in "hard endpoints", which has been a big challenge for the applicants. But their perspective has changed partially and the FDA now permits applicants to use surrogate endpoints for the approval of a new drug product, "*if well-controlled clinical trials establish that the surrogate endpoint is reasonably likely to predict a clinical benefit"* (U.S. Food and Drug Administration, 2017a). Also EMA, in their adaptive pathways approach, allows drug applicants to use surrogate endpoints for risk assessment in their marketing authorisation, if they can predict important clinical outcomes (European Medicines Agency, 2017a). This move also reflects the industry´s pipeline problem and authorities, as well as the industry, hope that this adaption can cut development times for new therapeutic drugs and make the R&D process more efficient.

Before the introduction of this regulation, some drugs had already been approved based on their effects on surrogate markers such as blood pressure, tumour size, serum cholesterol, and intra-ocular pressure (Katz, 2004). However, so far the FDA and EMA have hardly accepted any imaging biomarker to be used as validated imaging-based surrogate endpoint (Willmann et al., 2008). Many biomarkers quantitatively correlate with disease progression but have no clinically meaningful endpoint. They are not validated in showing a change in mortality, morbidity, quality of life and/or predicting the effect of the therapy (Katz, 2004; Temple, 1999). For regulatory agencies, surrogate endpoints can only be accepted if the clinical outcome (symptomatic or structural effects) cannot be practically achieved in "conventional" clinical trials (Katz, 2004). Moreover, correlating the surrogate marker with the clinical benefit requires large trials, time and capital (Willmann et al., 2008).

Imaging biomarkers are currently extensively used in oncology for screening, diagnosis and staging; treatment targeting; patient stratification, prediction and monitoring of disease progression (Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials Board

on Health Care Services et al., 2012; O´Connor et al., 2017). An outstanding number of 10,000 studies were published between 2004 and 2014 investigating new or established imaging biomarkers, but very few of these biomarkers guide clinical decisions (Hayes et al., 2013; Macleod et al., 2014; O´Connor et al., 2017; Poste, 2011). This lack of validation reflects, on the one hand, technical barriers such as questions regarding accuracy and availability, and secondly difficulties in the biological and clinical performance addressing the aspects of clinical outcome measurement (O´Connor et al., 2017).

Excursus: A Roadmap for the Qualification and Validation of Imaging Biomarkers

In a recent expert meeting, organised by the Cancer Research UK (CRUK) and the European Organisation for Research and Treatment of Cancer (EORTC), many of the top global organisations in cancer research discussed the ongoing challenges of imaging biomarker validation/ qualification. They called it "*The imaging biomarker roadmap*" and reviewed the challenges in the validation process for each domain and introduced recommendations for accelerating the clinical translation of imaging biomarkers (O´Connor et al., 2017):

Domain 1 – Discovery:

The expert panel recommends linking the funding of new imaging biomarker´s studies to a clear statement of how to achieve validation and qualification. Extended data on study design, protocols, quality assurance processes and standard operating procedures, as well as specifications on used software should be published. This should pave the way for the integration of an increased number of studies in meta-analysis, which can support the qualification and validation of imaging biomarkers (O´Connor et al., 2017).

Domain 2 and 3 – Technical validation:

Guarantee of repeatability (same equipment, software and operators over a short timeframe in in-vivo and/or in-vitro studies) and reproducibility (different equipment, different software or operators, or at different sites and times in in-vivo and/or in-vitro studies) in any geographic region will enhance the qualification process using these imaging biomarkers in large multicentre trials. These imaging biomarkers also need to have regulatory and ethical approval, be available, feasible, safe and well-tolerated (O´Connor et al., 2017).

For a quicker technical validation the experts, therefore, recommend having accredited imaging laboratories with standardised approaches. The imaging biomarkers precision should be validated in the early phase to guarantee technical and biological validity before the start of multicentre reproducibility (O´Connor et al., 2017).

Domain 2 – Biological and Clinical Validation:

"The terms 'biological validation', 'clinical validation' and 'clinical utility' describe the stepwise linking of biomarkers to tumour biology, outcome variables and value in guiding decision-making, respectively."(O´Connor et al., 2017)

Whereas biological validation only links the imaging biomarker with biological process (European Society of Radiology (ESR), 2013), clinical validation and clinical utility can already demonstrate influence on clinical end-points and shows a net improvement of health outcomes. The generated information is useful for diagnosis, treatment, management, or prevention of a disease (Hayes et al., 2013; McShane & Hayes, 2012; O´Connor et al., 2017).

Since the validation of an imaging biomarker is normally relatively late in the development phase (Waterton, 2013), the panel recommends to gather extensive preclinical studies to examine the relationship between the imaging biomarkers to pathology and effects of interventions. Pivotal is also the correct choice of the experimental model, with early-stage in-vitro models, suitable tumour models and in-vivo studies in the end. All data should be stored and essential data should be published to avoid selective reporting and publication bias. (O´Connor et al., 2017).

Domains 2 and 3 – Cost Effectiveness:

Successful translation into clinical routine is only possible if cost-effectiveness is confirmed by demonstrating an advantage regarding QALY (Waterton, 2013). This qualification evidence is costly and time- consuming (Gazelle et

al., 2005) and thus creates a barrier for investors to fund such research. Consortia of commercial and not-for-profit sponsors could possibly overcome this issue, but other challenges such as IPR and business related questions need to be addressed explicitly. A simultaneous development of the drug compound and the fitting companion diagnostic could be beneficial for healthcare payers and the pharmaceutical industry in the first place, but a failure in the translation of the therapy can diminish the market for the companion diagnostic and lead to an even higher business risk (O´Connor et al., 2017).

Consequently, the panel recommends finding new models for funding and regulation, and new imaging biomarker should be integrated into studies using existing and validated radiological tests. Larger trials should also evaluate the cost-effectiveness of the imaging biomarker versus the other tests (O´Connor et al., 2017)

Domain 3 – Qualification:

After steps in domain 2, the imaging biomarker are already validated to a biological process and clinical endpoints. But they may have not reach the "clinical utility" level since data from large clinical trials are missing. Qualification means that the imaging biomarker is able to show prognostic value in the selecting of patients with specific attributes who are likely to benefit most from this therapeutic approach. Generally, the biomarkers are qualified for multiple settings such as for specific tumour types, different therapies or different research questions (O´Connor et al., 2017; Shankar et al., 2009)

The panel recommends large multicentre clinical trials, a robust study design with adequate statistical methods (Sensitivity, Specificity, Receiver Operating Characteristic (ROC), Negative Predictive Value (NPV), Positive Predictive Value (PPV), Hazard Ratios, et cetera). These studies need enough power to demonstrate clinical influence on prognostic quality of life, progression-free survival and overall survival (Mcshane et al., 2005; O´Connor et al., 2017).

In order for the pharmaceutical industry to continue to engage on the results of academic research on biomarker development, the data obtained must already be very robust and quantifiable. Furthermore, imaging biomarkers should also be easy to use and already in the exploratory clinical development or post-development phase (Willmann et al., 2008). The drug industry is very interested in using surrogate end-points for their clinical trials, since this would have a significant effect on cost-savings in the R&D process (N Lassume et al., 2007; Paul et al., 2010; Pien et al., 2005; Richter, 2006; Shi & Sargent, 2009; Van Bröcklin, 2008; Van Heerter et al., 2015; Willmann et al., 2008). Especially PET could be very beneficial as it enables the validation of biodistribution, pharmacokinetics and pharmacodynamics from a cell culture setting to preclinical animal models to clinical applications (Massoud & Gambhir, 2003).

3.6 Regulation and Marketing Authorisation

3.6.1 Challenges in the Regulatory and Safety Approval Process

With the increased discussion around the topic of personalised medicine, the number of biomarkers used in practice was continually rising even to date only a small number of these markers really affect clinical decision making (O´Connor et al., 2017). In the period from 2004 to 2014, approximately 10,000 publications have dealt with new or established imaging biomarkers, coming from new modalities, new techniques or new analytic approaches (O´Connor et al., 2017).

There are two main groups of biomarkers: disease-related and interventional- related. Disease-related biomarkers are helpful in the identification, staging, monitoring and outcome-prediction in cancer patients (Ludwig & Weinstein, 2005; Richmond & Dunn, 2012) whereas interventional-related markers serve as predictors or surrogates of therapy response and may also predict or indicate drug toxicity (Richmond & Dunn, 2012).

However, regardless of the group, many of these biomarkers have not been translated into a clinical routine because they simply do not measure the relevant biological feature, improve diagnosis or

outcome prediction (O´Connor et al., 2017). Many fail in one of the "Translation gaps" such as the step from in-vitro evaluation in humans/ animals to the reliable use in clinical cancer research; and secondly the step from being a research tool to become a validated biomarker in routine patient care (O´Connor et al., 2017). Another group experience the challenges of regulatory and safety approval by the regulatory agencies in Europe and the United States of America. Especially since the implementation of specific pharmaceutical laws in the USA in 1962 and, e.g. 1976 in Germany, the drug approval process became more comprehensive over the decades. Authorities requested more clinical data, more randomised controlled trials and more data on safety and efficacy such as dose-response information, gender-specific data, long-term tolerability data, subgroup evaluation, et cetera (Woodcock & Woosley, 2008). At some point it was criticised that regulatory bodies are solely focusing on avoiding risk and safety issues, rather than finding the best balance of benefit and risk (Scannell et al., 2012). Notwithstanding the above, the higher regulatory requirements, among other things, reduced the approval rate of NMEs from the peak in end of the 1990s until the beginning of the 21st century (U.S. Department of Health and Human Services - Food and Drug Administration, 2004).

The stagnation of newly approved NMEs and rising R&D budgets was also recognised by the FDA, which published a white paper in 2004 dealing with the critical path in the development process. The paper proposed efforts for improvement, the need for new tools to evaluate safety/ effectiveness and offered help to the industry to identify critical burdens upfront in the review process. The agency was committed to make internal changes to better respond to crucial issues, support high-priority research efforts and to improve the cooperation with all stakeholders (U.S. Department of Health and Human Services - Food and Drug Administration, 2004). EMA was even first to implement a scientific advice in 1996 with the goal to improve the communication between the industry and the agency, advise sponsors on adequate risk-benefit assessment reports and therefore facilitate the access of new, safe and effective medicinal products (Hofer et al., 2015). EMA evaluated this initiative and concluded that the majority of applicants (76%) have used this service before pivotal trials, and those with EMA´s scientific advise had a higher marketing authorisation rate (78% vs 64%) compared to those without consultation (Hofer et al., 2015).

This initiatives suggest that EMA and FDA are transforming from the role of gatekeepers (focusing of safety and risk reduction) to enablers who are leveraging innovative ideas, methods, frameworks and become scientific advisors (Ehmann et al., 2013). They are now working closely together aligning regulatory requirements as much as possible and facilitate the transformation of scientific results into regulatory frameworks (Goldman, Seigneuret, & Eichler, 2014).

3.6.2 Regulatory Approval Process in Medical Imaging and Radiopharmaceuticals

In FDA´s critical path report the agency acknowledged the unique role of medical imaging and biomarkers in the development of future medical products and initiated a workshop to routinely use new imaging techniques and biomarkers in the development process (Harapanhalli, 2010). The aim is to reduce drug attritions, delays and costs and as a result speed up the development cycle. However, the key players such as the National Health Institute (NIH), academic institutions and the industry highlighted the regulatory and technical challenges of (imaging) biomarkers and the effect on the drug development- and approval process (Harapanhalli, 2010; Kelloff et al., 2005). The primary challenge for imaging biomarkers is the limited consistency within and across different imaging hardware based on manufactures systems; limited consistency of the RPs because of various production possibilities/sites; regulatory acceptance/ validation of the imaging tracer or method; few probes with few molecular targets or pathways (Harapanhalli, 2010; Kelloff et al., 2005). Therefore the FDA, with the assistance of

the NIH initiated a public-private partnership called “The Biomarker Consortium” in 2006. Stakeholders from the industry with pharmaceutical, biotechnology, diagnostic and medical device background, non-profit organisations, Medicare and Medicaid and academia were invited to help to accelerate the delivery of new successful technologies, drugs, therapies in the field of prevention, early diagnosis and treatment (Foundation for the National Institutes of Health, 2017). The European counterpart EMA also initiated a “Biomarker qualification process” in 2009 with the intention to advice on future study design and to demonstrate positive contributes. This is mainly achieved by getting the regulators agreement on objective and design of the studies, inform the regulators on current scientific progress and to establish an interdisciplinary discussion platform (Efthymios, Koch, Deforce, & Vamvakas, 2015).

3.6.2.1 Regulatory Approval Process in the United States and the Central Approval Process in the European Union

As in many other countries, radiopharmaceuticals have not been part of the original rules for medicinal products and procedures of marketing authorisation in Germany from day one. These products have frequently been ruled under national radiation protection regulations and pharmacopoeia monographs. In Europe, the European Council decided in 1989 to incorporate these products in Directive 89/343/EEC with the effect that the regulatory approval process is quite similar to classic medicinal products with just minor variations. These variations especially reflect the unique needs for safety and efficacy verification of imaging agents, and were tailored to reflect the use of imaging agents and biologics to diagnose and monitor diseases or conditions (U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CBER), & Center for Biologics Evaluation and Research (CBER), 2004). This is for example outlined in the FDA report “Guidance for Industry: Developing Medical Imaging Drug and Biological Products” specifying which data can be partially or entirely waived like for example data on long-term and repeat-dose toxicity studies in animals; long-term rodent carcinogenicity studies, reproductive toxicology studies et cetera. However, there may also be additional data requested like data on radiation exposure and absorption dose of the source tissue/organ and any other tissue, or specific data for paediatric patients.

Due to the special nature of RPs, which may subsequently become a challenge in regulatory approval, regulators in Europe and the US have given applicants the option to request so-called "pre-submission meetings". Those are free of charge and it is said to have a positive impact on the success rate of an application in the U.S. (Hall & Carlson, 2014; Tiwari, 2015), and a smoother evaluation in Europe. Both the FDA and the EMA send a highly qualified team addressing product-specific, legal, regulatory and scientific issues in order to facilitate subsequent validation and the assessment of the application (European Medicines Agency, 2017c). A service which could especially be beneficial for small and medium enterprises, as those companies typically have less experience and knowledge within the company than large pharmaceutical companies (Pammolli, Magazzini, & Riccaboni, 2011).

3.6.2.2 Regulations for Radiopharmaceuticals

Radiopharmaceuticals are classified as “medicinal products” and consequently underlying the same regulations as “conventional pharmaceutical drugs” if the radiopharmaceutical contains at least one or more radionuclides (radioactive isotopes), and it is intended to be used for the medicinal purpose (The European Parliament and of the Council, 2001). Additional to the industrially prepared RPs, also radionuclide generators, radionuclide kits, and radionuclide precursors used in small-scale productions sites, in research facilities, and in hospitals need to have a marketing authorisation based on Article 6 of the Directive 2001/83/EC (The European Parliament and of the Council, 2001). Regulations protecting workers, general public and environment are also in place on national- and European level (Directive

2013/59/EURATOM; Council Directive 97/43/Euratom; EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use -Annex 3 “Manufacture of Radiopharmaceuticals”).

Because of the unique nature of radiopharmaceuticals, the European legislator approved an “extemporaneous preparation” (Article 7 in Directive 2001/83/EC):

> “*A marketing authorisation shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorised, according to national legislation, to use such medicinal products in an approved healthcare establishment exclusively from authorised radionuclide generators, radionuclide kits or radionuclide precursors in accordance with the manufacturer's instructions.*” (The European Parliament and of the Council, 2001)

The special preparation allowance reflects the need to prepare the product near the patient´s bedside because radionuclides used for medical purpose generally have a relatively short half-life. This allowance, however, also empowers European member states to legitimate some institutions, such as academic sites, hospitals and public-private research centres to use the products outside the marketing authorisation track, conduct clinical research and drive innovation. Many clinicians in some EU countries heavily use this exemption and prepare their RPs in either small-scale industrial sites with GMP license or a non-industrial site such as hospital pharmacies and nuclear medicine departments. As this extemporaneously prepared medicines are unlicensed medicines, and thus not overviewed by regulatory safeguards, they are associated with some risks for patients, healthcare staff and organisations (Jackson & Lowey, 2010). To reduce the risk and at the same time improve the quality in facilities without GMP license, the Radiopharmacy Committee of European Association of Nuclear Medicine (EANM) guides their members: “Guidelines on Good Radiopharmacy Practice (GRPP)” (Elsinga, Todde, Penuelas, & et al., 2010). However, Article 7 in Directive 2001/83/EC has been implemented inconsistently in each European member state, give some member states more or less freedom in the in the application of the products.

Excursus:

Radiopharmaceutical Regulation in Germany

The use of radiopharmaceuticals is regulated in several national and international laws: The most important German law for pharmaceuticals, and consequently also for radiopharmaceuticals, is the Medicinal Products Act (Arzneimittelgesetz- AMG). But also other national laws regulate RPs such as the Pharmacy Practice Order (Apotheken Betriebsordnung –ApBetrO), the Ordinance of Radioactive Pharmaceuticals or Pharmaceuticals treated with Ionising Radiation (Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel - AmRadV), provision governing the manufacture and distribution of pharmaceuticals and agents (AMWHV) and the radiation protection regulation (Strahlenschutzverordnung – StrlSchV). Contrary to the European definition of a radiopharmaceutical in Directive 2001/83/EC, Germany has not adopted the same definition. Whereas the European regulators differentiate between the radiopharmaceutical (Art. 1 (6) Directive 2001/83/EC), radionuclide- generator (Art. 1 (7) Directive 2001/83/EC), - kit (Art. 1 (8) Directive 2001/83/EC) and -precursor (Art. 1 (9) Directive 2001/83/EC), the German regulators defined radionuclide precursors and generators to be seen as radiopharmaceuticals (§4 (8) AMG) and a “cold kit” as finished medicinal product. In contrast to the exemption for magistral and official formulation on a European level (Art. 3 (1,2) Directive 2001/83/EC), the German law maker strictly prohibits the placement of a RP on the market without a marketing authorisation (§ 7(1) AMG) and also exempts hospital pharmacies to prepare magistral and officinal RP (§ 13 (2) AMG).

But a loophole for radiopharmaceuticals exists in § 13 (2b) AMG:

"*An authorisation referred to sub-section one shall not be required by a person who is a physician or otherwise authorised to practice medicine on humans in so far as the medicinal products are manufactured directly under his/her professional responsibility for personal use by a specific patient. [...]*"

This exemption is now routinely used, especially after the abolishment of § 4 (a) AMD during the 15th amendment of the AMG in 2009. However, *the Ordinance of Radioactive Pharmaceuticals or Pharmaceuticals treated with Ionising Radiation (AMRadV)* further specifies the exemption of § 7 AMG for radioactive drugs (§2 (1-2) AMRadV):

"The prohibition based in § 7 (1) AMG is not valid for radioactive pharmaceuticals, which […] Beyond it is not effective for radiopharmaceuticals, which are used: (1) To identify the condition, state or function of the body, (2) prepared in a clinical institution on the basis of a manufacturing license according to § 13 AMG, and (3) administered to not more than 20 patients in this institution per week, in accordance with state-of-the-art medical science and based on a patient-specific medical prescription." (Bundesministerium für Justiz und Verbraucherschutz, 2017)

In general, all RPs being commercially "produced" or "prepared" in hospitals according to the instructions of the marketing authorisation holder (§ 13 (2a) AMG) are subject to a manufacturing license (§ 13 (1) AMG) under the supervision of a qualified person (§ 15 AMG). Excluded from this manufacturing license are those pharmaceuticals which are "*prepared by a physician or another authorised person to practice medicine on humans as the medicinal products are manufactured directly under his/her professional responsibility for personal used by a specific patient*" (13 (2b) AMG). Still, all regulations concerning radiation protection need to be fulfilled, the manufacturing needs to be reported to the authorities (§ 67 AMG), the manufacturer is responsible for having an adequate quality management system to monitor compliance and the manufacturing process needs to be in conformity with the international pharmaceutical rules (§ 55 (8) AMG) (Schweim & Schweim, 2011).

A comparison of the two central regulations for radiopharmaceuticals (AMG and AMRadV) shows that they contradict each other. Whereas the AMG allows the preparation of pharmaceuticals under the supervision of a physician (or otherwise authorised person to practice medicine in humans) the regulation AMRadV revoke this permit, probably because the legislation sees some risk in the use of ionising radiation. The legislator does not differentiate between those RPs with low radiation dose used for the diagnostic purpose and those with high radiation doses used for therapy. This is challenging for clinical routine and may not reflect the "real" risk associated with RPs. In the past, many believed that the marking of a carrier molecule with the radioisotope eluate could be performed under § 4 AMG "reconstitution", exempting the institution to hold a manufacturing license. However, the Federal Ministry of Health clearly stated in the legislative proposal that reconstitution is an "easy process" transferring the already pre-finished pharmaceutical product into a ready-to-use product by dissolution, dilution or mixing. However, in the case of kit based RPs the pharmaceutical is not present before the carrier molecule is marked with eluate, thus in the process a new pharmaceutical is produced, and it's not under § 4 AMG "reconstitution" and needs to be reported to the authorities (§ 67 AMG) (Deutscher Bundestag, 2009).

Radiopharmaceutical Regulation in other European Countries

In the United Kingdom RPs are classified as medicinal products since the 1960s, thus had only minor changes in their national law due to Directive 89/343/EEC and later 2001/83/EC. Concerning the manufacturing requirements, there is no exemption for the production of RPs. Thus full GMP is required as for any other pharmaceutical drug (Schuessele, 2012). All RPs must be prepared in either a licensed facility (special manufacturing license) or by a pharmacist in a registered pharmacy. Thus this systems works on the regulation of people and premises and not the product, which works well in the UK (Dence, 2008). In France, RPs can only be prepared in pharmacies under the supervision of a responsible pharmacist. These pharmacies can also be outside of a hospital but are obliged to have authorisation by the Agence Francaise de la Securité Sanitaire des Produits de la Santé (AFSSAPS). Spain regulates radiopharmaceuticals in several different laws, and allows the preparation in "Hospital radiopharmacies", exclusively prepare for in-house use of "extemporaneous RPs" from kit-based systems, blood-cell labelling and compounding of PET RPs. The "commercial centralised radiopharmacies" are either an authorised radiopharmaceutical laboratory or radiopharmacy unit, serve the nearby small hospitals and

nuclear medicine centre and do not support research and development activities. Directive 2001/83/EC does apply for the manufacturing of PET-RPs with marketing authorisation under GMP rules. Officinal preparation is prepared in the hospital radiopharmacies under national regulation (Good Pharmacy Practice) (Dence, 2008). Austria allowed the production and manufacturing of "magistral RPs" in (Institution-) pharmacies or nuclear medicine institutions or laboratories with a license and only for immediate application in patients (§63 AMG "Arzneimittelgesetz"). GMP is not required for the production of RPs.

3.6.2.3 The Use of Radiopharmaceuticals in Clinical Trials

Let's just briefly address the issue of the use of RPs in clinical trials because it has been a significant hurdle for these products so far. Investigational RPs for clinical trials has so far been regulated by the Directive 2001/20/EC "Implementation of Good Clinical Practice in the Conduct of Clinical Trials on medicinal products for Human Use". The Ordinance demanded full GMP and a manufacturing license for all pharmaceuticals, including radiopharmaceuticals. This meant that in Germany the RP has/had to be approved by the ethics committee, the Federal Institute for Drugs and Medical Devices (BfArM) and the Federal Office for Radiation Protection (BfS). With the introduction of Regulation No. 536/2014 by the European Union in 2014, some significant changes have been proposed, which should improve the organisation, handling and efficacy of clinical trials in the European Union.

Two changes will directly influence the use of radiopharmaceuticals in clinical trials:

1. "*The requirement to hold an authorisation for manufacture or import of investigational medicinal products should not apply to the preparation of investigational radiopharmaceuticals from radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions for use in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State*."
2. *"Investigational and auxiliary medicinal products should be appropriately labelled in order to ensure subject safety and the reliability and robustness of data generated in clinical trials, and in order to allow for the distribution of those products to clinical trial sites throughout the Union. […] Moreover, there are specific products, such as radiopharmaceuticals used as a diagnostic investigational medicinal product, where the general rules on labelling are inappropriate given the very controlled setting of the use of radiopharmaceuticals in clinical trials."* (The European Parliament and of the Council, 2014)

This regulation still needs to come in force (expected in 2019; status: September 2018), but may then speed up the approval process due to the single- authorisation procedure. The official timeline says that the regulation will apply not earlier than 28th May 2016, and it seems that the technical requirements such as the EU portal/ database registering all European clinical trials have not been finalised (The European Commission, 2017).

3.7 Uncertainty in Reimbursement and Revenue Planning

3.7.1 The challenge of rising healthcare costs

Over the last decades the healthcare spending, illustrated in rates of the gross domestic product, has risen substantially (Organisation for Economic Cooperation and Development (OECD), 2017). While spending in the 1970s was around two to six per cent in developed countries, this number has accelerated in the 1990s and the beginning of 2000s. Germany and Switzerland exceeded the 10% barrier of GDP already in 2002; other countries followed over the years (see Figure 15).

The sharply rising costs have been a challenge for many countries, and thus many are researching the influencing factors, changing existing health policies and trying to balance costs versus access to high-quality healthcare. Several attributes have been identified: an ageing population, increased public demand and expectations, personal income growth, rising prices of physician and hospital services (e.g. labour costs) and inefficiencies in the organisation and payment of care (Sorenson, Drermond, & Khan, 2013).

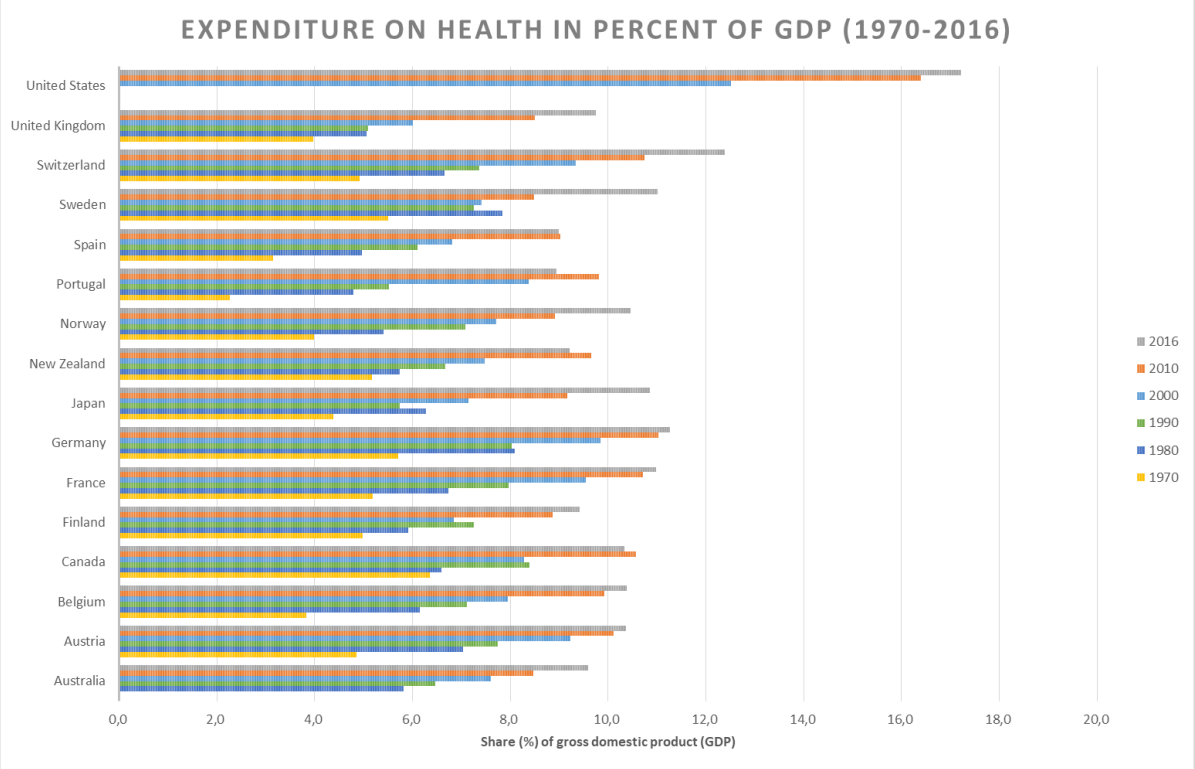


Figure 15 Expenditure on Health Care in a percentage of the Gross Domestic Product (GDP) from 1970 to 2016 in selected countries worldwide (Source: Organisation for Economic Cooperation and Development (OECD), 2017).

Very often new medical technologies (new medical devices in imaging, medical and surgical procedures, new healthcare IT systems and new drugs) have been blamed as one of the key cost drivers.

> "*Most, if not all, economists and policy analysts believe that technologic advance is a key driver of health expenditure growth (Aaron, 1991; Chernew, Hirth, Sonnad, Ermann, & Fendrick, 1998; Fuchs & Sox, 2001; Gelijns & Rosenberg, 1994; Newhouse, 1993)*" (Bodenheimer, 2005).

But the relationship between medical technology and healthcare expenditures seems to be more complex (Sorenson et al. 2013). Results from a recent meta-analysis suggest that some new technologies have a significant role in healthcare expenditures, but at the same time can increase the benefit of an even more enormous amount. Alternatively, some technologies are cost-effective for some group of patients, but not in others (Sorenson et al., 2013). Thus the impact of medical technology innovation needs to be assessed individually and carefully, even if the evaluation is more complicated compared to therapeutic technologies. When evaluating the cost burden of a medical technology one has to ask the questions: Does the new medical technology supplements an existing treatment strategy, or is it a (full or partial) substitute for current approaches? How does this new approach affect other services such as hospital days, physician visits, and some adverse events? (Goyen & Debatin, 2009)

We have to keep in mind that several other factors are driving the implementation of new technologies: demand by consumers with higher income, payment from some health insurances for new advances,

the interest of professional health workers to better serve their patients and gain prestige and reputation, commercial interest of healthcare providers and the healthcare industry et cetera.

3.7.2 Reimbursement – The Change of Systems

Rising costs mean that legislators have to adjust the reimbursement system and reimbursement values without significantly restricting access. For this reason, they borrowed the tool of technology assessment, with the primary goal of making informed decisions about coverage of health care services and to improve patient outcome, to assist in cost containment (Institute of Medicine (US) Committee for Evaluating Medical Technologies in Clinical Use, 1985).

The US, for example, implemented a National Center for Health Care Technology (NCHCT) in 1978 with the task to systematically assess new technology and to advice to the Health Care Financing Administration (HCFA) on safety, efficacy and cost-effectiveness. Over the period this had a significant impact on the federal reimbursement policy, primarily related to Medicare. The system changed from a "cost-based reimbursement" model, where all (e.g. technological) expenses had been retrospectively paid, to a prospective system where hundreds of illnesses with related costs, length of stay and resource consumption have been grouped to Diagnosis- Related Groups (DRGs) (Institute of Medicine (US) Committee for Evaluating Medical Technologies in Clinical Use, 1985). The DRG system aimed to train the institutions and payers to keep complete medical charts and identify their cost centres (resources) by analysing practices, equipment and a better view on their profits and financial losses. This way of thinking is well established among hospital managers, but not in the group of physicians, who do not weight into economic terms, but what they believe is best for their patients.

The DRG system followed the idea that there is a mechanism behind the appropriate use of technology:

> *"When a new technology becomes widely used, research and development costs will have been repaid, and volumes of services to which it is applied will increase. If there is a system in place for assessment, these forces should dictate a lower price for technology. If technology has a cost-beneficial effect on patient care, such as reducing the number of hospital days or preventing certain complications, that too should decrease the hospital price. However, sporadic technology assessment applied to new equipment and procedures has not yet brought a reassessment and price decrease once widespread diffusion has occurred.*
>
> *The primary objective of a DRG price adjustment process is to maintain equality across DRGs in the ratios of price to the cost of efficient care. This objective implies that as new cost-saving technology becomes available for use in specific DRGs, the relative price of these DRGs should be adjusted downward to reflect the new efficiencies. Alternatively, the development of new cost-raising technologies that improve patient outcomes enough to justify their use should be met with increases in the prices of relevant DRGs (OTA, 1983). In order to make price adjustments, an ample supply of data will be required."* (Institute of Medicine (US) Committee for Evaluating Medical Technologies in Clinical Use, 1985).

The DRG system is widely used in European- and other westerly countries and became the principle means to reimburse hospitals (Tan et al., 2014). At least in Germany, the DRG system can increase economic effectiveness and efficiency if the adverse effects (such as manipulation and up-coding) can be reduced (Böcking, Ahrens, Kirch, & Milakovic, 2005). Supplementary to the DRG cost-brake, many countries have also introduced a mandatory technological assessment before (and after) market introduction. In Germany, the responsible agency is called Institute for Quality and Efficiency in Health Care – IQWIG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen). Since 2004, it is by law

(§139a, 139 b, 139c, 35b, 130b, 137e, 303e “Social Security Code” V -SGB V) responsible to produce evidence-based reports and independently assess the benefit of drugs, non-drug interventions, diagnostic tests and screening tests, clinical practice guidelines and disease management programs (Institute for Quality and Efficiency in Health Care - IQWIG, 2017b).

The institute´s methods rely exclusively on evidence-based medicine (EBM): “*This proof should be obtained using the most objective scientific methods possible and provide reliable results*” (Institute for Quality and Efficiency in Health Care - IQWIG, 2017b). As a consequence of this methodological approach, the institute always compares Option A vs Option B (Institute for Quality and Efficiency in Health Care - IQWIG, 2017a).

> “*The term "benefit assessment" refers to the whole process of the assessment of medical interventions about their causal positive and negative effects, and compared with a clearly defined alternative active treatment, a placebo (or a different sham intervention), or no treatment.*” (Institute for Quality and Efficiency in Health Care - IQWIG, 2017a)

Criticism has been voiced because medical devices and diagnostic tests are evaluated according to the same scheme as drugs, including the same hard endpoints. But IQWIG argues that diagnostic tests can indirectly contribute to the mentioned patient relevant end-points by preventing risky interventions or changing the management towards different interventions (Institute for Quality and Efficiency in Health Care - IQWIG, 2017a). Information generated from diagnostic tests, which do not result in a benefit or harm to the patient and thus have no medical consequence, have no benefit from a social- law perspective. If either the diagnostic test has no predictive discrimination ability or the intervention resulting from the diagnostic tests is missing effectiveness, there is no benefit of the diagnostic test. Also in case of insufficient quality data, the IQWIG is not able to assess the medical innovation. Anyway, the IQWIG forwards their recommendation and reports to the Federal Joint Committee (GER: Gemeinsamer Bundesausschuss – G-BA), which decides on the inclusion or refusal of the service in the specification of all public health insurances.

Consequently, also diagnostic procedures need to show an existing and documented benefit, using the same patient-relevant endpoints as therapeutic drugs (mortality, morbidity and health-related quality of life). Though, only trails with the highest quality and which meet the inclusion criteria (e.g. a study comparing option A to option B, ideally randomised) can be used for the evaluation. The institute recommends some study designs with high empirical evidence: unconformity design (GER: “Diskordanzdesign”), interaction design (GER: “Interaktionsdesign”), prospective-retrospective design (GER: “Prospektiv- Retrospektiv Design”) and of course randomised controlled trials (RCTs) (Institute for Quality and Efficiency in Health Care - IQWIG, 2017a). Some researchers have expressed concerns that these types of studies are difficult to perform in academic research institutions with limited resources, and the requested statistical significance may not be reached due to a smaller patient group in orphan diseases.

3.7.3 Reimbursement of PET (PET/CT) Procedures and Imaging Biomarkers in Germany

In this section, we will focus solely on the situation and challenges in Germany. Germany is one of the world's most advanced research locations for the development of new radiopharmaceuticals, partly because, in certain exceptions, the use of these products is also permitted outside of an official marketing authorization. However, this does not mean that the products are approved or even reimbursed by the statutory and private sick funds. The decision on the reimbursement of these products for statutory sick funds is subject to the Federal Joint Committee (GER: Gemeinsamer

Bundesausschuss – G-BA). This body evaluates the therapeutic benefit, the medicinal need and the efficiency of a new type of treatment in hospitals (§ 137c Social Security Statute Book V [§ 137c SGBV]) as well as in the ambulatory setting (§ 135 SGB V). Based on the evaluation the committee decides whether reimbursement is justified.
In 2003, the German Federal Associations of Health Insurance Funds (GKV- Spitzenverband) asked the G-BA to evaluate Positron Emission Tomography (PET) for the use in the hospital setting based on § 137c SGB V, followed by a request from the Federal Association for Statutory Health Insurance Physicians (GER: Kassenärztliche Bundesvereinigung -KBV) in 2006. In the same year, the IQWIG was assigned to evaluate PET and PET/CT in several indications (Gemeinsamer Bundesausschuss, 2006).

				Reimbursed in the setting:	
Indication	**Date**	**Evaluated by**	**The benefit of the assessment report?**	**Hospital**	**Ambulatory**
PET for small- cell lung cancer (SCLC)	2008	Committee by G-BA	Positive	Approved primary-, recurrence staging and metastases	Approved primary-, recurrence staging and metastases
PET for non- small- cell lung cancer (NSCLC)	2006/ 2007	Committee by G-BA	Positive	Approved primary-, recurrence staging and metastases	Approved primary-, recurrence staging
PET for head-neck tumours	2011	IQWIG	Negative	Partially approved	Partially approved
PET and PET/CT in recurrent colorectal cancer	2012	IQWIG	Negative (not enough data)	Approved for proving	Approved for proving
PET and PET/CT in malignant lymphomas in children	2013	IQWIG	Negative (not enough data)	Approved for clinical trials	Approved for clinical trials
PET/CT in bone- and soft part tumours	2013	IQWIG	Negative	No decision	No decision
PET, Positron Emission Tomography, CT, Computer Tomography, G-BA, Federal Joint Committee, IQWIG, Institute for Quality and Efficiency in Health Care					

Table 24. Overview of benefit assessment studies being performed in Germany based on § 137c and § 135 SGB V for specific indications of PET and PET/CT.

Based on § 137c (3) SGB V all diagnosis and treatment methods, to which the G-BA has not made any benefit/ reimbursement decision (§ 1) yet, can be unrestrictedly performed in German hospitals, if they offer an alternative treatment and perform according to the rules of the medical art. This highly favourable legislation permits doctors to test and use new and innovative treatment- or diagnostic procedures very quickly. However, if the G-BA comes to a decision, a negative assessment can limit the use of the new technology in a very short time. In the case of PET and PET/CT the G-BA awarded PET for small- cell lung cancer (SCLC) in 2008 and PET for non-small-cell lung cancer (NSCLC) in 2006/07 a favourable opinion and thus enabled reimbursement for hospitals and the office-based sector. In contrast, IQWIG could not find a benefit for the indications PET for head-neck tumours in 2011, PET and PET/CT in recurrent colorectal cancer in 2012, PET and PET/CT in malignant lymphomas in children in 2013, and PET/CT in bone- and soft part in 2013. G-BA did not decide on the latter yet, but partially approved PET for head-neck tumours and allowed proving in the other two indications (see Table 24).
Two comments concerning the reimbursement of RPs in Germany need to be mentioned:

I. PET and PET/CT are just as useful as the underlying radiopharmaceutical can bind to a specific target and improve sensitivity, specificity, Negative Predictive Value (NPV) or Positive Predictive Value (PPV). The evaluation of “PET and PET/CT” in specific indications makes sense if the assessment is linked to a specific RP. Newer, and more effective tracers could substantially change the benefit of PET and PET/CT, and would, therefore, trigger every time another evaluation based on § 137c and §135 SGB V.
II. The G-BA asked the IQWIG to evaluate the benefit of “PET/CT in bone- and soft part tumours”. The assessment report was negative, mainly because of missing evidence due to

a low number of studies investigating the benefit of PET/CT and a lack of comparing- studies focusing on diagnostic accuracy. Neuroendocrine tumours, origin from the neural ectoderm (or neural tube epithelium), should have been included because, according to the definition, they fall into the range of soft tissue tumours. Unfortunately, the IQWIG assessment report did not consider any NET study, thus the extensively researched field of ^{111}In-Octreotate or DOTATATE PET/CT imaging was excluded. Just in one study, used to assess PET/CT as a primary diagnostic tool for bone tumours, the term "neuroendocrine" appeared in the description of tumour pathology. Otherwise, the report solely focused on radiopharmaceuticals based on Fluor such as ^{18}F- FDG and in the end did not find a patient-relevant benefit (lack of not sufficient data) neither a superiority in the diagnostic and prognostic quality compared to standard diagnostic procedures. The conclusion of the IQWIG: lack of not sufficient data and non-adequate study designs/ methodological approaches of the included studies (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2012).

3.7.4 Reimbursement as an area of uncertainty

Reimbursement policies have a far-reaching effect on the adoption and the usage of medical technology (Office of Technology Assessment, 1982) and as a result of investors willing to support R&D activities. Already years back it was predicted that the current coverage and reimbursement might be insufficient to support the development of new technologies (Secretary's Advisory Committee on Genetics Health and Society, 2008). Clarifying areas of uncertainty in regulatory and reimbursement issues will, therefore, facilitate the translation of new pharmacogenomics diagnostic tests into clinical practice (Fackler & McGuire, 2009; Faulkner, Annemans, Garrison, & Helfand, 2012; Secretary's Advisory Committee on Genetics Health and Society, 2008).

The FDA made clear that a new medical imaging agent intended for the indication diagnostic or therapeutic patient management must be able to improve patient management decisions or improve patient outcomes (U.S. Department of Health and Human Services Food and Drug Administration - Center for Drug Evaluation and Research (CDER) & Center for Biologics Evaluation and Research (CBER), 2004). Moreover, even if the imaging probe takes the hurdle of marketing authorisation, it is not guaranteed to get awarded with a sufficient reimbursement rate. As discussed in Chapter 3.2 "Market Size and Potential", newer molecular imaging probes tend to be very target specific with the consequence that the market becomes very small and revenue decreases. Assuming the development costs for an imaging agent is at least $ 200 million, and using the general rule of thumb that the development costs must be equal to the peak yearly earning, this means that in markets with 100,000 cases per year reimbursement must be around $ 2.000/case (Sinusas, Thomas, & Mills, 2011). This is out of sight, given the current cuts in health care spending by various governments.

A worldwide company in the medical imaging and radiopharmaceutical sectors describes the challenges like this:

> "*While these* [access innovative medical Technologies] *challenges vary by country, common challenges include misalignment between the value of a technology and reimbursement levels, cuts in government healthcare spending, higher requirements for evidence of clinical effectiveness for coverage, and opaque and complex reimbursement processes. […] Also, these challenges create disincentives for medical devices companies' innovation because uncertainties about coverage for reimbursement make it difficult to predict whether investments in new technologies will provide sufficient returns.*" (GE Healthcare, 2009)

Based on the US report of the "Committee on State of the Science of Nuclear Medicine" States, the lack of reimbursement and the regulatory obstacles are the most significant barriers for continuing development and the introduction of novel radiopharmaceuticals in nuclear medicine practice (Committee on State of the Science of Nuclear Medicine, 2007). Japan has already adopted their reimbursement policy for medical technology and introduced a new way to assess the cost-effectiveness of these technologies (Hernandez, Machacz, & Robinson, 2015; Shiroiwa, Fukuda, Ikeda, & Takura, 2017). Overall, very few of health technology assessment (HTA) programs have specific methods to assess the clinical and analytic performance, clinical utility, and economic impact of molecular diagnostic technologies (Garfield et al., 2016). It was therefore recommended that HTA organisations should better align with the industry, improve transparency, collaboration, communication, better advise on the required evidence data, and explain the links between the HTA and funding decisions (Garfield et al., 2016).

3.8 Different Goals between Scientific Community and Investors/ Industry

3.8.1 Different goals in Industry- and Academic Research

A cornerstone of any university institution, at least in the fundamental idea back in the early 12th century, is the academic freedom given to Universities in the sense of teaching and research (extended in the early 19th century) (Altbach, 2001; Atkinson & Blanpied, 2008). Academic researchers are more focused on the question rather than the answer, which is fundamentally different to any question asked in business (Cutright, 2000). In this concept of "basic research" the investigator has a different motivation:

> *"Basic research refers to research that is undertaken for its own sake – to advance knowledge; to develop theory; to solve an interesting theoretical puzzle; to address a curiosity of the researcher – without any immediate concern for whether doing so will produce anything "useful" or "practical" or "generalizable."* (Palys, 2008).

The publicly funded basic research is on the one side an essential booster for future innovations (Organisation for Economic Cooperation and Development., 2007), but should also correct "market failure" (Salter & Martin, 2001). Over the last decades, the university system experienced substantial changes in the way of setting objectives in teaching and research. Support by governmental structural funds declined fundamentally, and competitive funds from the industries took their place (Aldo Geuna, 2001). Universities were also encouraged (even by regulations) to collaborate more with private companies and get access to funds through problem-oriented or industry-oriented public programs (A. Geuna & Nesta, 2006; Aldo Geuna, 2001). This tighter collaboration between academic institutions and the industry segment was primarily seen in the field of life sciences, where the research converted from being independent to being fully interdependent and forced to commercialise the research (Powell & Owen-smith, 1998). Data from the US suggests that national funding for health research and development was overhauled by industry sponsoring in the late 1980s (Powell & Owen-smith, 1998). In 1994, around 90% of the US companies doing research in life-science had a relationship with an academic intuition and thus had access to substantial funding (Blerenthal, Causino, Campbell, & Seashore, 1996).

However, some specialities in life science sector, such as nuclear medicine, have not benefited much from this close industry engagement and collaborations. This branch is still highly dependent on public funding for basic and applied research (Committee on State of the Science of Nuclear Medicine, 2007; Schwaiger & Wester, 2011). One possible reason, among many others, is the complexity of the subject,

which is composed of technical, physical and medical knowledge. Without advances in the artificial production of radionuclides in nuclear reactors and accelerators, new chemical processes for synthetisation and new scanner technology, nuclear medicine would not be at the stage it is now (National Research Council (US) et al., 2007).

If we remember that academic research is focused on curiosity and the generation of knowledge, it is not surprising that the research objectives are substantially different to the industry. For the individual academic investigator a publication in prestigious journals is a way to receive recognition, enhance his/her job prospects and receive other beneficial goods and services (Committee on Responsibilities of Authorship in the Biological Sciences, 2003). Academic researchers typically publish numerous publications in a short time (Laterre & Francois, 2015), which of course has some influences on the quality of the research results, ranging from good, bad, unnecessary or distorted (Evans, Thornton, Chalmers, & Glasziou, 2011). Academics are also more likely to address the efficacy of an intervention or drug in a more severe patient group, with higher mortality risk and unmet clinical need (Laterre & Francois, 2015). These clinical trials are usually more prominent in size, involve a wide range of patients and try to answer a medical question rather than gathering data for regulatory approval (Institute of Medicine (US), 2010). Typically, academic sites have limited access to resources specialised in clinical trial organisation/ management, lack investigator research knowledge, have problems in executing research ideas and may not be familiar with the extensive regulatory requirements (Croghan et al., 2015). In biomedical and public research, and not explicitly in academic research, study designs are quite often not appropriate, sophisticated statistical methods are not used adequately and reproducibility is poor (Ioannidis et al., 2014).

Unfortunately, many data from academic institutions are not sufficient in quality to back up the safety and efficacy evaluation of new molecular entities in the marketing authorisation process. A good example is the case of DOTATATE and the FDA´s opinion on the quality of the (so far) conducted, academic clinical trials:

> In July 2015, the applicant (Advanced Accelerator Application- AAA) handed in an NDA to the FDA including a review of scientific literature and one single centre study from Vanderbilt University Medical Center to support the clinical efficacy of NETSPOT (kit for the preparation of Gallium Ga 68 Dotatate injection). Unfortunately the reviewers from the FDA noticed that none of the five studies (Deppen, Liu, et al., 2016; Haug et al., 2012, 2014b; Hofman et al., 2012; Srirajaskanthan et al., 2010) *"contained randomised, prospective trials with independent blinded image review designed for drug development. Furthermore, they assessed incomplete information in the articles did not allow one to determine precise diagnostic test performance (sensitivity/specificity) or to evaluate the role of the new imaging information on patient management and patient outcome".*
>
> The reviewers recognised that the overall scientific literature supports the product efficacy, but mentioned that the level of evidence is generally low. They criticised the studies designs, mentioned a patient selection bias and incomplete ascertainment of false positive rates. The reviewers concluded*: "These data although insufficient for the indication proposed by the sponsor, appear to support an indication similar to that for OctreoScan, i.e. localisation of tumours in patients with NETs."* (Center for Drug Evaluation and Research, 2016).
>
> In a follow-up meeting, the FDA explained that *"[…] it expects to rely on evidence from adequate and well-controlled trials for diagnostic and patient management claims for imaging drugs. […]", and mentioned "[…] that the agency has an interest in using data from the real clinical world experience for NDAs. This application provides an example of the challenges with this approach. […] DMIP (note:*

Division of Medical Imaging Products) has developed guidance for imaging standards and actively encourages standardising product manufacturing and specifications for investigational drugs and the use of uniform clinical protocols." (Center for Drug Evaluation and Research, 2016).

No further documentation on the clinical efficacy discussion concerning the proposed indication is available. The necessary bridging study was performed by the Vanderbilt University Medical Center and was satisfying about safety, efficacy, and dose response in the U.S. ethnic group.

This discussion highlights very well the different beliefs in "good quality" clinical trials and the challenge of complexity in clinical trial design. The regulatory agencies favour precise research plans, using randomised, prospective clinical trials with a systematic patient- and data monitoring. Academic research site may therefore never be able to contribute to "satisfying" clinical evidence for the FDA, as academic sites face the challenges of limited resources for medical research, reduced funding- and increasing costs for conducting clinical trials (Larkin et al., 2011; Sertkaya, Wong, Jessup, & Beleche, 2016). Furthermore, there is a lack of formal training, promotional opportunities and an unpleasant allocation of workload for the research coordinators (Larkin et al., 2011). So even if academic institutions are willing to make changes to their study design and adapt the objectives, it may still not reach the regulators requested level.

3.9 Limited Knowledge in the Scientific Community, outside the Nuclear Medicine Community

The number of nuclear medicine procedures is continuously rising from 23.5 million (1980 - 1984) to 37 million in the time from 1997 to 2007 (The United Nations Scientific Committee on the Effects of Atomic Radiation, 1988, 2008). The future even looks better: molecular imaging could improve cancer care through early detection and guide effective treatment (Hussain & Nguyen, 2014), and radionuclide targeted therapy shows promising results in end-stage cancer diseases (Bodei, Pepe, & Paganelli, 2010; Fendler et al., 2017; Rahbar et al., 2017; Rhee et al., 2016; Strosberg et al., 2017). Also, the successful implementation of ^{223}Ra-dichloride for castration-resistant prostate cancer created high awareness and had a boost for the nuclear medicine community (Fahey, Zukotynski, Capala, & Knight, 2014).

Previously, the benefits of nuclear medicine procedures in cancer detection and therapy were not widely acknowledged outside the nuclear medicine community (Zimmermann, 2013). This may have also been based on a general controversy and disagreements among scientific, technical or medical experts. In any medical discipline, the decision-making process became more complicated over the years also due to the sheer volume of information regarding risks, benefits, costs and preferences (Hunink et al., 2014). Many new treatments promise to improve the outcome for many conditions, but they may be "half-way" technologies as they improve, but do not cure (Hunink et al., 2014).

However, decisions in healthcare generally have significant implications, and therefore knowledge and evidence is the basis for every choice:

> *"In a decision analyses process we first make the problem and its objectives explicitly; then we list the alternative actions and how these alter subsequent events with their probabilities, values, and trade-offs; and finally we synthesise the balance of benefits and harms of each alternative."* (Hunink et al., 2014)

In the medical field, the most important evidence derives from the concept of evidence-based medicine (EBM). It combines the individual expertise with the best available external clinical evidence from systematic research (Sackett et al., 1996; Sackett, Rosenberg, Gray, Hynes, & Richardson, 1997). It is

basically a translation from knowledge, starting with “creation” via primary research (e.g. randomised controlled trials), to “distillation” via implementation of recommendations in systematic reviews and guidelines, and the step “dissemination” via the appearances in journals and presentations (Straus, Ma, & Graham, 2009). In the step distillation, the knowledge from EBM is formed into clinical practical guidelines (CPGs) with the intention to guide physicians, educators, and healthcare practitioners on how to prevent, diagnose, treat and manage diseases, disorders, and other health conditions.

> *“Clinical practice guidelines are statements that include recommendations intended to optimise patient care that is informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.*” (Institute of Medicine (US), 2011).

CPGs should set a standard of quality, allow measuring performance and assess the services delivered (Institute of Medicine (US), 1990). Both, EBM and CPGs have become an essential foundation for the international healthcare community in the 1990s and beyond (Lohr, Eleazer, & Mauskopf, 1998), even such guidelines existed in many European countries for much longer (Woolf, Grol, Hutchinson, Eccles, & Grimshaw, 1999a).

The principal aim of CPGs is to improve the health outcome for patients, the quality of clinical decisions for the physician and the efficiency of the healthcare system (Woolf, Grol, Hutchinson, Eccles, & Grimshaw, 1999b). A comprehensive literature review by Smith & Hillner (2001) demonstrated that evidence-based guidelines in cancer care could optimise the length of stay, reduce complication rates and also financial outcomes. Other studies showed a significant improvement in the process of care (Grimshaw et al., 1995, 2006; Grimshaw & Russell, 1993) and an improvement of patient outcome (Grimshaw & Russell, 1993; Nuffield Institute of Health, Centre for Health Economics, & NHS Centre for Reviews and Dissemination, 1994). Not only did CPGs influence the physicians treatment decision, but they also affected payers in their reimbursement decisions and slowed down the excessive rise in healthcare expenditures (Institute of Medicine (US), 1990; Schaaf, Seashore, & Randolph, 2015; Steering Committee on Quality Improvement and Management Classifying, 2004; U.S. Preventive Services Task Force, 1989). However, the amount of studies investigating the effect of guidelines on the individual patient outcome is weak and less convincing (Lugtenberg, Burgers, & Westert, 2009).

3.9.1 The Effect of Clinical Practice Guidelines on Nuclear Medicine Awareness

In the case of DOTATATE, guidelines for NETs have not been multidiscipline for a long time. They primarily focused either on clinical aspects (e.g. surgical procedures in specific tumour types) or tumour markers (Sturgeon, 2002). In 2001, the first multidiscipline guideline for diagnosis and therapy of MEN 1 and 2 (Brandi et al., 2001) was published, followed by the recommendations for carcinoma of unknown primary sites in 2003 (Bugat et al., 2003) and guidelines for the management of gastroenteropancreatic NETs in 2004 and 2005 (Kjell Öberg, Astrup, et al., 2004; Ramage et al., 2005). In 2004, the European Neuroendocrine Tumour Society (ENETS) published their first consensus statement on guidelines for diagnosis and treatment of neuroendocrine gastrointestinal tumours (Plöckinger et al., 2004). Most of these guidelines evaluated the use of ^{111}In- Octreotide as a diagnostic tool, but it was only recommended as a supplement to CT, MRI and EUS in some instances (Brandi et al., 2001; Kjell Öberg, Kvols, et al., 2004; Plöckinger et al., 2004; Ramage et al., 2005). One of the reasons may be the low number of prospective, randomised controlled trials. Even for newer RPs the data from RCTs are still low, but the nuclear medicine community still achieved to work out the diagnostic benefit of somatostatin- receptor imaging (^{111}In- Octreotide with SPECT and ^{68}Ga DOTA-TATE, -TOC, - NOC). In many of the current CPGs dealing with NETs, the use of scintigraphy is recommended (Janson et al., 2014; Öberg, Knigge, Kwekkeboom, & Perren, 2012). ENETS acknowledges the data from large series,

indicating a positive finding in many patients with certain primary tumours. Nevertheless the evidence to routinely recommend scintigraphy in high-grade gastroenteropancreatic NETs and neuroendocrine carcinomas is missing (Garcia-Carbonero et al., 2016). The current CPG for neuroendocrine tumours from the U.S. National Comprehensive Cancer Network (NCCN) does also not recommend the use of ^{111}In- Octreotide as a first line diagnostic procedure, but it may be used in appropriate cases (Kulke et al., 2015). In contrast to the European- and International working groups, the NCCN does not mention any of the new RPs being based on DOTA and used in PET and PET/CT (Kulke et al., 2015). Those working groups strictly follow the concept of evidence-based medicine, as it is currently the best available evidence in making clinical decisions (Lewiecki & Binkley, 2009). RCTs are the highest level of evidence (Abel & Koch, 1999; Byar et al., 1976; Hill & for International Organisations of Medical Sciences, 1960), thus a better awareness of the efficacy of nuclear diagnostic procedures can currently only be achieved via additional research evidence from prospective RCTs, such as the NETTER trial (Strosberg et al., 2017).

3.10 Special Manufacturing, Distribution and Handling of Radiopharmaceuticals:

3.10.1 Manufacturing:

The majority of radioisotopes used for nuclear medicine are artificially produced, either in a nuclear reactor, a nuclide generator or in an accelerator. Approximately 80% of all diagnostic procedures use the radionuclide Tc- 99m, which is obtained from the reactor-produced radionuclide Mo- 99 (Krijger, Ponsard, Harfensteller, Wolterbeek, & Nijsen, 2013). Worldwide only eight reactors (NRU in Canada, HFR in the Netherlands, BR2 in Belgium, OSIRIS in France, MARIA in Poland, LVR-15 in the Czech Republic, SAFARI in South Africa and OPAL in Australia) can produce Mo-99 for Tc-99m generators. These eight reactors also produce the majority of other medical radionuclides used for targeted therapies (e.g. Yttrium-90, Lutetium-177, Rhenium-188) and brachytherapy (e.g. Cobalt- 60, Iodine- 125, Iridium- 192) (Krijger et al., 2013). There are seven additional reactors in the USA, Russia, Germany and Korea, Argentina and Indonesia which are capable of producing medical radioisotopes, plus some research reactors which could be upgraded. However, these upgrades are costly and time-consuming and may not be worth it from a logistic and cost-effective perspective. The main bottleneck is not the reactor capacity, but the low number of processing facilities capable of dissolving the irradiated targets and extracting the radionuclides of interest (Krijger et al., 2013).

With regards to the production of Mo-99, the Nuclear Energy Agency (NEA) and Organisation for Economic Co-operation and Development (OECD) implemented a Full Cost Recovery (FCR) and Outage Reserve Capacity (ORC) policy in 2009, encouraging supply chain participants to continue producing Mo-99 and reward them with full cost recovery. These additional costs should be covered by governments via higher reimbursement rates (High-level Group on the Security of Supply of Medical Radioisotopes, 2014). Besides the production in reactors, several research groups are investigating how accelerators could be used for the production of these reactor-based radionuclides to secure the future supply of these radionuclides (Abbas et al., 2009; Mushtaq, 2012; Schmor, 2011). Another strategy is the substitution of reactor-based radionuclides with non-reactor radionuclides. However, the medical community and industrial partners first need to evaluate feasibility (Internal European Commission Ad Hoc Interservice Group, 2009).

3.10.2 The Challenge of Distribution and Logistics

The literature also suggested that logistics may be a major concern for potential investors (Zimmermann, 2013). Typically, the radionuclides used for imaging and therapy have a short- or medium half-live. While a rapid distribution is essential for diagnostic PET radionuclides, there is significantly more time for radionuclides used in therapy. However, these products are more time sensitive and require a well-organised production process and a secure, reliable and cost-efficient distribution network (Dash, Russ, Jr, & Pillai, 2013; Internal European Commission Ad Hoc Interservice Group, 2009).

Regulators are concerned about the potential hazardousness element of transporting radioactive material and have thus implemented special requirements (*IAEA Regulations for the Safe Transport of Radioactive Material (No. TS-R-1); UN Recommendations for the Transport of Dangerous Goods (Orange Book) and the modal regulations and agreements (e.g. ADR, RID, ADN) of the specialised international transport organisations; Community Regulations and Directives; a variety of international conventions, codes and agreements and of course country-specific National provisions*) to protect people, property and the environment (Internal European Commission Ad Hoc Interservice Group, 2009). Even transport costs usually have a minor part in total costs of production, logistics and handling of medical radioisotopes (World Nuclear Association, 2017), country-specific requirements can have a substantial impact on effort, time and technical and financial resources (Internal European Commission Ad Hoc Interservice Group, 2009).

> "*[…] there are indications that insufficient standardisation of international shipment standards or transport containers lead to repeated delays or denials with all related socio-economic consequences. Further, reduced commercial incentives for airlines to carry radioactive substances result in fewer carriers and fewer routes than historically available.*
>
> *The denial of shipment by some carriers, seaports and airports is a major issue for users of radioactive materials. There are problems with all modes of transport sometimes due to the perception of possible hazards rather than the reality."* (Internal European Commission Ad Hoc Interservice Group, 2009).

Compared to the transportation of conventional pharmaceuticals, this additional effort and cost-burden is significant, requires specialised knowledge and may quench investors.

3.10.3 Handling:

Radiopharmaceuticals typically consist of a bioactive molecule, which can be prepared in advance, and a radionuclide with a short half-life, which needs to be labelled to the molecule by a qualified person shortly before application. In Germany, this labelling process is (§ 13 (1a) AMG) not seen as a reconstitution-, but a "production" process (Bundesministerium der Justiz und für Verbraucherschutz, 2017).

Clinical sites preparing RPs on site are therefore categorized as a production facility and need to comply with the codes of current good manufacturing practices (cGMP), national/regional health authority´s regulations, effective quality assurance, quality control, the employment of qualified personnel and the use of authorised equipment (International Atomic Energy Agency, 2008). In Germany these requirements are stringent and governed in numerous regulations such as the Medicinal Products Act (Arzneimittelgesetz- AMG); the Pharmacy Practice Order (Apotheken Betriebsordnung –ApBetrO), The Ordinance of Radioactive Pharmaceuticals or Pharmaceuticals treated with Ionising Radiation (Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel - AmRadV),

provision governing the manufacture and distribution of pharmaceuticals and agents (AMWHV) and the radiation protection regulation (Strahlenschutzverordnung – StrlSchV).

All industrial, nuclear, chemical/radiopharmaceutical and clinical institutions producing radiopharmaceuticals, positron RPs, radioactive precursors and radionuclide generators need to follow those regulations (Deutsches Bundesministerium für Gesundheit, 2009). GMP is obligatory for the processes of chemical syntheses, purification, formulation and preparation and the aseptic step production or final sterilisation (see European Commission, 2017). Facilities preparing RPs for public pharmacies and hospital pharmacies need a production license (§ 13 AMG), specialised and expensive equipment, clean rooms and highly educated personnel (Bundesministerium der Justiz und für Verbraucherschutz, 2017; Bundesministerium für Erwelt Naturschutz und Reaktorsicherheit et al., 2017; European Commission, 2017).

Type of production	**Not GMP**	**GMP Part II & I (upward) including relevant supplements**			
Radiopharmaceuticals	Manufacturing process in a cyclotron or a reactor	Chemical syntheses	Purification steps	Formulation and preparation	Aseptic preparation or final sterilisation
PET Radiopharmaceuticals					
Radioactive Precursors					
Radionuclide Generator	Manufacturing process in a cyclotron or a reactor	Processing			

Table 25 Requirements for the production and handling of radiopharmaceuticals including precursors and generators.

Consequently, the manufacturing, handling of radionuclides demands knowhow, time, investment and highly qualified employees. Due to the individual national & international regulations, the number of sites owning the equipment to manufacture and process radioactive products is limited.

4 Empirical Results:

In this section, we will analyse the data from the semi-structured interviews with the various stakeholder groups. For better readability, we have decided to include only representative statements in this chapter, all summarised statements can be read in the appendix.

4.1 The Role of Imaging

Definition:

Biomedical imaging is one of the main pillars of comprehensive cancer care and has a substantial effect on the treatment and management of patients. In the clinical use, the application of imaging ranges from prediction to screening, biopsy guidance for detection, staging, prognosis, therapy planning, therapy guidance, therapy response recurrence, and palliation (Fass, 2008). Moreover, imaging is also used in research and development. Many major drug companies recognised the potential of imaging in the R&D process, established their own in-house imaging programs, and are using different imaging techniques in their preclinical and clinical programs (Higgins & Pomper, 2011a).

A Nuclear Medicine Physicist´s view:

"Because what is used so far are indeed methods that rely on biopsy or on local tissue samples, or just on primary tumor preparations.... But certainly in the course of pretreatment the tumor pathology already changed. That means we have in principle no real-time procedures, which can show the entire tumor biology. At the same time, of course, this is the power of imaging, especially biomarker-driven imaging. You can visualize, quantify in a non-invasive way in real time, throughout the body, in all lesions and not just a part of a tumor."

An Oncologist´s view:

"My estimation, functional imaging will further develop… what I have seen until now is fascinating… probably it will also save costs, many people have not recognized this yet. If we have the chance to avoid therapies in patients, stop a pointless therapy and start with a more sensible therapy, by using functional imaging or another method, this would definitely be economical meaningful."

A view from the Radiopharmaceutical Industry:

"It is all about the impact on whether the patients getting the appropriate therapy. And some of these therapies are quite expensive... Xofigo is a good example. So Xofigo it is quite expensiv...Bone scans are not desperately sensitive, so you know if you do bone scans and 10% of the patients are positive, but actually the real data from a PET scan, which show that 20 to 25% of those patients already had disease already in the bones ...So assuming you have positive bone scan then you got Xofgio, well if you had a different scan that meant to see twice as many patients, and then you clinical trial outcome should be better. I think."

A view from the Pharmaceutical Industry:

"Themain reason why we developed this imaging agent was as a research tool....biopsies are fine... but we want to see how that changes in time, over treatment....so we want to look at those kind of research questions and want to understand what changes... the nice things about imaging is, you cannot look at just one tumor you cannot just look of parts of the tumor, you can look the whole tumor and at more tumors throughout the body. And the hope is that this would be more valuable and it would do a better job in predicting patients response, but this is true or not time will tell."

Figure 16: Selected comments on the role of imaging biomarkers from interviewed stakeholders

The findings from the relevant stakeholder groups (Nuclear Medicine Physicists, Oncologists/ Specialists, Pharmaceutical Industry, Radiopharmaceutical Industry) overall suggest that the use of Imaging plays a pivotal role, in either the clinical patient management or within the R&D efforts of the industry.

All statements regarding this topic are in the appendix on page 200

I. The Nuclear Medicine View:

	Strong Pro	Neutral	Strong Contra
Value of imaging/in-vivo imaging biomarkers?			

As expected, nuclear physicians have rated the value of imaging in the patient management process very high. All interviewees see a higher impact of in-vivo imaging biomarkers compared to in-vitro biomarkers, especially because imaging is more precise in the location of the region of interest.

> *"And the therapeutic goal is usually not the treatment of the entire organism, but the treatment of a certain target region. In such a case, imaging is the more accurate biomarker method compared to an in-vitro assay taken from the blood. "*

Currently used methods such as biopsies, local tissue samples or primary tumour preparation show a local pattern of the disease, but not the overall heterogeneity and the disease dissemination.

> *"Because what is used so far are indeed methods that rely on biopsy or local tissue samples, or just on primary tumour preparations. However, certainly, in the course of pre-treatment, the tumour pathology already changed. That means we have in principle no real-time procedures, which represent the biology of an entire tumour."*

Overall, the interviewee´s pro arguments for in-vivo imaging biomarkers correspond with the arguments stated in the literature: precise localisation and characterisation of individual regions and organs, real-time visualisation and quantification, non-invasiveness et cetera (e.g. Carter, Halpenny, Ginsberg, Papadimitrakopoulou, & de Groot, 2017; MacFarlane, Shah, Wysong, Wortsman, & Herphreys, 2017; O´Connor et al., 2017; O´Connor et al., 2015).

II. The Pharmaceutical Industry´s View:

	Strong Pro	Neutral	Strong Contra
Value of imaging/in-vivo imaging biomarkers?			

Also, the Pharmaceutical Industry has a noticeable interest in imaging biomarkers, but almost exclusively for Research & Development efforts. All of the interviewees had a favourable opinion of molecular imaging and the benefit of their R&D process.

> *"But regarding an internal decision making we are using a number of these molecular ligands, and we have a very extensive back program where we are trying to develop ligands…. So we are using it for R&D decision making right now, for proof of mechanism on tissue markers, understand the distribution, understanding dosing. There are numbers of ways we are using radiopharmaceuticals…."*

One interviewee specified an example where molecular imaging is especially beneficial: e.g. proof of mechanism, proof of principles, proof of concept, and finding the dosing for Phase II. They mainly wish to get several questions answered which have a fundamental impact on R&D- attrition rates, success, and spending: "*Does the drug hit the target? Does it engage with the target? Does it modulate the downstream physiology?*"

Another remarkable note came from one top executive from a big pharmaceutical company:

> *"I can remember sitting at a top meeting one time and talking to one of our colleagues from [Big pharmaceutical company A], and that was actually before I was here, and someone from [My*

Company] was saying „if we did this, and we tried, we knew we hit the target, and so when the study failed we walked away from it". And she talked to me and said „you know at [Big pharmaceutical company A], we did four clinical studies because we thought we did not hit the target hard enough, it was this and that, and we kept trying. And we had not got the target engagement via PET tracer. We would have been walking away after the first failure."

Another interviewee reported that they had a close race with a competitor on a similar indication, but lagged behind. To catch up, they decided to use a diagnostic test to enrich the population. In the first two indications this helped to gain quick approval, and since there was a high disease prevalence, the enrichment had no adverse effect on their market potential. However, in the third indication, they observed a drop in the market potential.

"... when we were doing the advanced NSLC … we had a limited population that we could have the drug available for. Because we selected…. Whereas [our competitor] has spent the program for several years and they will be able to show that it worked in all the patients… So that kind of set us back for a little bit … oh, Jesus look what have we done? We have anchored ourselves…"

However, since they have put much work into the characterisation, application of the technique, and information gathering, they went again for the highly enriched population and could once again show a clear benefit.

"When we got our first line [therapeutic]*, we went again for the highly enriched population, we had shown a clear benefit, whereas* [our competitor] *didn´t do that. They went for a much lower bar, they did not look for the higher population, and their NSLC was a complete failure.* [2] *So obviously this was a big win and all of a sudden, wow Juhu the diagnostic is really, is critically important."*

III. The Radiopharmaceutical Industry´s View:

	Strong Pro	Neutral	Strong Contra
Value of imaging/in-vivo imaging biomarkers?	◆		

As expected, the interview partners of the radiopharmaceutical industry valued the clinical usability in patient management very highly.

"MRI and CT see the disease in about 15% of cases, [product name] sees the disease in about 70% of cases. And for that particular disease, the location of the disease had quite an impact on patient treatment… radiotherapy is expensive and hurt patients and some are getting inappropriate radiotherapy because the disease is already in the bones."

The interviewees acknowledge opportunities for these products in disease areas such as cancer, cardiology and neurology, with higher prospects for the latter ones.

"There are huge opportunities still in cardiology, I tend to think that cardiology and neurology are better."

Nevertheless, the interviewees are also well aware of the challenges and barriers of these products, and how this affects the implementation in the clinical patient management process, and their revenue.

IV. The Medical Specialist´s View:

[2] Note: What the interviewee is referring to is the cutoff for PD-L1 positivity of ≥ 50%, whereas competitors have been using 1 % to 5%. The therapeutic was consequently approved for the treatment of advanced NSCLC patients whose tumours test positive for PD-L1 using a specific assay (Dang, Ogunniyi, Barbee, & Drilon, 2016).

	Strong Pro	Neutral	Strong Contra
Value of imaging/in-vivo imaging biomarkers?			

Advanced imaging is also rated very highly by oncologists/ medical specialists, especially when the site of the tumour has a therapeutic consequence.

> *"But if the patient has any consequence from the localisation of a tumour, which cannot be shown with Liquid Biopsy, then it is of course just a question of tumour "yes" or "no". Or what kind of genetic alteration or mutation does the patient have. … And if this results has any kind of consequence… imaging with the appropriate sensitivity and specificity is still indispensable."*

However, our interviewees would not generally favour imaging, but would consider all available biomarkers which are able to solve the problem.

> "*It depends on the problem! I would say that if it is just about verifying therapy response… and everything else is not from interest, then you could wave imaging.*"

One experienced urologist explained that the in-vitro biomarker PSA (Prostate Specific Antigen), they have been using for decades, is easy to apply, cheap, and often very helpful. However, sometimes the treatment is not goal-oriented (in this case he refers to patients with biochemical recurrence) as the PSA rise cannot be assigned to a particular location. In consequence, the patient will receive systemic therapy.

> *"…that was not a target-oriented treatment, but it was shooting into the forest, with a great deal.*"

In the future oncologists/ specialists generally expect an even more precise localisation of metastases (distant- and lymph node metastases), mapping of the affection in a local tumour and consequently influence on the surgery planning with (evolving) imaging techniques. All physicians (100%) anticipate a combination of in-vitro and in-vivo imaging biomarkers.

> *"I believe the added value lies in the reasonable combination of both. I do not think that one will replace the other. But a combination of both will then be able to represent the best possible status of the patient.*"

V. Brief conclusion on "The Role of Imaging":

Overall our qualitative research results support the current opinion about imaging in the clinical routine and the value in R&D. Interviewees from the Nuclear Medicine area, Oncologist/ Specialist, and Radiopharmaceutical Industry emphasise the impact of imaging on patient management, and the need for further development. The pharmaceutical industry is pleased to have research tools with high sensitivity and specificity, which enables them to get an earlier and better insight in pharmacokinetics, pharmacodynamics, target binding and enrichment for clinical trials. It is conspicuous that there isn´t a real overlap between the physician´s and the industry´s area of application. The pharmaceutical industry made it very clear that they are not very enthusiastic about the commercialisation of these intrinsic imaging biomarkers.

4.2 Radiopharmaceuticals

In this section, the results are focused on radiopharmaceuticals, aiming at answering the reasons why investors are not willing to invest in the area of in-vivo, nuclear medicine imaging biomarkers and what attributes weight in the decision-making process?

There were numerous wide-ranging opinions of the interview participants, which we have coded in units and then grouped into categories as described in the methodology section. These challenges can be roughly divided into the areas of development, economics, regulations and technology. As in the previous section; the data is subdivided according to the stakeholder groups. The statements will show the stakeholder´s perspectives on the main barriers and challenges associated with the approval, commercialisation and use of diagnostic and therapeutic radiopharmaceuticals.

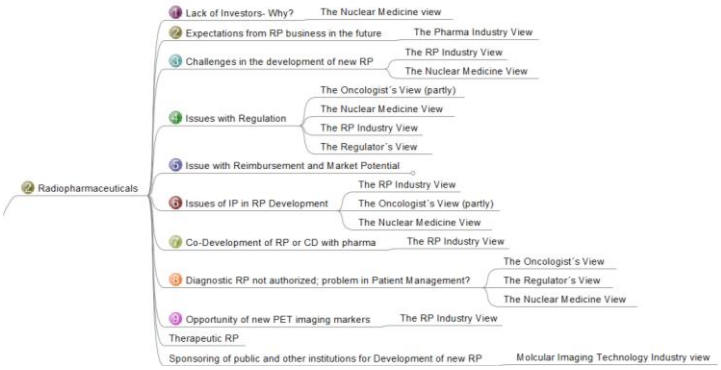


Figure 17 shows the coded topics, which have been extracted based on the interviewees responses.

An important detail: The data presented in Chapter 4.2 is linked to stand-alone in-vivo diagnostic agents/ in-vivo imaging biomarkers, the Chapter 4.3 dealing specifically with companion diagnostics. It is essential to differentiate between those responses as imaging biomarkers are subject to different utilisation, regulation, market potential and thus interest from the investors (Table 26).

Categorization of Imaging Biomarkers	
In-vivo Diagnostic Agents:	United States of America: *Medical imaging agents are generally governed by the same regulations as other drugs or biological products. However, because medical imaging agents are used solely to diagnose and monitor diseases or conditions as opposed to treating them, development programs for medical imaging agents can be tailored to reflect these particular uses* (U.S. Department of Health and Human Services Food and Drug Administration -Center for Drug Evaluation and Research (CDER) & Center for Biologics Evaluation and Research (CBER), 2004). Europe: *Diagnostic agents are medicinal products used for diagnosis or monitoring of a disease. The evaluation of diagnostic agents is governed by the same regulatory rules and principles as for other medicinal products. The principles used for the evaluation of medicinal products with respect to quality, pharmacology, toxicology, pharmacokinetics and safety apply to diagnostic agents. However, since diagnostic agents are used to diagnose and/or monitor diseases/conditions and not intendent to treat, the clinical development programs should be adapted for these purposes* (European Medicines Agency- CHMP, 2009).
Complementary Diagnostic:	A test, which is not essentially associated to the safe and effective use of a drug. The test identifies a biomarker-defined subset of patients that respond differentially to a drug and aids in the risk/benefit assessment for individual patients (Beaver et al., 2017).
Companion Diagnostic:	*A companion diagnostic is a medical device, often an in-vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps to determine whether a particular therapeutic product is beneficial for the patient and will outweigh any potential serious side effects or risks* (U.S. Food and Drug Administration, 2018a).

Table 26: Differences between in-vivo diagnostic agents, Complementary Diagnostic and Companion Diagnostic as defined by the Food and Drug Administration in the US, the European Medicine Agency in Europe and the literature.

4.2.1 Issue with Reimbursement

The reimbursement of molecular imaging procedures is globally very heterogeneous regulated, especially in PET/CT the coverage policies are variable and restrictive. Within the last years, there was increased coverage of oncological indications in the USA due to the "coverage with evidence development" (CED) program, whereas in the European Union the coverage still varies considerably and creates uncertainty (Fischer et al., 2016). Reimbursement policies have a far-reaching effect on the adoption and the usage of medical technology (Office of Technology Assessment, 1982), and consequently on the investor´s interest.

A Nuclear Medicine Physicist´s view:

"Yes, reimbursement is a huge problem, clearly. Reimbursement of costs is one of the main limitations for PET overall."

A view from the Radiopharmaceutical Industry:

"I think getting products reimbursed is the biggest challenge in Europe. Governments like to pay, just from a PET scan basis, governments like to pay for PET scan as an FDG rate."

A view from the Molecular Imaging Technology Industry:

"What one of the obstacles we are facing, at least in the US, we still have an automatic "No" from Medicare for any tracers outside of oncology. So the recent two approvals the Ga-DOTATATE and Axumin are both oncologic tracers so they went to local coverage decisions and got reimbursement. But let´s say we have a new tracer for Alzheimer, infection or heart disease we still have a standing policy of automatic no coverage, unless you got a full national coverage decision and that´s quite a daunting obstacle that is in the way."

A Pharmaceutical Industry´s view:

"Right, the question is from the payer's perspective "how much better does it have to be to make it worth to pay for it?" For their perspective that added cost has to take out costs out of the system somewhere else. They don´t want to pay more to get the same result, they want to pay less to get the same result."

Our empirical data suggests that reimbursement uncertainty is a challenge for the stakeholders who are developing radiopharmaceuticals, but also for the physicians using them. Nevertheless, the interviewees agree that the efficacy of new medical technology needs to be evaluated objectively before general reimbursement is granted. The criticism is more related to the heterogeneity in evaluation criteria, the extent of data requested and the speed at which a request is handled.

All statements regarding this topic are in the appendix on page 201

I. The Nuclear Medicine View:

	Strong Pro	Neutral	Strong Contra
Is Reimbursement a Challenge?	◆		

Typically, it is in the interest of the marketing authorisation holder to timely develop a strategy for product reimbursing in the key markets. However, since the development and authorization of RPs remains with the academic institutions, those are also responsible for getting appropriate reimbursement rates. Therefore, it is not surprising that four out of seven (57%) EU nuclear medicine physicists called reimbursement of RP unsolicited as a challenge.

> *"Yes, reimbursement is a huge problem, clearly. Reimbursement of costs is one of the main limitations for PET overall."*

The interviewees acknowledge the fact that the lack of an official marketing authorisation status also profoundly affects the reimbursement of these products.

> *"The non-authorisation and the reimbursement goes hand in hand. So under our current legislation, the admission is not fundamentally the problem, but due to the lack of admission, there is no refund. You can turn as you want, ultimately it is about that: it has to be paid in some way. "*

The majority of interviewed experts believe that there is sufficient clinical evidence to demonstrate the substantial effect of PET on diagnostic accuracy and patient management in specific indications. Therefore those procedures should be reimbursed by the health insurances.

> *"…and based on the German Social Code V PET/CT is actually a compulsory service of the statutory health insurance, in the pre-stationary area…. However, the health insurance companies simply refuse to pay the costs, and this sometimes leads to difficulties. So the patients have to file applications, the health insurance companies reject that in part, then contradictions are filed. This is sometimes a bit of a hassle, but it is just a relatively small part of the patients we are currently looking after. However, it could be easier. It would also make things easier, especially if the federal committee, which is responsible for approving or payment of RPs, would work a little faster."*

II. The Pharmaceutical Industry View:

	Strong Pro	Not mentioned	Strong Contra
Is Reimbursement a Challenge?	*One interviewee (33%) acknowledges the challenge, 66% no answer*		

Experts from the pharmaceutical industry have a good understanding of the pros and cons of imaging in the clinical workup. However, concerning the topic of reimbursement only one interviewee (33%) sees this as a challenge, the other two interviewees (66%) did not respond to this question. The interviewee who commented on this question primarily focused on the low reimbursement rate:

> *"…the margins are very low in diagnostics, there is more money in therapeutics, and we focus on the diagnostics we need to get the therapeutics approved and to people."*

Another interviewee did not refer to challenging reimbursement rates for the marketing authorisation holder, but to the high costs associated with imaging test in general. So the reimbursement rates, from a payer´s perspective, are substantially higher compared to in-vitro biomarker test which in fact could affect the number of users.

> *"And when you think about an imaging diagnostic test, it is a lot more expensive than that [in-vitro diagnostic test]. So the added value must be substantial … Right, the question is from the payer's perspective "How much better does it have to be to make it worth to pay for it?" From their perspective, that added cost has to be taken out of the system somewhere else. They do not want to pay more to get the same result; they want to pay less to get the same result."*

Another statement is leading in the same direction.

> "*From a business point of view: if the drug is cheap then they can afford to prescribe it to a lot of people, who won´t benefit as long as they are not harmed… And so tumour mutations has been a very productive area for cancer research, and in that area, you have to accept that imaging has a very difficult battle to fight. Because in many cases you can see these mutations in circulating free DNA…. Then if you have a 50 Euros test based on a blood sample, why would*

you use a $1,000 test based on nuclear medicine? And from the payer's point of view: if the drug does not cause harm, you are maybe better off treating more people Including those who do not benefit, then having a very expensive test to stratify."

There is a double burden for the developers of an in-vivo diagnostic test: a low margin and pressure from health insurance funds due to the relatively high cost compared to in-vitro test.

III. The Radiopharmaceutical Industry View:

	Strong Pro	Neutral	Strong Contra
Is Reimbursement a Challenge?	◆		

The expert´s response is distinctive: 100% of the respondents see the reimbursement of the products as a great challenge, at least for the European market. The interviewees made clear that there are two markets to compete: one in the USA, with reasonable pricing and reimbursement, and secondly the European Union, with less favourable reimbursement rates.

> *"No, I do not think so* [that it is a challenge in the US]*. I think they* [diagnostic products] *will not receive the reimbursement of a therapy… I think diagnostics will be appropriately reimbursed unless there are major changes in the structure of the US market. However, for Europe, it is probably the case. The average price of an oncology drug in Europe is 30% of the price in the US. And reimbursement of SPECT and PET scans are in most European countries, meaning the reimbursement of the pharmaceutical part, is under pressure. In fact, in some countries, there is no reimbursement of the pharmaceutical part but only the cost of the actual scan, the imaging part is reimbursed. And that is a problem. So two parts for that: No, not worldwide but yes in Europe."*

Heterogeneity in the reimbursement of PET for various indications creates uncertainty for investors. The interviewees made clear that a high portion of their investment decisions is based on the current reimbursement situation in the US, not so much in Europe. Statements indicate that if the US would have similar reimbursement rates/difficulties as in Europe, the industry´s investments in new radiopharmaceuticals would further decrease and/or products will not be introduced in some European countries.

> "*If the market for all PET and SPECT diagnostics is payment at either a technetium bone scan rate or an FDG rate, if that is the future, from now forever, for payment for nuclear medicine then at some point people will stop commercialise products in Europe.*"

However, even in the United States, the reimbursement of RP is not favourable for all indications. RPs for an oncological indication are reimbursed, but in other indications such as neurology, there are similar problems as in Europe. This interviewee gave the example of the new Alzheimer's RPs, which were approved in regulatory terms in 2012/13 but have not been reimbursed to date. Moreover, he predicts that this will continue for years to come.

> *"Getting past the FDA is not that bad, it takes time and money, but it is doable if you have a focused indication. But getting passed payment is a big deal."*

Even in Europe, the reimbursement situation is not uniform but differs from country to country. Some countries have a more open position than PET; others are very restrictive.

> *"So there are insanely conservative countries like England, which is perhaps 20 years behind Germany. There are advanced countries such as Denmark, where almost all indications are*

reimbursed, or France where FDG is relatively broadly reimbursed. Italy, for example, has six times more PET/CT examinations per million inhabitants than Germany. Because simply the reimbursement is better regulated. That is extremely different."

Related to the issue of reimbursement, an interviewee mentioned another issue that, from his point of view, creates another difficulty: the legal manufacturing of unauthorised products in some European member countries.

"*I think getting products reimbursed is the biggest challenge in Europe….And, if you develop a Lutetium therapy in Europe, you always got the concerned effect that somebody could make it in their own facility, as an unlicensed product. Not always to GMP. So if you are factoring the costs of getting a product approved that makes... it creates a difficult European market. That is not true in all European markets; there are well-regulated markets in Europe that remain good opportunities for development.*"

IV. The Molecular Imaging Technology Industry´s View:

Two, very knowledgeable interviewees, whose companies have been engaged in R&D of radiopharmaceuticals for a long time, also experience reimbursement as a significant challenge for RPs. Both interviewees showed good knowledge on the current reimbursement systems in Europe and the US and would rate the current reimbursement issue as a/ the primary reason why their companies pulled back from the development of new radiopharmaceuticals.

"*If a new test is developed that does not necessarily show the therapeutic benefit and the utility yet, then, of course, the reimbursement is also difficult. Especially when it comes to PET imaging, the question is: how high does the reimbursement have to be to cover the costs? For example, in SPECT, with technetium-based radiopharmaceuticals, the reimbursement is not that high, but you can still cover costs, which is much more difficult with PET.*"

Also one interviewee from this group mentioned the problem of the "no coverage rule" of Medicare & Medicaid with RPs outside of oncological indications. This rule has a high impact on businesses because of Medicare & Medicaid insures more than 55 million people in the United States. The new PET RPs Netspot (^{68}Ga- DOTATATE) and Axumin (^{18}F- Fluciclovine) benefited from this rule and got a local coverage decision and reimbursement.

"*But let´s say we have a new tracer for Alzheimer, infection or heart disease we still have a standing policy of automatic no coverage unless you got a full national coverage decision and that is quite a daunting obstacle that is in the way.* "

For one conversation partner, the situation in Europe is more difficult due to reimbursement via the Diagnosis Related Group (DRG) system. The bundled payments per case may mean that new, innovative technologies are not taken into account and thus not paid. This puts the user and the company under pressure.

"*We have a model of hospital bundled payments where they lerp the costs of RP in the general procedure code for the imaging procedure. So like a needle or gauche, and the bundled payment in many cases does not even cover the costs of the RP alone. So every procedure the hospital would do, they lose money, and that is a huge disincentive to then utilise the tracer and a huge*

disincentive for the commercial developer to try to recoup their clinical trial cost by having a very expensive RP charged. So the Amyloid agents, and some of the new RPs which have just emerged on the market, are in the thousands of dollars because they are trying to recover, in their short IP window, their own R&D investment. And yet the hospital gets only paid something less they charge for the RP for each patient; there is a huge disincentive."

The young start-up companies also consider this particular "DRG challenge" as discouraging to invest in the development of new products, an expert explains.

"*And the potential start-up companies are very aware of that and watching this closely. So if we sometimes meet with the small start-ups, that is one of the daunting things they find discouraging about investing heavily in new PET tracers. You can do all of this, and then you want to charge $ 2.000 or 3.000 a dose in clinical practice, the hospital would lose money on every dose, and thus don´t want to order a single dose of it. A real limiting thing on the horizon that is a bit discouraging.*"

V. Brief conclusion on the topic "Reimbursement"

	Strong Pro	Neutral	Strong Contra
Is Reimbursement a Challenge?			

The majority of stakeholders answering this question (67%) agree that reimbursement is currently a challenge with an impact on R&D decisions. From the physician´s point of view, adequate reimbursement leads to a successful clinical utilisation of new technology, since industry can better protect their investment.

Investors, such as the radiopharmaceutical industry, are closely assessing current reimbursement rulings and aligning their investment decisions. The interviewees confirm that in addition to the clinical benefit of the diagnostic product, the data for a successful reimbursement must also be simultaneously collected. As one health technology specialist, from an independent scientific institute assessing the efficacy of medical technology and drugs in Germany, summarised: "*If I just want to bring a diagnostic test in the market, then it is completely enough to prove that the test can show the results it is intended to show…. For the regulatory approval of the tracer that is enough. Er, then to proof that you have a beneficially changed in treatment is much more difficult. That is the way the world is, just prove that "there is something", that is no longer sufficient.*"

The only expert from the pharmaceutical industry responding to this questions acknowledges that the margins in the diagnostic business are too low to engage in R&D activities and commercialisation. For the radiopharmaceutical industry, this topic is critical and at the same time one of the most significant challenges. Especially in Europe, but also in non-oncological indications in America. Should there be a further tightening in Europe, from an expert's point of view, there is the chance that some products will not be launched in Europe. The interviewees from the molecular imaging technology industry agree with statements from the radiopharmaceutical industry experts and additionally challenge that the DRG system in Europe is not well positioned to implement innovative technologies. This further discourages start-up companies to invest.

4.2.2 Challenge with Regulations

Medical imaging agents generally are governed by the same regulations as other drugs or biological products, in the USA and the European Union. Since 1989, radiopharmaceuticals are classified as "medicinal products" and consequently underlying the same regulations as "conventional pharmaceutical drugs" if the radiopharmaceutical contains at least one or more radionuclides (radioactive isotopes) and it is intended to be used for the medicinal purpose (The European Parliament and of the Council, 2001). However, additional to the Medicinal Product Acts, radiopharmaceuticals also have to follow specific national regulations on radioactivity such as the "Ordinance of Radioactive Pharmaceuticals or Pharmaceuticals treated with Ionising Radiation" and the "Radiation Protection Regulations".

> "*Radiopharmaceuticals are amongst the most highly regulated of materials administered to patients because they are controlled both as medicinal products and as radioactive substances*" (Sampson, 1994)

A Nuclear Medicine Physicist´s view I:

"And the problem that we have in the legislation, and I assume that this is more or less the same all over the world, that you have laws for medicines, and also PET tracers are classified as medicines. And on the other hand, you have the legislation for radioactivity, right? ... It is simply that the approval of a new PET tracer, a diagnostic tracer, is simply laborious because it is classified as a drug."

A view from the Radiopharmaceutical Industry:

"We think that, we think the market will get more regulated. Er, we don´t think the market will get less regulated, so er so we think there is a fantastic opportunity. Ah, and it looks like a good place for investment. I think, so we think the regulation will kick in at some point. And it will become a more regulated market."

A Nuclear Medicine Physicist´s view II:

"I don´t think that the regulatory agencies are the bottleneck here. Actually they are doing really well. They have an interest to get this done. I am actually fairly positive about their work"

A view from the Molecular Imaging Technology Industry:

"And I think everybody's outlook got better, with the recently two approvals ... and the fact that these companies successfully found more creative ways to get through the FDA process and got reimbursement. The mood in general is much better than it was a few years ago where it seems all the big companies got out."

As already outlined in chapter 3.6 the radiopharmaceuticals are possibly amongst the tightest regulated medicinal products worldwide. Even after several attempts of harmonisation since the 1980s, radiopharmaceuticals are still subject to different national regulations worldwide. In the constituent treaty of the European Union, health care remained a national competence, which is why different interpretations of European regulations occur within the member states. This permits some treating physicians in the EU to administer a non-licensed product to their patients, under their responsibility. This heterogeneity is also reflected in the statements by the interviewees.

All statements regarding this topic are in the appendix on page 202.

I. The Nuclear Medicine View:

	Strong Pro	Neutral	Strong Contra
Is Regulation a Challenge?	◆		

There are striking different views regarding the topic of regulation. German, Austrian and Swiss nuclear medicine physicists perceive the regulations to be too strict and many criticise that RPs should not be

categorised like therapeutics. Interestingly, some German nuclear medicine physicists believe that "*Germany is very restrictive*" although the German national regulations give doctors more freedom in the use of non-authorised products than in other European countries. Some perceive that the national rules in Germany are part of the success of the nuclear medicine research field in Germany.

> "*So in Germany, it is not a problem. Part of our success is that we can work with non-approved drugs. However, we are very much dependent on the German framework conditions and if at some point, in the course of internationalisation/globalisation, these full rules are standardised and the same everywhere, then we get a problem in Germany.* "

Many nuclear medicine interviewees value the possibility of having quick first-in-man studies and experiments with new RPs, but there are also voices that criticise the quick administration. Two interviewees proactively mentioned that they feel that new RPs should follow more structured preclinical safety and dosimetry studies before being administered to the patients.

> "*Germany leaves them any freedom, which I welcome. I think that is great, but the problem in Germany is that you have room to do scary things, and then, if you really want to introduce the tracer to the market, then the hurdles in Germany are even more prohibitive than they are here.*"

Another interviewee believes that the current legislation in Germany supports research in Germany, but does not back up the nuclear medicine field as a whole "*… that we in Germany tend to go with the substances very quickly in the patient and do not worry about how we can create sustainable evidence of benefits."* However, certainly the data, which has also been collected in Germany, is indeed beneficial for new drug approval applications, such as for a new diagnostic RPs being currently in the approval process in the USA:

> "*… the requirements* [for a USA drug approval application] *where really minimal and we were allowed to use European data… So based on that idea, there was essentially no Phase I trial required…. in the process we kind of bypassed the Phase III trial, because we made the argument, that FDA seems to be open to it, that Phase III is not needed given the extended patient population which has been studied in Europe, and also a large number of patients we have done.*"

The interviewee from the USA is generally more positive about the attitude of the regulatory agency compared to the physicists in Europe. "*I do not think that the regulatory agencies are the bottleneck here. Actually, they are doing really well. They have the interest to get this done. I am actually fairly positive about their work...*" He also believes that Europe will fail to bring new tracers on the market, and it will be the responsibility of the US to do so. In his belief the current regulations allow to generate valuable retrospective, but not prospective data which is needed for a successful drug application:

> "*The strategy has to be that one goes through it in a structured and organised way, which cannot be done in Europe … So we have to, I think the FDA is very helpful, and you have to go through a stepwise process, and it may take a bit longer, but we are imaging already, and we are treating PSMA patients. We are behind Europe, but that is not so much because of the process, this is because we were in hibernation in the US and overslept the whole thing."*

Last but not least, European nuclear medicine physicists hope that harmonisation in the EU will take place and a more reasonable standard will emerge. However, they are also aware that any change in rules can affect their national practice, positively and the negatively. A very knowledgeable interviewee expects the following:

"*There are developments that barriers will decrease in countries with high barriers. However, there is also the tendency that for countries that have barely now barriers, new barriers will open up. So there are certain tendencies for harmonisation at the most diverse level. So on the side of the regulations themselves ... then, of course, also from the law enforcement authorities.*"

II. The Radiopharmaceutical Industry View:

In opposition to the majority of nuclear medicine physicist, the radiopharmaceutical also industry see "regulation" as a challenge. But in the sense that it is not strict enough, so 100 percent contrary to the view of nuclear medicine group. In general, they do not explicitly criticise the current regulatory requirements, but see good cooperation.

"Yeah, so we have a good experience with the regulatory agencies. The regulations that are in place are clear, and er you can have guidance from them. So we think the regulatory bodies do a good job."

However, the experts of the radiopharmaceutical industry criticise the permission to use non-authorised RPs. This allowance differs across the EU, depending on how the European directives have been implemented, but creates the challenge for the radiopharmaceutical industry to compete against unlicensed products.

"*Er, you know I think that there is an interesting research community, there is an interesting situation in Germany under § 13.2b regulations whereby doctors can administer a RP outside of a clinical trial process…"*

These exemptions are not explicitly for radiopharmaceuticals, but this field has made the most of this rule. It had a very positive effect on the research community, but on the other hand, limits the industry´s efforts in R&D and the authorisation of new products. The interviewees from this group visualize an opportunity if the market becomes more regulated with time.

"*We think that we think the market will get more regulated. Er, we do not think the market will get less regulated, so er so we think there is a fantastic opportunity.*"

So both, the nuclear medicine interviewees and the experts from the radiopharmaceutical industry believe that the regulation will change, but in a different way. One interviewee from the radiopharmaceutical industry group can imagine that the large pharmaceutical company, which has just recently entered the market with a new therapeutic radiopharmaceutical, will no longer tolerate the use of unlicensed products in the same indications. Even if those institutions would use a different compound. Pressure from a powerful pharmaceutical lobby group could especially stress federal exemptions in regulations in Europe. On the other hand, as one interviewee from independent international cooperation confirmed, there is a high-level task force consisting of many significant global nuclear medicine associations with the aim to harmonise regulations in the EU and "educate" regulators.

III. Brief conclusion on the topic "Regulation"

In the group of nuclear medicine physicists, the German, Austrian and Swiss experts generally perceive the regulations to be too strict and many criticise that RPs should not be categorised like other

therapeutic drugs. The chance to have first-in-man studies relatively quickly are perceived positive, but for half of the interviewees this is sometimes too fast.

The radiopharmaceutical industry also regards regulation as a challenge, but in their eyes, this is not strict enough. They, therefore, expect regulations to become more stringent, which would result in a limitation in the production and use of unauthorised RPs in European countries. So presumably regulations are already in motion mainly in Europa, although it is not yet clear in which direction this will change. Both the academic side and the industry are both very confident that the regulations are moving in their direction.

Within the group of nuclear medicine physicists, one group of interviewees generally do not believe that regulations will harmonise, others expect a positive harmonisation and the third group fear a change to their detriment. However, any change could have a significant impact on the use of radiopharmaceuticals, at least in European countries.

4.2.3 The Issue with Market Potential

In general market potential is defined as the entire sales value or sales volume of a market for a specific product and period. Especially in the health care sector, the sales volume is closely connected to the reimbursement rates of the product. A change in reimbursement rates can lower or increase the sales volume, thus increasing the potential revenue for the competing companies. In this case, the return on investment (ROI) is the return earned from the investment made by the company. The ROI in drug research and development by the pharmaceutical industry was 3.2% in 2017, continuously declining since 2010 (10.1%) (Terry & Lesser, 2017). With the declining ROI, the pharmaceutical companies have shifted their focus on specific therapeutic areas with higher prices enabling them to maximise their ROI such as in the field of central nervous system (CNS) and oncology (Terry & Lesser, 2017).

A Nuclear Medicine Physicist´s view:

"The profit margin you get with the commercialization of a diagnostic test, that's just not as high as with a therapeutic substance."

A view from the Radiopharmaceutical Industry:

"We think there is a fantastic opportunity … in molecular imaging."

A view from the Molecular Imaging Technology Industry:

"Well, I would say the problem ... having a relatively specific patient population, then developing something with a very specific target, and then you have to do the full Phase I, II, and III studies, which will cost you 100 to 150 million. And then, in the end, this is not necessarily a huge commercial market, and then it's a big problem. Because of course, the margin is not as large in PET imaging as it is in contrast media or in SPECT nuclear medicine. You need to create your own local infrastructure or work with companies that locally produce the PET molecule and then deliver it accordingly."

A Pharmaceutical Industry´s view:

"...the margins are very low in diagnostics, there is more money in therapeutics and we focus on the diagnostics we need to get the therapeutics approved and to people."

All statements regarding this topic are in the appendix on page 204.

I. The Nuclear Medicine View:

	Strong Pro	Neutral	Strong Contra
Market Potential a Challenge?	◆		

In the group of Nuclear Medicine physicists, five interviewees (83%) perceive low market potential to be a substantial challenge.

> *"Well, I believe that in diagnostic tests, unfortunately, the profit margin that one has with the commercialisation of a diagnostic test so that just is not as high as having a therapeutic substance."*

Interviewees from Europe, especially Germany, are generally more pessimistic about the situation in their home market whereas the interviewee from the USA has a favourable view of the radiopharmaceutical market and the introduction of new products.

Europe:

> *"And, for example, in the field of outpatient care, only a few indications (PET/CT) have been added, and even in EBM PET/CT is still not anchored. So that's a big obstacle for the industry I think that's, of course, not so nice. But they are of course targeting the US as a market, which is a very large market and where the approval of new RP has recently increased significantly in speed."*

USA:

> *"If you look at the list of companies that have entered the imaging market it is quite stunning. There are a quite bunch of companies that come in. And also pharmaceutical companies are attracted by theranostics because that is the market. There is a big need."*

The reason for this pessimism in Europe? Well, the market potential is very much affected by the existing regulations and the reimbursement rates, and many interview partners have highlighted this connection. One of the interviewees is very self-critical and says that the nuclear medicine community is partially to blame for this low market potential since they have developed and produced the new tracers themselves, lost the chance to patent them and thus lost the investor´s interest.

Some of the interviewees do not believe that sufficient profits can be realised with diagnostic RP.

> *"One thing is for sure, that with a ... diagnostic product ... it is difficult to generate returns. If I think of Fluor-18 marker now, for Fluor-18 I need infrastructure around that ... and writing pharmaceutical profits is very difficult ... plus, because it is just diagnostic, you can, of course, charge a lot less .... with Ga-68 kit markings, I do not have the problem of logistics, but ... the margins are still worse and all reimbursement systems ... are never ready to pay as much as for therapeutic drugs."*

However, some interviewees are very keen on the concept of Theranostics and expect the approval of therapeutic RP will also boost diagnostic RPs. The situation with therapeutic RPs is entirely different, as explained by a very knowledgeable interview partner from the US.

> *"AAA will charge 47.000$ per cycle DOTATATE… so that accounts for 80.000$ or so per patient. Let's have 10.000 patients, 40.000 cycles so you can calculate the significant amount of money. Now if you think of prostate cancer, you suddenly have, conservatively estimating, 40.000 patients for 160.000 cycles. And each of them is 20.000$ or 25.000$ or 30.000$ than you can calculate, that this is multi-billion Dollar business. So that is we are talking, now they are coming in and like that stuff. Money being made."*

Some interviewees anticipate that the concept of theranostic will not only attract new investors, but diagnostic tests will also be able to swim in the wake of this concept, allowing it to gain more and more acceptance and receive marketing authorisation in the end.

II. The Pharmaceutical Industry´s View:

All interviewees of the pharmaceutical industry confirmed that market potential is a definite challenge and they currently have no interest in the commercialisation of imaging biomarkers.

> *"…the margins are very low in diagnostics, there is more money in therapeutics, and we focus on the diagnostics we need to get the therapeutics approved and to people."*

An expert told us that they needed an imaging biomarker for a therapeutic drug and refunded a company the full development cost, to get access to that tracer. Moreover, even though they paid for the whole development, they did not wish to enter this challenging, low-margin business segment.

> *"There are companies out there, which are developing molecular diagnostics and they have the same problem. They have very small margins that is a tough business. And in fact what happens, we did not develop the PDL-1 tracer, but we paid the company to develop it. Every penny they needed for it because we needed to have that test."*

Another interviewer has told us a similar strategy, where a company has also developed various imaging biomarkers for R&D of new drugs. Although they invested quite a lot of effort and budget in the development of these various markers the company has no interest in marketing these imaging markers.

> *"In fact, we are developing a number of these molecular markers with academics. But I think the real question is "Are we really developing to use it all the way into a Companion Diagnostic?" and "Are we using, are we developing it all the way to make a business?" The answer to the last two is: probably no. Because this is not our primarily stream business."*

III. The Radiopharmaceutical Industry´s View:

Contrary to the pharmaceutical industry, the respondents in the radiopharmaceutical industry do not see "market potential" as a great challenge. Three of the interview partners (60%) expect the RP business to be a good investment with excellent growth opportunities in both the diagnostic and therapeutic segment. At least in the USA, which accounts for approximately 40% of global demand (Dubois et al., 2015).

> *"PET biomarkers are a fairly big business. The PET market in the US is about 275 million a year, this year 2018. That is all PET in the US, revenue. So 275 million…"*

However, one must note that the interview partners come from small and medium-sized companies and not from large pharmaceutical companies. So a market potential of 275 million Dollar is minor compared to the revenue of "big pharma", as one interviewee also recognises.

"The market opportunity for such a product is a niche compared to a therapeutic drug… A pharmaceutical company would say "Actually it costs me a significant amount of money and the market opportunity is low."

However, there is a relatively positive view of the respondents concerning the market potential of new diagnostic RPs, of course, if the new product can show the clinical utility and gets reimbursement.

"If you brought another biomarker to replace FDG, for example, you would never make a business case for this. Because FDG is good enough and it is cheap. But if you have a very specific unmet clinical need, you can find basically a niche market. That is what Ga-68 NETSPOT/ Ga-68 DOTATATE did, that is very specific. Very small market, but they charge 5.000$ a dose. So it is a business!"

However, while respondents have a positive assessment of the market potential in America, they are concerned about developments in Europe. Restrictive access to novel radiopharmaceuticals due to negative assessments by national authorities, lack of market authorisation or low reimbursement rates also creates problems for the current market participants (see more comments in the appendix on page 204).

"If the market for all PET diagnostics and SPECT diagnostics is payment at either a technetium bone scan rate or an FDG rate, if that is the future, from now forever, for payment for nuclear medicine then at some point people will stop commercialise products in Europe."

A concern is also the self-production of unlicensed products in Europe, which was mentioned by a few interviewees. Industry cannot compete against these prices and would lose a significant share of the market. However, all interviewees from these stakeholder group expect a stricter regulation, which would strengthen their position in Europe. *"We think that we think the market will get more regulated. … and it looks like a good place for investment."*

The interviewees also expect the concept of Theranostics to give the RP market a boost, even attract big pharma. "*The reason why AAA is worth 4 billion is not because of the Gallium diagnostic, is because of the Lutetium therapy."*

IV. The Molecular Imaging Technology Industry´s View:

	Strong Pro	Neutral	Strong Contra
Market Potential a Challenge?	◆		

Historically, the medical device industry has always been a significant contributor to the development of new radiopharmaceuticals. The major players in this division have bought up specific companies, and engaged in the development of new products. However, the drop in market prices accelerated a wave of consolidation and terminated R&D activities. Our interview partners from this industry, therefore, had good knowledge on the topic.

"So we had a discovery program, at one point we had maybe seven tracers in various steps of clinical development, and ended up closing it down. So we are not actively in the discovery phase anymore… But the little start-up companies are doing well and finding creative ways to do things. Moreover, maybe this kind of innovation belongs, it is lean and quick and finds creative ways to get it done. So I think the mood, in general, is quite good."

Moreover, these responders agree that the market is difficult because costs of development are comparable to other pharmaceutical drugs, but the revenue is much smaller.

V. Brief conclusion on the topic "Market Potential"

Three out of four stakeholder groups agree that the low market potential of diagnostic radiopharmaceuticals is a challenge and may detain investors from the commercialisation of new innovative radiopharmaceuticals. The interviewees from the nuclear medicine physicians, the pharmaceutical- and the molecular imaging technology industry group agree that the market is tight and the profit significantly lower, compared to traditional pharmaceutical products. The radiopharmaceutical industry, on the contrary, sees excellent opportunities in the diagnostic- and therapeutic RP business, at least in the United States. In this market new diagnostic RPs with an oncology indication have achieved much higher reimbursement rates compared to FDG, which in effect dramatically increased the market potentials. However, the RP industry experts also acknowledge that there is an entirely different situation in Europe. Companies struggle with the reimbursement of the products and currently compete against hospital in-house production centres in some major European markets. However, both interviewees expect that the regulation will become stricter in Europe, increasing the attractiveness from a market potential point of view.

4.2.4 The Issue with Research and Development

The term Research and Development (R&D) describes "*any creative, systematic activity undertaken in order to increase the stock of knowledge, including knowledge of man, culture and society, and the use of this knowledge to devise new applications* (Organisation for Economic Cooperation and Development, 2018)". This covers activities from fundamental- to applied research and the development to the finished product. The pharmaceutical R&D process is said to be especially challenging because it is associated with high costs, long duration and high attrition rates in all stages of the R&D process (Schuhmacher et al., 2016). Even despite new approaches and technologies it is not precisely understood how drugs would work and late attrition in the costly phase III stage are still common (Retzios, 2009). Without a financially strong investor, it is provoking to get pharmaceutical products through the market approval process, especially the clinical (phase III) trials require a considerable amount of resources and capital to demonstrate the safety and efficiency criteria of the regulatory authorities.

All statements regarding this topic are in the appendix on page 206.

A Nuclear Medicine Physicist´s view:

"You know what the major issue is really costs too, who pays for it. If you don´t have stakeholders like in the pharmaceutical industry, which is now changing a little bit with Novartis having bought AAA. That changes the game, but as long as you don´t have stakeholders with a lot of money who is paying for it? That is really complicated, who is paying for the development."

A view from the Radiopharmaceutical Industry:

"Yeah, I think the really shared challenges with other therapeutic platforms is the cost of exploiting them. So I think the advantage currently in the RP world is that there is a recent history of home production and of clinical use of RPs. Meaning that projects have been de-risked and therefore less expensive."

A view from a Regulatory Specialist:

"The costs, the costs. If a study is complex and cheap then it is more likely to be done than if it is easy and expensive.

A view from the Molecular Imaging Technology Industry:

"Well, I would say the problem, especially in oncology, is that you have a relatively specific patient population. You develop a very specific target, and you have to do the full phase I, II, and III studies. This costs you 100 to 150 million and in the end there is commercially not necessarily a huge market."

The responses were wide-ranged. The literature search has linked the category "R&D" above all with the argument of the “costs of development”, but the interviews revealed other issues such as speed of development in the therapeutic sector, regulatory hurdles et cetera also play a role.

I. The Nuclear Medicine View:

	Strong Pro	Neutral	Strong Contra
Is Cost of Development a Major Challenge?		◆	

The interviews have shown that all interviewees are very sensitive to the issue of cost, whether in connection with new product development or reimbursement. Due to the structure of the interview, the interviewees were not directly addressed on the subject of development costs, but they should name the biggest obstacles in the approval and the barriers and why there are no investors in the field of diagnostic radiopharmaceuticals. However, astonishingly, four out of seven responders (57%) mentioned costs of development being a challenge for new diagnostic RPs.

> *“You know what the major issue is really cost too, who pays for it? … as long as you do not have stakeholders with much money, who is paying for it?”*

Another interviewee linked the costs of development in his response with the high burdens imposed by regulatory requirements and the rising study requirements.

> *“So if we want to use a new tracer today ... just for research purposes, I have to spend 100,000 CHF to do a toxicology study. This will stifle any research project immediately. So that is the problem with the PET tracers."*

However, in addition to the argument of costs, other challenges in R&D were also addressed. Interviewees mentioned that due to the rapid pace of development in the therapeutic field, diagnostics research is far behind and can usually not close this gap.

> *"So there's a number [of challenges] and also keeping pace with the rapid development of new therapeutics. We cannot keep up with the development of diagnostics that would fit for therapeutics."*

Remarkably, nearly half the interviewees have also admitted errors in their actions regarding the development and commercialisation of new tracers. Three interviewees reflect on the expeditious administration of new, experimental diagnostic and therapeutic RPs in massively ill patients by the national regulation of § 13.2b AMG.

> *"And that is actually a problem; I think that is a problem of our system that we in Germany tend to administer the substances very quickly in the patient and do not worry about how we can create sustainable evidence of benefits. So somewhere there should be a compromise… Although it is possible in Germany, but the global success is held back by the regulations."*

These interviewees acknowledge the fact that in order to have successful commercialisation of a new diagnostic RPs they would be happy to have the industry´s support to speed up the development of these new diagnostics, but also the desire to learn how to plan and conduct clinical trials.

> *“... what we urgently need in academic research is the support from the industry. So the thinking of the development steps: of phase 0-III; what are the requirements? How can you do something specifically?”*

Improving the quality of the trials by following the current EU regulations is a request by an experienced radiopharmacist, who is also engaged in an international committee and has a good overview on current academic research.

> *"(Academic research must) conduct more clinical trials, and a clinical trial means, in accordance with current EU regulations, as notified drug trials. These studies need to generate data that is really usable for approval. Moreover, that is not as difficult as it is often portrayed. Of course, it takes money and time, yes. Moreover, it will not work for everything that you would like to have...and there is already pressure from the authorities and also (the nuclear medicine physicists) see the reason. There are already more controlled studies! For example, where, in the simplest case, one can accurately portray safety and say it is a registered study whose primary objective is safety. For example, this is something which was never done for DOTATOC."*

II. The Radiopharmaceutical Industry´s View:

	Strong Pro	Not specifically mentioned	Strong Contra
Is Cost of Development a Major Challenge?		◆	

The interviews with the radiopharmaceutical industry experts illustrate that the companies do not make one problem prescient, but factor in all the challenges that arise in the development process. Because there is such a strong correlation between costs of R&D initiatives, regulatory requirements of the approval process, and expected reimbursement rates, one needs to see all the challenges in context.

> *"The PET biomarker industry in the US is very difficult, it is difficult to get approval from the FDA, and it is even more difficult to get reimbursement from CMS."*

However, the interviewees also acknowledge the fact that due to academic research in the RP field, the development of specific RPs was de-risked because the compound has already been used in first-in-man studies, in compassionate use situations or tested in preclinical models by academic researchers. However, this does not mean that total investment will decrease.

> *"So effectively, those initial data, what they have done is, they de-risked the chance that the therapy fails. However, they have not decreased the total investment you have got to make the product into eh, something the regulator will approve."*

Extensive research in the academic field may create more challenges than benefits for the industry. Many academic clinical studies do not meet the general- and quality requirements of the FDA and EMA, thus the data is not useful for an official approval process. One interviewee is especially surprised that in Europe non-authorised diagnostic RPs quickly find the way in the official guidelines, and to his mind this is not acceptable.

> *"And then they want to get ahead of themselves. As soon, they do... they kind of proof that technology works, and then before it actually been through a formal approval process, they start to incorporate it into guidelines, and the European Association of Nuclear Medicine promotes a lot of unlicensed RPs. And it is probably not the correct thing for them to do."*

It is confirmed that the cost or low efficiency in the development of new diagnostic RPs has deterred many of the "old" RP industry participants, leaving them out of the market.

> *"I just wanted to stress that [our company] was in the biomarker development business in the US for a decade, spend a tremendous amount of money. Hundreds of millions of dollars and got out of it because it was such a drill hole."*

However, the "new" start-up companies usually already have a sound concept to attract investors and have substantial knowledge of the costs of development. Moreover, it seems that these new actors are not bothering specifically about the cost of development, but rather about the high regulatory requirements in the approval process and costs associated with commercialisation.

> *"But the little start-up companies are doing well and finding creative ways to do things. And maybe this kind of innovation belongs, it is lean and quick and finds creative ways to get it done."*

We wish to briefly cover the therapeutic RPs research program because it seems that there will be some momentum going into this area. One interviewee expects that the acquisition of Advanced Accelerator Applications (AAA) by Novartis as not being the last acquisition we will see shortly.

> *"From a discovery point of view, the one big advantage of RP will have, it will be possible to go back over the back-catalogue of large pharmaceutical companies and find compounds with very high specificity, but don't have a therapeutic effect. So I think that will be an interesting and less expensive development in the next couple of years. Things that have failed and have been written of, because basically, they did not work. But they accumulated in a target; they might be of use if they can be labelled with radiation."*

III. The Molecular Imaging Technology Industry´s View:

	Strong Pro	Neutral	Strong Contra
Is Cost of Development a Major Challenge?	◆		

It is no secret that many of the top molecular imaging technology manufactures have also engaged in R&D activities around new diagnostic radiopharmaceuticals, which is also true for the two interviewees in this study. Both companies sell molecular imaging equipment and service, one company also focuses on the "life cycle management" of their RP portfolio, whereas the other company also has an associate company, which produces and distributes radiopharmaceuticals on behalf of other enterprises.

For these two companies, however, it is true that the enormous costs of development, combined with the low success rate of approved RPs, were the deciding factors to pull out of this business.

> *"Well, I would say the problem, especially in oncology, is that you have a relatively specific patient population, you develop a particular target, and you have to do the full phase I, II, and III studies. This costs you 100 to 150 million, and in the end, there is commercially not necessarily a huge market."*

Some insights from one interviewee revealed that his company had launched an RP a few years back, which had development costs of around $ 100 million. Due to a challenging global market situation, this RP has not paid off yet. As a consequence, a new product for the same disease is put on hold. "… *and (the company) has no interest in repeating that with the (new) imaging molecule.*"

However, due to the close integration of radiopharmaceuticals with imaging devices, both interviewees reassure us that their companies will continue to support clinical trials and specific research institutions in their research effort.

> *"We probably do not do enough, in my opinion, because we could do more. Of course, that is always a matter of money, and I still see much academic interest in developing new molecules. We internally decided not do discovery and early phase research anymore, but in principle, we should try to be a little bit more active. This would allow us to license promising projects at a later time. So the pipeline is no longer internally but externally, but so we can also boost research*

through collaborative research. Thus that would be a logical consequence of deciding that we do not do so much by ourselves."

VI. Brief conclusion on the topic "Research & Development":

	Strong Pro	Neutral	Strong Contra
Is Cost of Development a Major Challenge?			

Among nuclear physicians and the industry, the topic of R&D is closely linked to the argument of costs. Together, the responders from all stakeholder groups see this issue to be a challenge (57% of total answers). However, there seem to be other challenges as well, which keep all stakeholders busy. On the nuclear medicine side, this is regulatory requirements for clinical research, as well as the collaboration with the industry or developers of new therapeutics. Moreover, some of the nuclear physicians have also realised that their research approach (especially in Germany with § 13.2b AMG) may negatively influence the global success of RPs. The radiopharmaceutical companies have not explicitly mentioned costs of development as being a significant challenge, probably because they are well aware of these costs and have taken sufficient account of them in their business plan. The administration and use of un-licensed RPs in some big European markets seems to be a greater challenge for the industry as it creates a secondary market the industry cannot compete.

The interviewees of the MITG reported about their difficulties in the development of new radiopharmaceuticals, especially regarding cost and efficiency. These companies continue to support public and private institutions in developing new diagnostic radiopharmaceuticals and hope for a flourishing market in the future. Generally, R&D in the RP business has changed, with big companies leaving- and new start-ups entering the market: they are "*lean and quick and find creative ways to get it done*."

4.2.5 The Issue with Intellectual Property Rights (IPR):

When speaking about Intellectual Property Rights (IPRs), we refer to the assigned rights through patents, copyrights and trademarks, which allow the holder to have an exclusive monopoly position over a specified period (Khemani & Shapiro, 1993). In general, IPRs stimulate innovation by "*increasing private research investments in new technologies by allowing inventors to capture a higher share of the social returns to their inventions."* (Williams, 2015). Especially the healthcare industry experiences high R&D costs and relies heavily on IPRs since many of the pharmaceutical drugs are easy to replicate and thus have no technological barrier for competitors. However, IPRs are not excluded from country-specific laws, which in effect could undermine those rights (Williams, 2015). The official allowance on the use of unlicensed products in hospital settings, in some European countries, needs to be considered.

All statements regarding this topic are in the appendix on page 208.

A Nuclear Medicine Physicist´s view:

"They only get an industrial partner, if they really have a patent on their academically developed product. This has to be accelerated, and again it is important that this is simple to implement for the academics."

A Pharmaceutical Industry´s view:

"Well, IP is very broad. So if you have a tracers you can develop IP on the composition of matter, if you have an imaging biomarker which is based on a CT signature or we talked about Ferriscan, so the MRI R2 that is not a tracer that is a relaxation time and you don´t get IP on the relaxation time because it was discovered by physicists 50 years ago or more. Where you can develop IP on is in copyright and business processes."*

A view from the Radiopharmaceutical Industry:

"I think that is the cause of everything we do, is having a strong IP position. So you know, if we had an academic collaborator coming to us and say that is great technology and it is not patented, that would be just a really big red flag for us. I know AAA effectively has a generic product and they have invested, er which is fantastic but er, from our perspective we would have looked for a reason with strong IP position."

A view from a medical specialist:

"So completely different (situation between Europe and the USA). In every internal meeting there was always a lawyer present, which took me by surprise. He proactively approached us and offered to at least check whether a patent can be obtained. The hurdle was also relatively low, that the patent was filed. But when I developed this [idea], I called the [University in Germany] lawyer at the hospital. The hospital told me: "We do not have a Patent attorney anymore, that's what the university does itself." ...and he [the university attorney] said that it does not pay off at all, that's such a hassle and he does it only in justified exceptions."

The topic of intellectual property concerns all stakeholders and everyone is aware of the impact on the development of new radiopharmaceuticals. It turns out that industry experts are very knowledgeable in this area and can even pinpoint to the different types of patents. The view of the physicians is a bit more superficial, but they are also aware of the consequences.

I. The Nuclear Medicine View:

	Strong Pro	Neutral	Strong Contra
Are IPRs a Challenge?		◆	

Apart from one interviewer, the challenge of IPR was not independently mentioned by any of the interviewees. One interviewee did not directly use the word IPR but referred to the problem of lacking patenting with diagnostic RPs. *"Well, we are partly to blame ourselves, because we do it ourselves because it is not patentable often."*

During the interview, the interviewer addressed the issue of IPRs to the experts, with five interviewees explicitly responding. Generally, the interviewees confirmed that there must be some protection to attract investors and enable further development. Three interviewees consider the issue of IPR as a challenge (60%), one response was categorised as "neutral" because he believes there are many options to protect your product.

> *"Of course it helps if something is protected… In my opinion, it is not true that only products that are protected will be developed. It can also be a certain protection exclusivity of other things, for example, from a certain time advantage you have. "*

Of the two respondents, who regard IPRs as a challenge, one believes that ultimately all existing problems are due to patents. The second responder took the opinion that a patent for a substance with low market potential -such as many diagnostic RPs- could prevent others from entering this disease area and therefore delay the introduction in the clinical routine.

“In the end, the problems are always related to patents. You have to own a patent so you can make money in the pharmaceutical industry. Moreover, if the regulatory hurdles are extremely high, then you have a patent, and so you can use all the crap it may take ten years. Then half has already expired."

"*I will give you a concrete example now, the Gallium PSMA-11 tracer. Which is probably the second most used clinical tracer, after FDG. If Gallium PSMA-11 had been patented, it would not be there today. Because it would have taken much longer for this to be implemented."*

However, there are also statements from experts who regard this story with a much more relaxed attitude because IPRs can readily be agreed on in advance. Especially in the "classical" industry-academic partnerships, one interviewee sees this topic as “*relaxed*” and another “*does not think this is a problem*”.

"Intellectual property is always a problem; you have to define it beforehand ... Researchers are also beneficiaries in my view because you have the same partner during exploitation and you do not completely lose the patent. … as a researcher you can be happy to participate financially. This is also just an advantage."

However, regarding the negotiation and agreement of IPRs between industry and academic institutions, four interviewees believe that the academic aspect primarily causes the challenge. The responders explained that securing intellectual property is a complicated process in many universities.

"I think the challenge is more on the university side, that such patenting can be done efficiently, non-bureaucratically and standardised. Nowadays, if you have something new and you have no patent, than it is not worth anything to the industry."

"They only get an industrial partner, if they have a patent on their academically developed product. This has to be accelerated, and again it is important that this be simple to implement for the academics."

Additionally, the topic of royalties became relevant. An experienced nuclear medicine doctor argues that the universities have the task of securing their rights, but need to be careful not to overstate their royalties and thus create another hurdle.

"And when they (the university) starts to say:" I have to care that the university earns a stupid amount of money", then this patent can again have prohibitive/negative consequences."

II. The Pharmaceutical Industry´s View:

	Strong Pro	Neutral	Strong Contra
Are IPRs a Challenge?			

We attempted to question the pharmaceutical industry about the topic of IPRs, because literature suggests that the pharmaceutical industry i.e. heavily relies on their patent rights (H. G. Grabowski, DiMasi, & Long, 2015).

Unfortunately, the result is not representative because we received only one statement. This interviewee explained that he is very interested in IPR, but he also acknowledges the fact that there are multiple ways of protecting the compound/ product. Therefore, not having the patent of the chemical entity does not seem to be a reason for a complete blockade from his point of view. During the interview, it quickly became apparent that this company knows pretty well how to protect its products and developments.

"Well, IP is very broad. So if you have tracers, you can develop IP on the composition of matter, if you have an imaging biomarker which is based on a CT signature or we talked about Ferriscan, so the MRI R2 that is not a tracer that is relaxation time. You do not get IP on the relaxation time because it was discovered by physicists 50 years ago or more. Where you can develop IP on is in copyright and business processes. So with Ferriscan the IP there is on the copyright of the software, the business process, the whole procured for validating scans and giving the physician validate R2* measurements. Moreover, again I would urge you to think... Imaging is not just out of proprietary tracers, even in PET FDG has a very important role to play, and even there is no property to secure on that anymore."*

III. The Radiopharmaceutical Industry´s View:

	Strong Pro	Neutral	Strong Contra
Are IPRs a Challenge?		◆	

Following the withdrawal of large industrial companies from the radiopharmaceutical business, the current oncological market is increasingly composed of small and medium-sized (start-up) companies, with some big pharmaceutical companies still being engaged in the neurological RP field. This should be mentioned only briefly in advance because this has an impact on their capital structure and consequently on their view of IPR.

If one summarises all the answers of the interviewees from this industry group, then IPR does not seem to be a challenge, but it is an essential aspect. In one case, it was difficult to evaluate the interviewee's answer, as on the one hand, he explained that without IPR nobody would invest in the product, but on the other hand, he sees "IPR as not too important". We have therefore included both answers in the evaluation.

"…So somebody stepping in… moreover, they will not do that unless there is… unless they can get patent protection on their investment. One thing that mitigates in the US a little bit, if you bring what is called a new chemical entity to the FDA… you get 5 years of exclusivity. Independent on any patent, the FDA will not approve another application with that biomarker for five years. So you have five years basically to try to recube your investment. … So the patent is not too important."

One interviewee explained how they targeted IPR and built a "protective wall" around the product. He made clear that he would/could not wave the chemical property patent due to their external funding from an investment firm.

"So from our perspective, when we build up our IP portfolio we don´t rely on one piece of IP. We like to have the chemical entity, and then we build a whole layer of onion around it. About different IP that covers the manufacturing process for the product, how the product is being used in the field. So you can build, but not having the chemical entity IP is definitely something that when we go to investors, to ask to invest in new ideas we got, the first question they ask is: "What is the IP position?" And it is a big red flag for them if you don´t have chemical entity protection, from an investor perspective. But the [pharma] guys also know that there are ways to get around it. But there aren´t always ways to explain that to investors (laughs)."

This interviewee also comments on a move from a competitor, who decided to continue the development of a product with on expired patent. *"I know AAA effectively has a generic product and they have invested, er which is fantastic, but er from our perspective we would have looked for a reason*

with strong IP position." AAA managed to have a patent on the labelling process, but also profits from the orphan disease status awarded by EMA and FDA with extended exclusivity protection rights.

A further interlocutor talked about his experience with academic institutions and how they agree on license fees.

> *"Er, no I don´t think so. I think the market will determine the price, so IP…. In terms of the royalty percentage for the IP, I think that is only market forces. Some universities take a very reasonable approach and have 3-4 % royalties. Others insist of a much higher percentage, and I think the market will just determine, so I don´t think that is a problem."*

Of course, the interviewees prefer the patent protection of the substance and see the responsibility in the hand of the universities.

> *"And academic need to think about that IP and protecting it. So there is an asset worth investing in. (laughs)."*
>
> *"Academic institutions are very variable in their approach to IP. And you know there are some really smart about it, and they understand that they need to protect it and protect it well, and there are others. But I think, maybe the academic community understands that more every year."*

One interviewee explicitly stated the consequences, which could happen and had happened with a promising substance: *"That was a big move for Heidelberg around Ga- PSMA PET, for instance, they didn´t patent it. And now there is a good technology that is available so could have relevance in prostate cancer. But there isn´t really a company who wants to invest in it. Because Heidelberg failed to patent it."*

Finally, the radiopharmaceutical industry sees the academic research community as a fruitful place for new ideas and products. Therefore they engage in close collaborations with the chance to gain early access to new ideas. But again, for this specific responder, they are happy to engage in further discussion if the offered technology or idea has protection or protection is still feasible.

> *"Interviewer: So you also tried to gain IPR through these collaborations, is it a goal for you?*
>
> *Interviewee: Yes, yes. I think that is the cause of everything we do, is having a strong IP position. So you know, if we had an academic collaborator coming to us and say that is a great technology and it is not patented, that would be just a really big red flag for us."*

IV. The Molecular Imaging Technology Industry´s View:

In this case, just one interviewee answered the question about IPR, and his answer goes along with the other representatives of the industry.

> *"Yeah, there is, if I can I will break that into two categories because there are some very interesting RPs they do not have IP protection anymore. Even they have never filed for a patent in the first place, or they have been around so long that the patent has effectively been expired. Moreover, those are interesting, but a company have not really get behind it because they would spend all the money on clinical trials and the approval process and then anybody could make a generic."*

VII. Brief conclusion on the topic "Intellectual Property Rights":

	Strong Pro	Neutral	Strong Contra
Are IPRs a Challenge?			

Summarizing: IPRs are regarded as necessary by all stakeholders, but overall it does not seem to be a challenge. The Nuclear Medicine Group acknowledges the relatively high R&D costs associated with the development of new agents and thus admits that this investment must be protected. For some of the European nuclear medicine interviewees, the universities have failed so far to establish a system where ideas and inventions can be registered quickly and non-bureaucratically. A medical specialist had himself experienced how fundamentally different the process of IPRs protection is handled in Germany and the United States.

> *"So completely different (situation between Germany and the USA). In every internal meeting (in the USA) there was always a lawyer present, which took me by surprise. He has proactively approached us and offered to at least check whether a patent can be obtained. The hurdle was also relatively low that a patent was filed. However, when I developed this [idea], I called the [University in Germany] lawyer at the hospital. The hospital told me: "We do not have a Patent attorney anymore, that is what the university does itself." ...and he (a patent attorney from the university) said that it does not pay off at all, that is such a hassle and he does it only in justified exceptions."*

In a partnership with the industry, the nuclear medicine group does not regard IPRs to be a challenge, because terms can be defined and negotiated in advance.

The interviewees from the industries confirmed that protection of their investment is essential. However, opinions differ about the type of protection. A pharmaceutical industry interviewee sees the possibilities of protection very versatile, with the patent on the chemical entity being not so important. In contrast, a radiopharmaceutical interviewee regards the patent on the chemical entity as very important. However, he agrees that there are other forms of IPR protection, but not having the patent on the chemical entity is a red flag for investors.

4.2.6 The Issue with Manufacturing, Distribution and Handling

Compared to conventional pharmaceutical products, radiopharmaceuticals pose a challenge to manufacturers and users regarding production, distribution and handling. The production is, compared to typical pharmaceutical production, on a small scale but the compliance of cGMP makes the production difficult and expensive (International Atomic Energy Agency, 2008). The regulation requires *"qualified personnel, use of controlled materials and procedures, availability of qualified equipment, production of the products in designated clean areas, applying validated processes and analytical methods, full documentation of the process and release of the final product by a qualified person* (International Atomic Energy Agency, 2008)*."*

The radioactive substances itself, used to mark the biologically active compound, are either produced on site in a suitable facility (e.g. cyclotron for diagnostic RP) or are produced in large research reactors at short notice and then delivered immediately. The legal requirements for the transport, import and handling of these substances are detailed and require optimal logistics in order to bring these substances to the customer. For diagnostic RPs, the time component is essential because of the short half-life of radionuclides. Many institutions, therefore, use their own cyclotron for the production of, e.g. fluorine-18, or use a generator such as Gallium-68 to have the radionuclide available any time. Radionuclides used for therapy are mainly produced in reactors, have a longer half-life and therefore have a more suitable situation regarding distribution.

A Nuclear Medicine Physicist´s view:

"And the problem with the radioisotopes, which are relatively short compared to SPECT with technetium, I consider not to be problematic. I believe that the availability of PET is not really a problem, at least in Germany, not even in the US, I do not think this is a problem in any industrialized nation."

A view from the Radiopharmaceutical Industry:

"You have high fixed costs, a lot of cyclotrons, chemicals labors, people, but you can still make a good margin on that."

A Pharmaceutical Industry´s view:

"… drug companies develop drugs for global markets and so the imaging also needs to be available in that global market. And that are really difficult problems, the academics often miss."

A view from the Molecular Imaging Technology Industry:

"On the other hand, PET is problematic because you need PET centers to make the tracers locally and thus the margin is always worse than in SPECT. And that's unlikely to change. Either you need your own infrastructure, which will increase base costs, or you'll be working with local partners who manufacture PET tracers."

In general, the issue of manufacturing, distribution and handling was not a hot topic in all stakeholder groups. None of the interviewees proactively mentioned that this would be a "serious" problem. Still, the interviewee from the pharmaceutical industry stressed that this could be a problem if regarded an RP as being a companion diagnostic for their therapeutic drug. Otherwise, this topic was mostly mentioned in connection with the topic of reimbursement and regulations.

All statements regarding this topic are in the appendix on 209.

I. The Nuclear Medicine View:

	Strong Pro	Neutral	Strong Contra
Manufacturing, Distribution and Handling a Challenge?			◆

There were very few comments from this stakeholder group on this topic, assuming that manufacturing of RPs does not cause any significant obstacles. However, the complicated process has an impact on business margins:

> *"Now, when I think of 18- Fluorine 18 labelling, for F-18 I need infrastructure ... and (pause) generating typical pharmaceutical profits is very difficult."*

The short half-life of radionuclides is particularly challenging in the field of PET imaging but has been mitigated by the availability of Ga-68 generators and new labelling capabilities. Logistics becomes even more comfortable with therapeutic RPs, as the half-life increases significantly.

> *"... these therapeutics typically have half-lives in the range of days and not in the range of hours. This changes the whole logistics. So they can produce Lutetium DOTATATE in Holland, and from there they can flood the world."*

II. The Pharmaceutical Industry´s View:

The interviewees of the pharmaceutical industry currently have had hardly any experience with the manufacturing, distribution and handling of RPs, because it is not in their portfolio. However, they see challenges associated with the manufacturing and distribution of RPs.

> *"When the drug company is developing the drug it is developing it for a global market… they think if you can sell it in the United States and EU, they are also thinking about China, Philippines,*

Brazil, Indonesia. These are important markets! … If you are going to have diagnostic in your label you want to make sure it is available in every hospital in China, Philippines, Brazil otherwise you would not sell this drug. From that point of view you have PET agents... at least..., carbon is out of the question, fluorine can be challenging because of the half-life. Technetium is much more attractive. Gallium obviously with PET is more attractive, because you can use a generator and a nuclear medicine department can make it locally. Moreover, if I were looking at developing a personalised healthcare compound, I would be very cautious about the fluorine agent."

So logistics is a topic from the pharmaceutical perspective. As we can see in the statement above this responder would even prefer an RP for SPECT, because it would at least simplify the logistics process.

III. The Radiopharmaceutical Industry´s View:

	Strong Pro	Neutral	Strong Contra
Manufacturing, Distribution and Handling a Challenge?			◆

For the radiopharmaceutical industry, the manufacturing, distribution and handling of these products is a core competence. None of the interviewees from this group has proactively identified this topic to be a severe problem. However, one can see that the expansion of manufacturing needs to be planned carefully and gradually developed.

"And what we are doing now is rolling out the manufacturing infrastructure to make the product available... That gives us an opportunity to provide a product that is Er, the same in all markets effectively."

The production of these products is associated with high costs, consisting of costs for technical equipment, raw materials and qualified personnel.

“You have high fixed costs, many cyclotrons, chemicals labours, people, but you can still make a good margin on that."

In the meantime, there are even companies that produce the product and take over distribution on behalf of the license holders.

"So [the company] is sort of, not an R&D organisation, we are a biomarker production and distribution company. We are the market leader in the US, we have 43 pharmacies, we have about 48% market share, we do about 1 million doses a year, and we supply these doses to about 1 million patients a year… work with other partners, other businesses that are in this field and need a commercial outlet for the biomarker."

IV. The Molecular Imaging Technology Industry´s View:

One interviewee from this group, who has experience with manufacturing and distributing of RPs, did not complain directly about the high costs but points out the connection between production costs and reimbursement.

“And in principle, especially as far as PET imaging is concerned, the question is how big reimbursement has to be to cover costs of the test… SPECT is much simpler. And especially technetium-based products, even reimbursement is not that high, you can still cover costs, which is much more difficult in PET."

Moreover, the production costs of PET RPs may not decrease significantly in the future. Thus there will be continuous pressure on margins. One could also choose a subcontractor, but this would lead to an even greater trimming of the margin.

"On the other hand, PET is problematic because you need PET centres to make the tracers locally and thus the margin is always worse than in SPECT. Moreover, that is unlikely to change. Either you need your own infrastructure, which will increase base costs, or you will be working with local partners who manufacture PET tracers. Of course, they also want to have some of the profit, so the margin will always be worse than with SPECT. There are also certain countries where, apart from the big cities, logistics in SPECT is easier than in PET imaging."

V. Brief conclusion on the topic "Manufacturing, Distribution and Handling":

Each of the interview partners is aware that the manufacturing, distribution and handling of radiopharmaceuticals are not comparable to traditional therapeutics. Due to the short half-life of radionuclides, especially in the diagnostic field, logistics plays an important role. For the group of nuclear physicians, who have always "produced" the products in the radiopharmacies on their own, this is no new challenge. This topic is therefore not perceived as a "special" obstacle. The pharmaceutical industry, however, sees a potential issue in this more complicated process, mainly because these companies have a global marketplace in mind. The interviews revealed that the pharmaceutical industry is currently not interested in the commercialisation of imaging biomarkers, even if a RP serves as a companion diagnostic for one of their new therapeutic drugs. For the radiopharmaceutical industry manufacturing and distribution is a daily business, therefore they did not proactively complain either. However, the responders confirmed the high costs associated with the production of the products, with PET RPs remaining costlier than SPECT RPs or contrast media. Still, there seems to be a fair margin to be made, with the current reimbursement rates in the US.

4.3 Diagnostic Radiopharmaceuticals used as Companion Diagnostics

As discussed in chapter 4.2 diagnostic radiopharmaceuticals, as independent in-vivo diagnostic agents, are facing some challenges. Nonetheless, there have been two successful introductions with 18-F flucoclovine and 68-Ga DOTATATE in the USA and Europe in recent years. With the push towards new molecularly targeted cancer therapeutics, patients will be screened more often for the intended target in a sensitive, specific, cost-effective, quick, and robust way (Ludwig & Weinstein, 2005). Biomarkers should improve cancer staging, personalise the therapy and overall lead to a better outcome for the patients. Primarily in-vitro biomarkers, but also in-vivo imaging biomarkers, compete in this field and both have their assets and drawbacks. There was the hope by some nuclear medicine physicists that the widespread adoption of biomarkers will also push imaging biomarkers and the number of approved diagnostic RPs would rise.

The big difference between such a companion test and a "standalone" in-vivo diagnostic agent: the companion test is linked to a specific therapeutic drug, can detect or monitor a disease according to regulatory requirements and decides whether the therapeutic drug can/should be administered or not (see Table 27). Consequently, the Companion Diagnostic (CD) provides essential information related to the safe and effective use of the corresponding drug or biological product.

Complementary Diagnostic:	*A test, which is not essential the safe and effective use of the drug but the test identifies a biomarker-defined subset of patients that respond differentially to a drug and aids in the risk/benefit assessment for individual patients (Beaver et al., 2017).*
Companion Diagnostic:	*A companion diagnostic is a medical device, often an in-vitro device, which provides information that is essential for the safe and effective use of a similar drug or biological product. The test helps a health care professional determine whether a*

	particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks (U.S. Food and Drug Administration, 2018a).

Table 27: Differences between a Complementary- and a Companion diagnostic test from a regulatory view.

Due to the combination of the (mandatory) diagnostic test with the therapeutic drug the whole economic situation for the diagnostic test changes. The Companion Diagnostic can be seen as a gatekeeper for the administration of drug, and therefore the pharmaceutical industry has an interest that those tests are simple, inexpensive and applicable everywhere. Due to the significant price difference between the costs of a therapeutic drug and a diagnostic test, the profit of the diagnostic test itself typically becomes secondary. The primary purpose of complementary and/or companion diagnostics is backing up the application of the corresponding therapeutic drug. So "…*the drug developer wants the most accurate test available, to the greatest number of physicians, at the lowest cost, in the shortest period, with all attention focused on selling the greatest volume of pharmaceuticals*"(Agarwal et al., 2015).

The empirical data will highlight the stakeholder´s view on the potential use of diagnostic radiopharmaceuticals as a CD, the challenges associated with the classification and how CDs will, in general, affect the treatment of patients

4.3.1 The Stakeholder´s Definitions of a Companion Diagnostic?

In order to classify the stakeholder's statements, we first had to check the interviewee's knowledge on the term CD and their (personal) definitions. Our results confirm statements in literature, which suggest that experts have quite a different description, categorisation, and idea of a CD (e.g. J.P.B. O´Connor et al., 2017). Particularly the statements of nuclear medicine physicians and the industry differ considerably.

All statements regarding this topic are in the appendix on page 210

A Nuclear Medicine Physicist´s view:

"A diagnostic test that directly influences the therapy decision, a key test that describes whether a patient is eligible for therapy or not. Later the results tells us if the therapy was successful or not."

A view from a medical specialist:

"With the CD tool I have to be able to select patients who have the disease. Furthermore I have to identify in which stage the patient is... both with a certain prognostic relevance. Er, and thirdly it would be desirable that I can use the diagnostic as a predictive marker, i.e. as a marker for treatment response."

A view from a regulatory specialist:

"Companion biomarker and complementary biomarker, but understanding the difference in important. Complementary biomarker provides information on how they threated, a tool to monitor progression, monitoring success of the therapy. Companion diagnostic is a mandatory element in the therapy measure. So the companion is necessary if it is not part of the therapy."

A Pharmaceutical Industry´s view:

"So to my mind a companion diagnostic is a subset of predictive biomarker that specifically developed in conjunction with a therapeutic."

A view from the Molecular Imaging Technology Industry:

"Sure, the companion diagnostic in general in my view qualifies a patient for a certain therapy and also monitor the patient on that therapy. The examples are in widespread use are very types of tissue markers, before put on a cancer drug like HER2, before getting Herceptin. And many many examples like that even if they are blood based or tissue based test before being put on a cancer chemotherapy. And because this is all about diagnostic imaging there has been some general lack of companion diagnostic using molecular imaging as that qualifying test before being put on a drug. And even though we keep holding out that it is potentially very interesting, we have some emerging areas that would probably fit the definition."

I. The Nuclear Medicine View:

In general, nuclear medicine practitioners have well described the use and meaning of companion diagnostics, but the answers show a different level of knowledge on this topic compared to representatives of the industry. Two of the interviewees imagine that a CD is purely an imaging test, and do not refer to other possibilities such as in-vitro companion diagnostics (ICD).

> *"For me, the CD is medical imaging that stimulates follow-up. In a way, that compensation for a therapeutic drug are made if the CD test has been performed… So a practical example: … one would perform an FDG PET or PET after two months to show that a tumour is actually responsive."*

Others have presented an in-depth knowledge and have talked at length about the need of biomarkers and how they will add value to the patient management process.

> *"In principle, in the age of precision or personalised medicine, we are increasingly seeking therapies for precise targets or target structures, because, say, there are modern biological therapies that are highly efficient, but where the patient selection is essential. Moreover, we know that current patient selection on the basis of, for example, tissue biopsies or on the basis of original primary tumour preparations is not sufficient. Because we assume that we are based on considerable genetic and proteomic tumour heterogeneity, we need procedures that predict the presence of treatment-relevant targets with greater accuracy."*

It turned out that the categorisation into prognostic and predictive biomarkers is not yet consolidated among the interview partners. However, this is not surprising as even the EMA has not yet agreed on a uniform definition of a CD.

> *"Interviewer: That means we speak on the one hand of prognostic biomarkers, but also of predictive biomarkers?*
>
> *Interviewee: De facto it is the same. So if I make a prognosis, then I am making a prediction. "*

All interviewees agree that molecular imaging is very well suited as a CD and could play an essential role in both the selection process and also for therapy monitoring.

> *"... we really see ourselves as a CD, so that patients can be assigned to the right treatment by the biological characterisation of the individual clinical picture."*
>
> *"Basically, the CD is the idea of better utilisation of therapeutic drugs, by using imaging tests to identify patients who are firstly eligible for the procedure and secondly responding to the procedure. So you could summarise this briefly. Which in itself is a very good idea, under certain circumstances could improve the outcome of therapeutics, if substances are used only in patients where the appropriate target is available."*

II. The Pharmaceutical Industry´s View:

Compared to nuclear medicine physicians, experts in the pharmaceutical industry have much more profound knowledge in this area. They specifically distinguish between companion- and complementary diagnostic, in-vitro and in-vivo biomarker, and prognostic and predictive markers.

> *"The first thing to say is you really need to understand the difference between a prognostic biomarker and a predictive biomarker. Many cases people failed to understand that, and the literature is full of papers, even from people who should know much better, who think they have discovered predictive biomarker whereas, in fact, they have discovered prognostic biomarkers."*

"In the US we have these terms companion diagnostics and complementary diagnostics. A companion diagnostic means that you must have the diagnostic test done and have positive results to be able to use the drug. Complementary means there is a diagnostic that adds information to make a decision, but you do not need to use it."

One interviewee explained how they have been using biomarkers in R&D and how this helped to close a gap between them and their competitor.

"When we got our first line NSLC we again we went again for the highly enriched population we had shown a clear benefit, whereas [the other company] didn´t do that. They went for a much lower bar, they did not look for the higher population, and their NSLC was a complete failure. So obviously this was a big win and all of a sudden, wow Juhu the diagnostic is really is critically important."

III. The Radiopharmaceutical Industry´s View:

The radiopharmaceutical industry also has a good understanding of Companion Diagnostic, partly because the company of an interview partner himself was in a situation to decide whether the diagnostic test should be approved as a CD or as a standalone diagnostic test.

"Yeah, so I think the regulatory definition for a CD is one which again [our company] would tend not to support. In other words, [our company] doesn´t see the value of calling its product a CD. Which gives it potentially a more restrictive application. Clearly, the diagnostic product will have an indication, or requests for indications from the regulators, based on the data that is in the file. Moreover, if that data involves diagnostic or prognostic, as well as therapy, then it will essentially be registered as a drug by in its own right. Not as a CD. So that is an important distinction."

They decided to go for a "drug by its own right" approval for economic reasons. It seems that the interviewees from the radiopharmaceutical industry, as well as the pharmaceutical industry, primarily think about the regulatory and economic consequences resulting from the registration of a diagnostic test as a CD.

"So in my definition of a CD agent, there would be two levels. One level would be; it is actually only approved label for the therapy. So the FDA would approve a therapy, and on its label, on its official use, it would say: you can only use the therapy once you have done this test. This would be a completely tied and connected CD. The other, maybe more practical version, is the payment. So insurers would say, I am not going to pay for this therapy until you have done this diagnostic test that shows me the application. So there. I have not seen a true FDA labelled CD; the FDA is not really supportive of that. However, insurers always require testing, proofing, especially for therapy which is expensive."

IV. The Molecular Imaging Technology Industry Group´s View:

Even the two experts in the MI technology industry know the term CD very well and know which tasks this test has to fulfil.

"Sure, the companion diagnostic in general in my view qualifies a patient for a certain therapy and also monitor the patient on that therapy. The examples are in widespread use are very kinds of tissue markers, before put on a cancer drug like HER2, before getting Herceptin. Moreover, many many examples like that even if they are a blood-based or tissue-based test before being put on cancer chemotherapy. Moreover, because this is all about diagnostic imaging, there has been some general lack of companion diagnostic using molecular imaging as that qualifying test before being put on a

drug. Even though we keep holding out that is potentially very interesting, we have some emerging areas that would probably fit the definition."

V. The Medical Specialist Group´s View:

Within the group of specialists there were the most deviations from the definition of CD. One interviewee had a good understanding of the term CD:

"With the CD tool, I have to be able to select patients who have the disease. Furthermore, I have to identify in which stage the patient is... both with certain prognostic relevance. Er, and thirdly it would be desirable that I can use the diagnostic as a predictive marker, i.e. as a marker for treatment response."

…for others, one must assume that they are not yet familiar with the term or the currently prevailing definitions of literature.

"Yes, we have several, I would not call it a companion diagnostic, but a diagnostic agent that one uses in certain indications, because you cannot use everything for everything. But one has to know exactly which investigation is best. Of course, what I've been busy with lately is the PSMA scan."

One of the interviewees is a medical specialist and additionally leads a laboratory team researching the development of new molecular in-vitro CDs. For him also PET is a CD that dramatically supports the treatment of patients with lymphoma.

"Among CD's, I would also see PET. It helps us to make therapy decisions on some lymphoma entities, in Hodgkin's, at least in clinical trials. We really value having PET-positive findings, which we then treat accordingly such as irradiation. Otherwise, my lab is doing much research on biomarkers, but we are far from seeing this in clinical use. One lab is looking at genetic markers, especially gene mutation in molecular lymphoma because there is nothing stratified what has long bothered me as a clinician."

VI. The regulatory specialists:

Compared to the US Food and Drug Administration (FDA), the European Pendant (EMA) still has no official definition of a CD. This is being drafted, and the new regulation will enter into force in 2022. The definition will be based on the content of the American definition, but according to the statement of an interview partner not be identical.

"Okay, so when you ask about the definition I mean at the moment there is no agreed definition, at least in Europe. Obviously, there is a definition around the FDA providers, but in the regulations, I am sure you read it, the definition going forward in terms of CD is very similar, but not identical to the FDA definition. You are aware of the new regulation that will come into effect in 2022, correct?"

Another expert from a national authority in Europe defined the meaning of a CD very carefully and described the regulatory requirement at its core.

"God oh god. For me, a CD in the narrower sense is a diagnostic procedure, in the sense of a yes / no answer, which is linked to a drug via a registration document. So actually, CD's are just the diagnostic tests that are required according to the registration, which is really defined in that document. So it is not optional, but a must-have-criterion that needs to be performed so a drug can be administered. After all, drugs are classically approved for a tumour mutation, and then it is clear that I can prove these tumour mutations with a biomarker."

Finally, one interviewee made an obvious statement regarding the use of RPs as CD:

"I think in the future the CD will have to be well certified. Meaning that there will be an assessment biomedicine, if it meets the definition of a CD… PET RP would not fall into the new regulation, only if they work in the device regulation…. However, pharmaceuticals should not be affected."

This statement suggests that in-vivo biomarkers are either not included in the regulation, or that the prescriptions in the regulation will not apply to RP because they are still defined as drugs and therefore generally more stringent safety requirements and efficiency.

VII. Brief conclusion on the definition of Companion Diagnostic:

In general, most of the stakeholders show a good understanding of the role of a CD. Above all, the nuclear medicine doctors described in their statements how they believe that CD will impact patient management and stratification. The industrial representatives already show a detailed knowledge regarding the categorisation of these biomarkers into predictive and prognostic markers. They also differentiated between the companion- and complementary diagnostic and seemed to be aware of how CDs will influence their business.

Representatives of the molecular imaging industry are also well aware of the importance of a CD. The group whose definitions differ mostly from the opinion prevalent in the literature are specialists in the field of oncology. Also in the group of the national regulatory authority experts, the definition varied reasonably. The interview partners from the international regulatory authority did not wish to speculate about the definition as this term is currently being developed and will be implemented in 2022. According to this statement, radiopharmaceuticals are not included in this regulation.

4.3.2 The Benefits and Challenges associated with Companion Diagnostics in General

Currently, there are few companion diagnostics approved by the FDA or the EMA genuinely meeting the definition of a CD. By 2014, a total of 19 CDs were approved by the FDA (U.S. Food and Drug Administration, 2014), compared to a total of 1.453 approved drugs in the USA (data until 31/12/2013) (Gaffney, 2014). A better patient stratification, more targeted use of new therapeutics and improved patient monitoring are expected. Despite the benefits, only a few of these individual diagnostics have received regulatory approval to date. We have therefore asked the stakeholders what reasons this may have.

A Nuclear Medicine Physicist´s view:

"…which is a very good idea in itself and could possibly improve the outcome of therapeutics, if substances are used only in patients where appropriate target exists."

A view from a regulatory specialist:

"The difficulty, of course, is that these subgroups get smaller and smaller. So in tumor mutation, there are two or three mutations that cover most of the patients, 80% maybe 90%. For the last 20% I need a lot more tumor mutations and I have to take a closer look. These are rare mutations and, of course, relatively small subgroups remain at the end, which are difficult to study and of course are not that lucrative."

A view from the Molecular Imaging Technology Industry:

"I think that is a very interesting step into theranostics that will get a lot of things opened up."

A view from the Radiopharmaceutical Industry:

"When Pharma uses RP they can end up with a really

pre-selected, to have the enrichment to be able to get approval. Whereas [the other company] has spent the program for several years and they will be able to show that it worked in all the patients…. So that kind of set us back for a little bit, and there was a lot of... you can imaging… oh Jesus look what we have done. We have anchored ourselves…"

A view from a medical specialist:

"The interest of the clinicians is of course there, but they will wait, I think, for a long time. Because such a development is similar to a development of a drug. That costs millions, you have to say that very clearly."

All statements regarding this topic are in the appendix on page 213.

I. The Nuclear Medicine View:

Benefits:

The great benefit of a CD is the ability to stratify patients more efficiently before treatment begins: *"Treatment would be more restrictive but more targeted.",* with the idea that this improved stratification may also lead to a better outcome, at least that is the prediction of several interviewees.

> *"…which is a very good idea in itself and could possibly improve the outcome of therapeutics if substances are used only in patients where appropriate target exists."*

Also, the pharmaceutical industry could benefit from the use of these biomarkers, since a more targeted selection of the study population significantly increases the likelihood of the success of a new therapeutic drug.

> *"On the other hand, it is the case that the therapeutic substances ... are targeted only to hit the tumour cell, i.e. targeted therapy. Moreover, if they treat the same 100% again, then in many cases they will get a negative result. The conclusion would be: the therapeutic substance is not effective. Now, if you identify and treat the right 30%, then they will see the therapy is highly effective. If the industry really wants to make tumour-specific substances, targeted therapy, and want to obtain approvals, then they are extremely interested in the CD."*

Challenges:

The main concern for the majority (57%) of interviewees is that there is no added value for the pharmaceutical industry, but on the contrary, the market becomes limited. Interviewees do not expect industry to pursue this development.

> *"It is not a good incentive for the industrial side to implement such diagnostic tests in our system right now. The academic community has an extreme interest in it, but the industry partners not necessarily."*
>
> *"Biggest obstacle: there is no financial gain for those who offer a therapeutic agent."*
>
> *"The snag is that it sounds good, but it is often not so interesting for the pharmaceutical companies that are supposed to be the driving force. Because of course, in a nutshell, they have a commercial interested that their substances are broadly applied and not in selected cases."*

Also, some interviewees see a challenge in the availability and validation of a CD, especially an imaging CD in the clinical setting. In some cases even more than one biomarker must be used to demonstrate the target structures.

> *"The other is the situation that there can be multiple positives, positive for breast cancer, but still for another factor. That would require multiple imaging procedures, which is certainly difficult."*

Summarizing, this group is very positive about the benefit of a CD but fear that the challenges not so easy to overcome. For an interviewee it is relatively simple: either the Nuclear Medicine Community manages to provide the proof of the efficacy of the CD itself, or a drug producer realizes that there is any benefit for himself.

II. The Pharmaceutical Industry´s View:

Benefits:

The pharmaceutical industry interviewees confirmed that a diagnostic test, able to detect an appropriate target, leads to an increased therapeutic benefit.

> *"…if the mutation is not there they have no chance to responding. If the mutation is there, they have a good chance to respond. However, there is not black and white with the checkpoint inhibitors. Which makes it complicated."*

One of the interviewees had an excellent historical overview of the use of predictive biomarkers and CDs and could precisely name the fields of disease in which these markers had an influence and which previously had brought little benefit.

> *"There are four disease areas where predictive biomarkers and companion diagnostics, personalised medicine, has really had an impact historically. 1. Cancer, 2. Infection, 3. Rare diseases and 4. Drug metabolism… And as you know many cancers are driven by tumour mutations, and so you can identify, by the right mutation, you can choose the right drug. It is less true that predictive biomarkers/ CDs had an effect on major diseases like asthma, myocardial infarct, diabetes, dementia, depression, psychosis. "*

We also wish to highlight a statement that illustrates very clearly the usefulness of CDs in the development of new therapeutics. With this specific biomarker, the company was able to catch up to a close competitor with a similar indication.

> *"When we got our first line* [disease] *we again we went again for the highly enriched population we had shown a clear benefit, whereas* [the other company] *didn´t do that. They went for a much lower bar; they did not look for the higher population and their* [product] *was a complete failure. So obviously this was a big win and all of a sudden, wow Juhu the diagnostic is really is critically important."*

Challenges:

The last statement shows very clearly the benefits of a CD, but also the impact of this tool on the market potential and thus sales number of individual companies.

> *"Ah in* [this indication] *it helped us to get an approval rapidly, but when we were doing the advanced* [indication] *the... ah... we using that method, we had a limited population that we could have the drug available for. Because we selected, have pre-selected, to have the enrichment to be able to get approval. Whereas* [the other company] *has spent the program for several years and they will be able to show that it worked in all the patients. And in the advanced [indication] patients you get a benefit to chemotherapy by using the [drug], and you did not need to enrich it with the diagnostic. So that kind of set us back for a little bit, and there was a lot of… Oh, Jesus look what we have done. We have anchored ourselves…"*

Another interlocutor points to another challenge, associated with the reimbursement of therapy if the CD test shows negative results. Since a CD test does not always detect the target, the drug may still be useful.

> *"However, even if you do not see* [the target]*, also these patients respond. So it is in the interest of the dynamics between the oncologists, who want to make certain that the patients have any chance to benefit from the drug that could help them. Moreover, the payer who are saying "well wait a minute, this is an expensive drug, and we cannot give it to every patient", who might be... We have to focus on the patients who do benefit. So the way it plays out varies from country to country."*

Additionally, the close link between the diagnostic test and the therapeutics can have substantial economic implications, especially for the company providing the CD test.

> *"As you know in drug development, in every hundred projects the industry starts, if they are lucky one becomes a medicine. So you have huge, you have huge attrition. And of course, you have attrition in the diagnostic. So for the academics working on Etarfolatide and indeed for the company developing it, they got nothing out of it. Even it was a great tracer when the therapeutic died the market for the diagnostic died as well. So it is a very unattractive place to be in."*

III. The Radiopharmaceutical Industry´s View:

Benefits:

The positive statements regarding CDs are limited in this group, even though they have already acknowledged that CDs will have a great benefit for patients (Chapter 4.3.1).

> *"…if you select, for HER2 for instance, HER 2 and HER receptors you know, Herceptin does not work unless you got HER receptor breast cancer. So that is a fantastic combination of patient selection…"*

Challenges:

Only two of the five interview partners commented on the challenges of the CD and agreed that the economic impact for the developer/ manufacturer is enormous. Registering a diagnostic test as a CD limits the market and thereby aggravates the problem of profitability.

> *"When pharma uses RP, they can end up with a really small indication, and your return is even harder to get. Where a broad indication in a diagnostic is much better because you have many more opportunities to sell you scan."*

Another argument that has already emerged in the nuclear medicine- and molecular imaging technology expert's groups: the risk that the diagnostic test will be successfully implemented, but the therapeutic fails or that another therapeutic agent works better in this indication. The combination of the test with the drug increases the economic risk.

> *"I guess part of it is how broad the indication is… By the time you come out … you do not actually have a really big patient pool to sell to. Because you can only sell it to patients in that cancer (laughs), with that therapy. And there is always the risk that a different pharmaceutical company … finds a different therapy that is better in that cancer. Er, the whole linking to pharmaceuticals is really difficult from a commercial perspective because your market potential is quite small."*

Discussions with experts in this group show that they do not see any advantage in classifying their (future) products as CD unless it is a commissioned work by a pharmaceutical manufacturer.

> *"… [the company] doesn´t see the value of calling its product a CD, which gives it potentially a more restrictive application."*

IV. The Molecular Imaging Technology Industry ´s View:

Benefits:

The interlocutors of this group are once again using their experiences of the Radiopharmacy Business to provide concrete answers to the benefits and challenges. Both emphasised benefits in stratification and therapy monitoring:

> *"... the diagnostic testing partly helps to decide which patients are likely to respond to certain therapies and therefore should or should not get this therapy."*

“And in the course of the therapy give information on how successful the therapy is and which interventions should take place ... So to get confirmation that the therapy is effective and can be continued."

An interviewee from this group also expects much from the concept of Theranostics: *"I think that is a very exciting step into Theranostics that will get many things opened up.”*

Challenges:

The answers match the statements of the stakeholder groups. One interviewee has detailed strong arguments for each challenge in the area of, "technical & scientific", "economic constraints" and "regulatory”.

"The challenges of both technical and scientific nature. First, you really have to develop this CD so that the test itself works as a CD."

"But on the other hand, of course, there are the economic challenges, because the diagnostic test is linked to the success of the therapy." In general, the success chances of a diagnostic test is greater than the chance of success of a new drug. So the chances to launch a product on the market decreases for the developer of the CD. "

“Of course, the third challenge is the regulatory side ... obviously, there is no way to submit the diagnostic test and therapy as a package to the BfArM, EMA or FDA. One has to negotiate with each authority, so there are also challenges."

Especially in the field of Molecular Imaging, an interviewee expects RPs to have a hard time being used as a CD. According to his discussions with the pharmaceutical industry, the method is too complicated, too expensive and the availability is low. The pharmaceutical industry would always look for ways around imaging biomarkers, unless they are forced to do so by the regulatory authorities.

"And I believe that is because the pharmaceutical companies do not want a potential market limiting step on the way using their drug. I had some conversation with the imaging teams inside big pharmaceutical companies, which gave me that hint, not as an official policy but they believe that MI is used widely in their clinical trial process, but they never wanted it to be a mandatory step underway using their drug. Because unlike a blood test driven tissue test, they still looking at MI as a complex, expensive hard to find the thing that would limit their market for their drugs. So even if it could lead to a better patient population that take the drug, they view that as market limiting and unless the regulatory body or payer absolutely required it, it tried to find a way to get the drug approved without it."

V. The Medical Specialist´s View:

Benefits:

This group again speaks about the benefits from a medical point of view and what benefits the CD will have for the patient.

“With the current therapies, we can control the disease in many, many patients. However, there are approximately 20 to 25% of patients who have a rapidly progressive course, which die very early… We must stratify these patients early for other therapies, experimental therapies. We have access to these therapies, but we only use them when the standard therapies have failed. But if we could predict that the standard therapies would not work in the first place, we would help a lot."

Challenges:

The challenges are also taken from a medical point of view, i.e. validation and thus specificity and sensitivity.

> *"Well, biomarkers have to be first established, validated so we can use them in clinical routine. It needs to be robust, reproducible, which also means harmonisation and standardisation."*

Moreover, another specialist sees the tumour specificity or tissue specificity as a challenge, but an even more significant challenge is the detection of the small quantities.

Another responder reported from his personal experience, how the industry neglected to support the development of a biomarker in this institution.

> *"And we have got a relatively large lab, and we have been trying to develop biomarkers. That costs money and the company, I do not name them, that sells [the product] ultimately gave us no money. Understandably, why should they sponsor a biomarker development that in the end says: "Okay, in this case, you should not give this drug"? They hold us back for a long time, but I knew from the beginning that they would not give us any money. So I would say the development of these biomarkers will be difficult."*

VI. The Regulatory Specialist´s View:

In one interview with a regulatory specialist, we directly questioned him if industry may lack interest in developing CDs for their new therapeutics. The answer of this interview partner was conclusive:

> *"So probably we need to distinguish broad categories of drugs where say the more traditional, even if not very clearly targeted drugs, where the biomarker simply means a restriction in indication. So you try to avoid to develop it too specifically, to target a bigger population that could be the industry´s interest. But I think the whole other bunch of drugs, which unless you are very specific and fish out what is the right population, they will simply not work. "*

Again, we heard arguments that partially agreed with other groups, but also new arguments/ challenges. One regulatory specialist believes that the low rate of approved CDs also results from the lack of cooperation between the "diagnostic" and the "therapeutic" industry.

> *"And the second reason why there are not so many CDs, because the world of industry is set up differently. There were and are classic drug manufacturers, they were just looking after therapeutics, and on the other hand, there are diagnostics manufacturers, who only took care of diagnostics. Moreover, yes, only in the last 10 to 15 years has there been this realisation that with molecular oncology, it is actually necessary that the industry there work much closer together to bring successful products to the market."*

And while we have heard in the previous statements that small patient subgroups are financially not attractive, the regulatory expert believes that there is no way to avoid it from a technical/ scientific point of view.

> *"The difficulty, of course, is that these subgroups get smaller and smaller. So in tumour mutation, there are two or three mutations that cover most of the patients, 80% maybe 90%. For the last 20%, I need a lot more tumour mutations, and I have to take a closer look. These are rare mutations and, of course, relatively small subgroups remain at the end, which is difficult to study and of course are not that lucrative… So I have to do a lot of screening work, in clinical trials, until I find the patients."*

VIII. Brief conclusion on the benefits and challenges associated with Companion Diagnostics in general:

All interviewees who commented on the "benefits of CDs" also see an advantage in these individual diagnostic tests. Benefits include more targeted therapy, better outcome, better patient stratification, and better clinical trial outcomes.

Regarding challenges, we again see the different perspectives of the stakeholder groups. The physicians are increasingly concerned with the topics of efficiency generation, validation and standardisation, while industry recognises, above all, the economic constraints that can arise from this classification. The medical professionals argue that CD will have a complicated way ahead because there are currently no incentives for the industry to implement those tests. On the contrary, the therapeutic drug market will most likely become limited. The interviewees from the radiopharmaceutical industry group made clear that it is out of the question that they would register a new diagnostic test as a CD on their own. This classification would negatively affect their already small market potential. Interesting, but not very surprising, was the testimony of an interviewee from the Molecular Imaging Technology Group who learned in personal discussions with the pharmaceutical industry that molecular imaging will have a hard time to be accepted as a CD. The hurdles are just too high compared to blood- or tissue tests. Finally, the statements of the experts from the group of regulators were very informative. They acknowledge that implementation will be a challenge, especially for small subgroups, but new, specific therapeutics will not be able to prove their benefits unless they have identified the right population by CD in advance.

4.3.3 Pros and Cons of In-Vivo Imaging Biomarkers compared to In-Vitro (molecular) Assays

A view from a medical specialist II:

"Will Molecular Imaging have a role in new, future therapeutic strategies?"

"It depends on the topic of treatment and if you have a biomarker that is good enough that the concentration of the biomarker tells us" ok, does the patient have a response or not? ". … then you could do without the imaging diagnostics."

A Nuclear Medicine Physicist´s view:

"The differences are clear! A blood sample will characterize the patient as a whole, but imaging can accurately characterize individual regions and individual organs. At least with our nuclear medicine techniques, we visualize the whole body and we can look at individual regions. You cannot do that with a systemic marker, and the main goal of therapy is not to treat the entire organism, but to treat a certain target region."

A view from the Radiopharmaceutical Industry:

"…I think the problem that pharma companies always had with PET is the availability of the product. And so if you were to compare testing the Cerebrospinal fluid, with PET then effectively anyone, who can do a lumbar puncture, can get cerebrospinal fluid… If you used CFS testing then maybe you therapy get access in 90% of the available patients, if you got a PET/CT scan in front of it then you go to reduce the access of your therapy to patients."

A view from the Molecular Imaging Technology Industry:

"Well, I would say, one thing we have not discussed so much yet, which is very important to me. What are the disrupters, what is threatening molecular imaging? ... As you can see on the amyloid side, there is already the CSF test and there is intensive research on blood-based tests. And the disruptive innovation for molecular imaging is if a test exists which is much simpler and has the same amount of information. In the end the question arises: "Why do I have to image?"

A view from a medical specialist I:

"And I do not think that one will replace the other. I believe the added value in the reasonable combination of both."

A Pharmaceutical Industry´s view:

"In oncology imaging has a different burden, imaging is more like a clinical workup scenario… You do use imaging a lot, readout and protocol itself….they are not really a stratification or something in diagnostic use."

A biomarker is a *"defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to exposure or intervention, including therapeutic interventions"*

(Biomarkers Definitions Working Group, 2001; O´Connor et al., 2017). Fundamentally, two different types of biomarkers can be distinguished whose task is to diagnose-, monitor the disease, to identify risks and to select the best individual therapy in the sense of personalised medicine. The most widely used type is molecular diagnostics, which uses in-vitro assays to detect biological markers in the genome and proteome. For these tests, a small amount of blood is enough to detect the smallest amounts of a molecule and to characterise a tumour based on the molecular signature (DNA and mRNA) (Jain, 2015). A keyword in this area is also Liquid Biopsy, a method using a blood sample to detect circulating tumour cells and cell-free tumour DNA in cancer diagnostics. The second method is in-vivo imaging, which can noninvasively, and in real time, visualise cellular processes at the molecular or genetic level. Compared to the in-vitro assays, however, in-vivo imaging can additionally visualise the anatomy and represent the origin of the physiological and molecular function (Bleavins, Carini, Jurima-Romet, & Rahbari, 2011)

All statements regarding this topic are in the appendix on page 217.

I. The Nuclear Medicine View:

As expected, the Nuclear Medicine Group agrees that the benefits of molecular imaging being used as a CD are very high. The unanimous opinion is that in-vivo imaging biomarkers (IVIBs) can accurately represent specific regions in the body, which is not possible with in-vitro companion diagnostics (IVCDs). The IVCD test can only give a general status over the entire body.

> *"The differences are clear! A blood sample will characterise the patient as a whole, but imaging can accurately characterise individual regions and individual organs. At least with our nuclear medicine techniques, we visualise the whole body, and we can look at individual regions. You cannot do that with a systemic marker, and the main goal of therapy is not to treat the entire organism, but to treat a certain target region."*

The interviewees very often address exact localisation, visualisation of the tumour's heterogeneity, real-time quantification and non-invasiveness.

> *"In other words, we do not have* [relating to in-vitro assays] *any real-time procedures there that can represent the biology of an entire tumour. Moreover, of course, this is the strength of imaging techniques, especially biomarker-driven imaging techniques. Because you can basically visualise and quantify in real time, realistic, non-invasive the entire body, so all the lesions and not just part of a tumour."*

The interview partners also do not shy away from the comparison with the gold standard, the biopsy. For an interviewee therapy decisions being made on a biopsy results are "outdated" since it is first of all hard to take the sample from the right place, and secondly the tumour pathology changes in the course of therapy.

> *"Yes, well, the in-vitro assays, you have to say brutally, almost exclusively focus on the primary tumour. So the tissue that was removed during the primary tumour surgery will be used, at a later time if there is a recurrence, to decide on the further therapy. Of course, it is often the same, but if you look for example at breast cancer, then you know that in about 30% of women, who express Herceptin receptors in a primary tumour, the status will change.*

The precise localisation of a tumour plays an important role, not only in primary diagnostics but also in therapy monitoring. While the IVCD can most likely accurately predict if a recurrence has occurred, the IVIB test can accurately pinpoint to the recurrence and detect metastasis, which may be surgically treatable.

“Of course, imaging is important in many situations: if a tumour disseminates in the body and extracts a substance, then ultimately an integral value, which is the tumour marker, really does help us a lot. It may be that certain clones respond to the therapeutic, but others do not, and so you cannot treat them specifically."

"In principle, you can have a patient with liver metastases, or lymph node metastases in the lungs and metastases in the lungs respond to the therapeutic drug, but the liver metastases continue to grow. Thus [with imaging] *you can specifically tell if you need surgery or not. "*

One interviewee agrees that IVIB have many advantages, but he also tried to be realistic. From his point of view, it just does not need an imaging biomarker for everything. One should focus on areas that create added value.

"You know Imaging people usually are quite limited in their understanding of medicine. They are tunnel blinded … Because they believe that you will be able to have, for any drug, a biomarker, an imaging biomarker. That is, of course, total nonsense. So you have to focus on the stuff that is really needed."

Another interviewee noticed that molecular imaging is an expensive procedure, which is why he also believes that nuclear medicine should focus more on areas where stratification would be beneficial due to the high cost of therapy.

“The main disadvantage is the cost ... that it is much more laborious and comes with costs ... I would not develop a PET biomarker for cold medicine. Because if a snuff preparation costs 20 €, then I cannot make a PET scan for 500 €. However, if that is a new generation immunotherapeutic for € 100,000, then perhaps a PET is indexed.”

II. The Pharmaceutical Industry´s View:

Pros:

The distribution of pro, neutral, and contra-statements shows very clearly that the group of pharmaceutical industry experts is very contrary to nuclear medicine. Few opinions would favour IVIB over IVCD, besides using them as a research tool in R&D (see chapter 4.1).

"But the motivation for us to develop it is that we want to see how that changes in time overtreatment … one of the reasons you have a higher response rate with chemotherapy and checkpoint inhibitors [product name] *is that in those patients the chemotherapy killing of cells, you got all kind of DNA, and the immune systems are activated trying to clean things up. Then you get the checkpoint inhibitor in there, and it can really just finish it off. So we want to look at that kind of research questions and see to understand what changes... we are also trying to develop tracers for CD8 and other aspects of the immune system. To really use it as a research tool."*

Above all, the interviewees appreciate the possibility of considering the heterogeneity related to a primary tumour as well as the metastases invasively and over a specified period.

“So when you do IHC [immunohistochemistry] *you have a limited sample of a tumour... so what the nice things about imaging are, you cannot look at just one tumour you cannot just look of parts of a tumour, you can look a whole tumour and at more tumours throughout the body. And the hope is that this would be more valuable, and it would do a better job in predicting patients response, but this is true or not time will tell."*

However, in general, it has to be said very clearly that the people in this group are not interested in using molecular imaging as companion diagnostics. According to a statement, maybe also because so far *"We do not have many good examples of an imaging assay that is a companion diagnostic."*

Cons:

These pharmaceutical experts, who are specifically dealing with the topic of molecular imaging or companion diagnostics in their companies, have several arguments against the use of IVIB as a CD.

> *"Imaging has the entire business of radiopharmaceuticals and its maturity in the clinics. Right, if something that is in my view more relevant in terms of therapeutic diagnostics. So something which is established, like a perfusion scan with technetium, those I can still see as clinical criteria for treatment and maybe reference criteria. But I do not think there is any example outside of oncology that is using it as a CD."*

Specifically, in oncology, IVIB have difficulties in portraying the entire tumour's mutations, whereas in-vitro assays can detect all mutations in a single test.

> *However, really for tumour mutations (imaging) has a tough struggle. It is also the truth, the case that the imaging tools we have are not as precise as the free circulating DNA tools. In the MICAD [Molecular Imaging and Contrast Agent Database] database there are hundreds of eGFR tracers, but remember there are many mutations, such as mutations which yet are discovered. And ideally, you would need to profile every molecular imaging tracers against all mutations, known and unknown. Which is almost an impossible thing to do."*

In addition to the scientific barriers, there are also regulatory and economic hurdles that are not favourable for an IVIB. A very knowledgeable interviewee narrates that for the regulatory dossier you need to get the patient segmentation is locked down from the beginning, which is easy for a blood test, but a challenge for the imaging test.

> *"In order to get the regulatory dossier, for registration, you need to have your patient's segmentation done right from the beginning of Phase II or even Phase I in oncology. And that is actually quite easy to do if you have a blood test. But it is very very difficult to do it with an imaging test. To get an imaging test logged in before you have seen any patient. That is the challenge."*

And finally, high costs and low global availability of PET/CT are against their use. The sale of the therapeutics and therefore the gatekeeper should be as easy as possible to overcome.

> *"The other side, one of the lessons I learned working on the IHC diagnostics... Firstly I see it is much more of an issue in Europe, where there is a lot more cost consciousness. There are hospitals given a certain amount of resources to take care of the patients, and that is it. In the USA there is no control, the only control is that the label says you cannot administer this if you do not have the test. So you get the test done, the same thing can happen in Germany. The German government was tough for us and with our organisation. They are going to say "yeah ok, so you need to have that test done, but 125 Dollars is too much. We do not have the money in our system to pay 125 Dollars for this test. So, we need to get that test for 45 Dollars."*

III. The Radiopharmaceutical Industry´s View:

We can keep this analyses short and concise because most of the arguments have already been mentioned in other chapters. The representatives in this qualitative research would not take the path to develop a CD. There are pro-arguments, but few. For example, one interviewee believes that there is

even more significant potential for IVIB markers in cardiology and neurology. Another interviewee reports that his company has also been approached by pharmaceutical companies with the request to develop a suitable imaging biomarker that can be used in clinical trials as an inclusion criterion.

> *"Pharma has recognised that biomarkers and imaging are critical in the disease development… Today they recognised the use of biomarkers in the drug development, using imaging biomarker as inclusion criteria. Pharma companies are clearly coming to us with the intention of appropriate patient selection. They are very interested in researching biomarkers, in the development point of view."*

However, in principle, the interviewees believe that IVIBs will have a hard time being used as a CD. An important argument, which was already mentioned by an expert from the pharmaceutical industry is the availability of PET and PET/CT. Easy access is the fundamental prerequisite for a CD. Otherwise, the therapeutic drug cannot be used at all according to regulatory requirements.

> *"…I think the problem that pharma companies always had with PET is the availability of the product. And so if you were to compare testing the Cerebrospinal fluid, with PET then effectively anyone, who can do a lumbar puncture, can get cerebrospinal fluid… If you used CFS testing then maybe your therapy gets access in 90% of the available patients, if you got a PET/CT scan in front of it then you go to reduce the access of your therapy to patients."*

IV. The Molecular Imaging Technology Industry´s View:

Similar to the other industry groups, there are few pro-arguments. In this case only one, but it is important to note that only answers in which the IVIB is used as a CD were considered. The pro-argument concerns the possibility of IVIBs to provide information such as localisation of metastases, the inclusion of lymph nodes et cetera. Demonstrating the value of imaging is crucial.

> *"In oncology, with secondary diseases such as metastases, the involvement of lymph nodes, and so forth, you can see that imaging can provide more information than a PSA test ... Hopefully, imaging can deliver much more information such as localisation or spreading of the disease. You really have to find the sweet spot of molecular imaging. Show that the test as such also makes sense and provides the information that contributes to the management of the patients."*

Otherwise disruptive innovations such as new in-vitro tests could be dangerous for molecular imaging. The interviewee recommends careful observation of these new techniques and consideration of the added value of MI.

> *"Well, I would say, one thing we have not discussed so much yet, which is very important to me. What are the disrupters, what is threatening molecular imaging? ... As you can see on the amyloid side, there is already the CSF test, and there is intensive research on blood-based tests. And the disruptive innovation for molecular imaging is, if a test exists which is much simpler and has the same amount of information. In the end, the question arises: "Why do I have to image?"*

The second interlocutor agrees that MI lacks availability and is too expensive to compete against in-vitro biomarkers.

> *"Because unlike a blood test driven tissue test they (pharmaceutical industry) still looking at MI (Molecular Imaging) as a complex, expensive, hard to find the thing that would limit their market for their drugs."*

Using an example from Alzheimer's diagnostics, an interviewee predicts that if blood tests achieve equivalent information as the imaging tests, imaging will soon decline and will only be used in selected cases.

“However, if the CSF test, and the future blood tests, can provide information that is equivalent to the information of the imaging test, then I can well imagine that at least the use of imaging will decrease and you will first perform a cheap blood test. Moreover, for those who need an additional imaging test, for whatever reason, the imaging test will be performed in certain groups."

V. The Medical Specialist´s View:

The group of specialists commented very positively on the possibilities of molecular imaging, but not in the context of the CD. Although the question was formulated this way, the interviewees unfortunately talked only about current experience with existing diagnostic tests and not about imaging biomarkers as CDs. Therefore, no pro-arguments can be noted.

However, some statements have been summarised under the point "Neutral". For example, one such statement is that this urologist does not wish to give advantage to the in-vivo imaging marker over the in-vitro marker since he is only interested in getting any kind of useful marker that supports his work.

"No, whether that is a liquid biopsy or something else, actually, I do not really care. We have been looking for a better marker, compared to the PSA value, for years. PSA is not a good marker in primary diagnosis, but it is the best that we have, and one we have learned to deal with."

Those statements that predict a combination of both test variants were also neutral. Half of the respondents believe that there will be a combination of both procedures and that in the future this will be the best way to describe the status of the patient.

“And I think there will be a combination. I do not think that one will replace the other. However, a combination of both will be able to represent the best possible status of the patient."

For an interviewee, Liquid Biopsy is the future, because it will be easy to get the molecular information out of blood and potentially get a prognostic and predictive market.

“The big cue of the future is Liquid Biopsy. That one gets the molecular information about a tumour by markers in the blood, be it circulating tumour cells, exosomes or something similar. You get a prognostic or predictive marker."

IX. Brief conclusion on the topic “Pros and Cons of In-Vivo Imaging Biomarkers vs In-Vitro Assays”

Not surprisingly, the group of nuclear physicians is very positive about the use of imaging biomarkers as companion diagnostics. The many pro-arguments highlight the advantages of imaging compared to blood and biopsy tests. These arguments range from the possibility of the exact localisation of the target structure, detection of heterogeneities, monitoring of changes in tumour pathology in the course of therapy, as well as the detection of metastases and many more. One interviewee from the nuclear medicine group, however, believes that many of his colleagues may be asking too much and one must be realistic and accept that imaging does not make sense everywhere. Amongst others, molecular imaging is expensive so his advice would be to focus on areas where the test makes sense.

The pharmaceutical industry is not as receptive to the topic of the use of imaging biomarkers as a CD. Although they recognise the value of the method, which they also used extensively in the area of R&D, they believed that IVIBs have, compared to the in-vitro panel tests, a particular disadvantage in the field of oncology. Since new therapeutics will target tumours with a specific mutation(s) and imaging test will not accurately show the mutation spectrum. So a pretty big hurdle.

Two of the interview partners from the pharmaceutical industry believe that imaging has established a strong foothold, especially in the clinical workup process, but is unlikely to be suitable for stratification.

The radiopharmaceutical industry also sees the benefits of molecular imaging but believes its low availability is an obstacle for the pharmaceutical industry. Also, these interviewees have already stated on another topic that they would not classify their future products as CD, but as a stand-alone diagnostic product.

The interviewees from the molecular imaging technology industry are aware of the danger that the in-vitro test outdoing the imaging tests. Since a simple, cheap test provides the same information provides it will be difficult to survive.

Finally, the group of medical specialists who would not prefer the in-vivo imaging over the in-vitro tests, but want a useful CD test. Both liquid biopsy and an imaging marker would be an alternative, but in general, they believe a combination of both techniques will get the best result.

4.3.4 Should Biomarkers Be Mandatory Prescribed by Regulatory Authorities?

Since the successful launch of the HercepTest, as one of the most widely used companion diagnostic test to date, there has been hope that many more companion diagnostics will follow. However, so far, instead one hears that the development is slower than expected (Towse, Ossa, Veenstra, Carlson, & Garrison, 2013), that the potential is not yet realised (Trusheim et al., 2011) and the utilisation is constrained (Luo et al., 2016). So we asked the nuclear medicine, the pharmaceutical industry, the medical specialist and the regulatory specialist groups the provocative question, whether they believe that biomarkers will soon be mandatorily prescribed for new (expensive) therapeutics?

A Nuclear Medicine Physicist´s view:

"... the way we really have to go! Whether it's easy to walk, I vaguely doubt it. But that's the only true way."

A view from a medical specialist:

"That's a good question. I can imagine, I can just imagine it. Right now, of course, it's fictional, because there's no marker that's so good that it could justify that. But I could imagine that the health insurances say: "yes only this and this patient we will cover costs". It also depends a little bit on the fact that biomarkers driven clinical trials need to be performed… And that something is prescribed by law is absolutely conceivable! The question is, of course, this is contrary to the interests of the pharmaceutical industry. That will be interesting to see. Of course they want everyone to get it."

A Pharmaceutical Industry´s view:

"Well, the regulators are not concerned about the cost of the drug. That is a different question for the health care systems."

A view from a regulatory specialist:

"Well, I mean such would not be the right concept. But if a CD would be required to identify a patient population that benefits from the drug in some way, yes. Because if you need a test to identify the right patient population for your drug, I think in an indirect way you could, you know someone would use the word mandatory, but you know the company would need to show the evidence and that is sort of in an indirect way. They would need to have the evidence to support that."

All statements regarding this topic are in the appendix on page 221.

I. The Nuclear Medicine View:

	Strong Pro	Possibly	Strong Contra
Mandatory Companion Diagnostic?	◆		

The Nuclear Medicine Group supports the idea that biomarkers should be used, while the majority foster the idea to have those mandatorily prescribed (83%).

"... the way we really have to go! Whether it is easy to walk, I vaguely doubt it. However, that is the only true way."

It is interesting to note that almost all the interview partners mainly have the costs of drugs in mind and have fewer arguments on the impact of this test on patient health/ outcome. Only one doctor explained that it is unethical for him to continue exposing patients to chemotherapy, even though there is no benefit.

"I think there should be CDs; I think there should be biomarkers to select patients appropriately. Yeah absolutely, because there are two ways in oncology. There is one way that you try something and treat, and you got six cycles of chemotherapy, and in the end, you may know if it worked or not. To me, that is unethical, especially after one or two cycles you could do a simple FDG glucose metabolic imaging and see if the treatment works or doesn´t… that would be my first biomarker requirement. Is your glucose metabolism going down? If not, stop the treatment. However, we have not reached that point."

The rest of the interviewees mostly recognise the possibility to save costs. As one interlocutor explained: PET will not save lives of patients with bronchial carcinoma, but it will save costs.

"Yes, I think that will happen more and more. Because our health care system is already groaning enormously under the current costs. Moreover, in the future, the new therapeutics will certainly not be cheaper but rather more expensive. If you compare the costs of new therapies such as KART cells, ranging from € 200,000 to € 300,000 or more per treatment cycle, and costs of therapeutic agents such as 5-fluorazil, which have been developed in the '90s and' 80s and have total lifetime costs of less than 100 D-Mark or Euro per patient have, than you just see the gigantic difference."

However, some nuclear physicians believe that the path of introduction will not be accessible. In principle, from the point of view of an interviewee, the authorities could effectively even been regarded as allies and actually should have the interest to implement CDs to save costs. However, there is the belief that such a political process can only be initiated if the costs become uncontrollable due to expensive drugs. Moreover, even then, the authorities first have to realise that a diagnostic test can reduce costs.

Finally, there is still the question of what kind of diagnostic test is required. From a discussion partner, this will be decided above all by the pressure and the commitment of the industry.

"Yes, they will be demanded, definitely. It is just the question which tests required. Of course, the pressure and commitment of the industry will be crucial regarding which detection methods and biomarkers are required. However, that will come as surely as that Amen in the church! It is already happening now."

II. The Pharmaceutical Industry´s View:

	Strong Pro	Possibly	Strong Contra
Mandatory Companion Diagnostic?			

In this group, only one interviewee has answered the question and denies that CDs will be mandatory, at least not for every new drug.

"I do not think it is going to be mandatory for every drug; it is going to depend from drug to drug, indication by indication."

In principle, however, the interviewees expect that it will be used more frequently in the future. However, the argumentation of an interviewee is clear that if the manufacturer manages to prove the benefit of the average population, then there is no benefit to the diagnostic and the product will be approved without this CD.

> *"What benefit does the diagnostic have? …If you can show in all common population, right, without a diagnostic that the benefit to the patients is substantially more, without the diagnostic, the current therapy, right, so if you can improve the outcome significantly, they will approve the drug. Certainly, outside the US, they approve the drug, but the payers are not going to pay for it. So I think the way the diagnostics come in, the primary driver for that is there are two drugs. The one is "do you need to select that population to show a significant benefit", right, that is the one. Moreover, the second one is "if you do not have the diagnostic to show a significant benefit, is that given the costs of the drug, is that significant benefit enough to not have to use a diagnostic".”*

Specifically, outside the United States, three interviewees expect the payer to drive the use of biomarkers.

> *"Interviewer: Will they (regulatory authorities) demand a CD, maybe an imaging CD for like very expensive therapeutic drugs?:*
> *Interviewee: So yeah, very short: it could become important, it does not say it is right now, but it could become important either by the regulatory agency or by the sphere (e.g. insurance companies). And the sphere could be a big driver/ player here.*
>
> *“The payers have a similar view because they want to maximise the cost-benefit regarding patients who benefit and minimise the cost of harm."*

An interviewee differentiates very clearly between the regulatory authorities and other actors in the health system. Because to his mind, the regulatory authorities are only interested in the fact that the use of a biomarker increases the patient´s benefit and lowers harm effects.

> *“So I think regulatory authorities are very interested in stratifying patients so you identify as many as possible who benefit and as few as possible who will have harm. … You could stratify patients with purely clinical observation, stratify them by standardised biomarkers you have in any lab: PSA, lung functional. Or you could stratify them on the basis of a brand newly developed biomarker which is approved at the same time, in other words, a Companion diagnostic. But don't think the regulatory authorities care how you do it, all they care about it is whether you maximise the number of patients who benefit and minimise the number who have harm.*

Moreover, an interviewee predicts that molecular imaging will not be used as a CD, the hurdles for a pharmaceutical company are too high.

> *"No (Molecular Imaging used as a CD), as far as the costs are concerned of molecular imaging tracers in cancer research. The three things you need to look at. Firstly, the assay needs to be locked down before you start and that is extremely difficult. Secondly, if you are competing with a 50$ blood test that could be done in a lab, it is hopeless. And thirdly, the drug companies develop drugs for global markets, and so the imaging also needs to be available in that global market. Moreover, that are really difficult problems, the academics often miss."*

III. The Medical Specialist´s View:

	Strong Pro	Possibly	Strong Contra
Mandatory Companion Diagnostic?	◆		

All physicians in the group of specialists envision that CDs will possibly be mandatory in the future, three (75%) believe that it will undoubtedly be mandatory. However, they believe that this process will take some time. Two of the interviewees instead see the implementation of biomarkers into clinical routine through guidelines:

> *"…I am firmly convinced that if you show the clinical benefits ... that the authorities require these measures. As it is already the case with acute leukaemia, where a detailed molecular diagnosis is carried out. This is also required according to the WHO classification, and there is no reason that this should be different in my area of research. This will almost certainly happen with lymphoma."*

However, the interviewed specialists argue that this is only possible if good biomarkers for stratification are available.

> *"That is a good question. I can imagine, I can just imagine it. Right now, of course, it is fictional, because there's no marker that's so good that it could justify that."*

From a specialist's point of view, it will be interesting to see how industry will react to this initiative because the introduction of starting CDs is contrary to the interests of industry.

IV. The Regulatory Specialist´s View:

	Strong Pro	Possibly	Strong Contra
Mandatory Companion Diagnostic?		◆	

Except for one responder, no one believes that these biomarkers will become mandatory. An interviewee from an international regulatory authority does not believe that this is the right concept. In his opinion there will be no way around using biomarkers anyway, because only with the help of these markers can the right patients for clinical studies be selected and thus a significant benefit can be proven.

> *"Well, I mean such would not be the right concept. However, if a CD would be required to identify a patient population that benefits from the drug in some way, yes. Because if you need a test to identify the right patient population for your drug, I think in an indirect way you could, you know someone would use the word mandatory, but you know the company would need to show the evidence and that is sort of in an indirect way. They would need to have the evidence to support that."*

Another interviewee from a national authority also denies that this could be imposed. It is up to the companies to make that decision.

> *"No, no under no circumstances, under any circumstances ... If the company says they would need it in combination, we will look at it. And if the company says they will go without it, then we will also look at it."*

Only one interview partner can imagine that. He does, however, refer to the situation that the pharmaceutical entrepreneur, who wishes to gain approval for the therapeutic drug, submits results from the clinical trials where biomarker(s) have been used to stratify the study population.

> *"Yes, I think that is very real. This is a situation where a positive study shows that a drug helps in marker-positive patients. Moreover, the approval would say that it can be used in these marker-positive patients. Now the Joint Federal Committee (GBA) is facing the decision, what to do? So you have to join this dichotomy in marker-positive and marker negative. The alternative*

either would be that you do not reimburse the drug, which would be a disaster! Because the drug also has a benefit. And vice versa, the other alternative would be that the GBA releases the drug for all patients, regardless of marker status. This would also be a disaster because that is a charter for non-complying use of approved drugs. So that does not work either, so there is no way around it…"

V. Brief conclusion on the topic "Mandatory Prescription of Biomarkers by Regulatory Authorities"

Again, there are apparent differences in the statements between the group of physicians (nuclear physicians and specialists) and industry and the regulatory authorities. The majority of nuclear medicine physicians can well imagine that regulatory authorities will require biomarkers in the future. Their argumentation is not so much based on medical benefits (one argument), but more on the burden of costs for the health system caused by novel, very expensive therapeutics. Most of the nuclear medicine doctors assume that a biomarker test will come sooner or later, the question is which type of test will prevail.

The pharmaceutical industry's answers to this question are not explicit, except for one. This interviewee assumes that biomarkers will not be compulsory, at least not for all medications. The decision will be made on a case-by-case basis. However, all interviewees expect this issue to become more critical in the future.

The majority of the final group of regulatory experts do not expect mandatory biomarkers but believe that the companies must decide this for themselves.

4.4 What is the Stakeholder's Stake in a Public Private Partnership (PPP)?

The concept of public-private partnership (PPP) has increased significantly in recent decades, especially in the area of public infrastructure in Europe. The idea is to involve the private sector in the development, financing and supply of community projects. There is no exact definition of PPP, but it can be described as "*a long-term contract between a private party and a government agency, for providing a public asset or service, in which the private party bears significant risk and management responsibility*" (World Bank Group, 2018). This concept has also been transferred to the life science sector, hoping to launch new products in less-researched areas. In 2008 the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Union (EU) launched the largest PPP worldwide in the field of life sciences. So far, also 16 imaging projects have been initiated, ranging from amyloid imaging in Alzheimer's Disease (AMYPAD), research into new markets in carcinogenesis (MARCAR), surrogate markers as hard endpoints in diabetes disease (SERMIT), and imaging biomarkers for the safe use of drugs (TRISTAN).

Due to the weak interest in the development and commercialisation of new, innovative diagnostic radiopharmaceuticals, we evaluated whether the concept of PPP could help to allow more diagnostics RPs approved. Because this topic also concerns the partnership of the stakeholders, we asked the interview partners how cooperation works well or not.

A Nuclear Medicine Physicist´s view:

"In principle, I think that makes very much sense. In Germany, this has often failed due to the extremely strict regulatory framework. It is not simply a PPP to the mutual benefit, it should be a win-win situation for both. From my experience, putting this on a solid legal basis so it can be a success is the biggest problem. Because there is so much bureaucracy associated with it, it also looks daunting. I think that needs to be greatly simplified to be successful."

A Radiopharmaceutical Industry´s View:

"Er, I guess the probably needs to be a better understanding in the academic community of the difference between having a technology that shows interesting data from non-prospective studies (laughs). So when, for a lot of these agents that look interesting and therapies that look interesting, to get approval for it you need to get back to the drawing board to do a proper dosimetry study to support that."

A Pharmaceutical Industry´s view:

"But now coming on to PPP. The first thing I should say, that IMI is an experiment. It is a 5 billion Euro experiment, it is not guaranteed to work. Historically the drug industry has been very bad a PPP. If you look at other industries: defense, transportation, agriculture. A lot of the R&D risk is shared by the public and private sector. When even in the USA, the pentagon carries a lot of R&D risk for the defense. In the EU we are very used to the idea that agriculture works in PPP. For historical reasons the drug industry is been very happy to carry the entire risk of R&D on its own. And then get the entire benefit to exclusivity…in comparison to other industries that is a very unusual model…"

A view from the Molecular Imaging Technology Industry:

"Concerns are that it is sometimes difficult to get consensus between all partners. We are also involved in a few IMI projects, and you see that the academic side thinks academically, and the industrial partners come with the industrial mindset into the project. Agreement is not so easy, in the sense that it works for everyone."

A view from a Medical Specialist:

Example of a Disadvantage:
"The pharmaceutical industry has the legitimate interest to make profit, but they slightly tried to dominate the study design and the rational of the study. And I see that as a problem. The concrete shortcoming that different companies are difficult to bring together and to work together."

A view from a Regulatory Specialist:

"Now in this sense you are going into subpopulations, small, rare cancers etc. that is normally the area where collaborations between industry and academia is stronger, because really industry then needs the academic, needs centers of references, networks and all of this stuff. And perhaps those could be right, right frameworks for some of these PPP."

All statements regarding this topic are in the appendix on page 224.

I. The Nuclear Medicine View:

	Strong Pro	Neutral	Strong Contra
Value of Public-Private Partnership		◆	

In the group of nuclear medicine experts, 5 out of 7 interviewees (71%) answered this question, and from those 60% are in favour of Public-Private Partnerships (PPP). However, we must assume that some of the interviewees may have thought of a "classic collaboration", not necessarily about the concept of PPP. The following statement may suggest this assumption:

> *"So the value is tremendously high, PPP is basically what drives the bulk of the research. The otherwise publicly funded research, so by DFG or EWIF, consists of 90% mechanistic research, which is also important, but has nothing to do with the whole issue of implementation… PPP research is exactly what drives the field, which we are extremely interested in."*

However, particularly one German interviewee sees the challenge in setting up such a PPP. The legal basis must be robust to have a win-win situation for both partners, and currently bureaucracy is still too complicated.

> *"The industry partner wins because he gets better diagnostic tests, or tests in general, for his therapy and the area of application. Moreover, on the other side, the academic partner wins because he has a better sense of where, in the future, the things he or she is dealing with scientifically, could have a clinical relevance on a broader spectrum."*

Two of the experts disagree as to whether such a PPP is more straightforward to be implemented in Germany or the United States. Again, suspicion is expressed that both interviewees had a different concept of collaboration in mind.

The interviewee is talking about…

The United States	*…another about Europe:*
"I think government agencies are not well suited to invest. The reason is that then the whole story starts, what is the payback? That is something even the NIH never tried. Because the NIHs provides grants for all kind of stuff, so then you could get IP which was in part funded by taxpayers. So therefore money should go back to the NIH also to the FED. That never has been done, because than it gets so complicated. That you cannot ask the Americans to do that. The American philosophy is more we support you, you make the money and then taxpayer revenue comes in anyway."	*"Yes, I think they are extremely useful. Er, there are many more approaches possible, not so much in Germany. In the United States more often, where they are trying to create a PPP between industry and certain university research institutions or even public research institutions. So I think that makes extraordinary sense."*

Another interviewee commented "neutral" on this topic, seeing such collaboration as an "*instrument that does not harm*". However, he argues on difficulties in the arrangements, since the interests of the partners can be very different, and he experiences the imbalance of power.

> *"There are other examples, where this was purely driven by academic, and only at the very end someone has put it on a commercial track... The IMI is something special, which always had the constraint ... an instrument where the industry forces the others what to do… The EU has initiatives where it promotes cooperation with companies. Companies can join, but the academic*

side is stronger. This is normally areas where the industry is not interested. There are federal instruments that provide incentives to participate. For example, we participate there."

Collaboration with the industry to develop a Biomarker?

	Very good	Neither good nor bad	Very bad
Collaboration to develop a biomarker?		◆	

In this context, the interview participants were asked whether they are currently working with an industrial partner to develop companion diagnostics. This question has been answered by five interviewees, two confirmed cooperation, two denied and one participant explained that a different partnership exists. Also, in this case, there is a suspicion that some interviewees may not be explicitly participating in a PPP, but collaborate in a "traditional" partnership.

"Yes, we do that ... we were once part of a study where a companion diagnostic was evaluated, but then, unfortunately, it failed ("ging in die Hose"). That was not necessarily a success story."

"No! That would be a PPP; we do not have that. What we do is we collaborate in research collaborations with other departments that develop therapeutics and then have them patented. Moreover, there we are trying to test the effectiveness of these substances at a preclinical level, just as early as possible."

How the collaboration with the industry works

In a further question, the interviewees were asked how the cooperation with the partner, in this case, the industry, works. This question was answered by two interviewees (28%), one sees the collaboration as "neither good nor bad", the other one extensively described various projects, but a clear statement cannot be identified.

"It varies from company to company, but I could not say that everything is good or bad ... It depends a lot on the companies because we have partners from the technology industry who do not have that much money. That is a whole different order of magnitude, so you cannot expect [company name] *to be able to fund big clinical trials. They do not have budgets for those things. They are trying to support us, but not in a huge way. Also because we in Germany are no longer the largest market."*

II. The Pharmaceutical Industry´s View:

	Strong Pro	Neutral	Strong Contra
Value of Public-Private Partnership		◆	

All interviewees responded to the question, with two-thirds of the respondents having a positive perception of this concept (67%). One of the interviewees has a leading role in two IMI projects.

The industry values PPPs in areas where the development of tools does not bring a competitive advantage but is essential to all industrial partners.

"No matter what the context, the main value of that is, it allows us to address issues that are important for the field as a whole, but none of us has the resources to do ourselves. Of each of us is trying to do it ourselves, it is completely inefficient. And there no competitive advantage to doing that. So that is biggest value: bringing all these people together, focusing on issues of common problems that cross the border to move the field forward to give us the tools we need to."

The statements show that the industrial experts value the work of the academic institutions very much and that this expertise is urgently needed for research and development, be it in connection with a PPP or other partnership.

> *"We do not have all the expertise internally, so we need to be able to partner as a company... Partnerships are absolutely critical. You cannot do anything without them. That is not something which is unique to PPP. You do not need PPP for that, that is my point."*

The interviewees also talked about their experiences from such PPP projects and to what extent their companies have participated so far. In this PPP concept, the interviewees value not only the performance of the academic capacity, but also the input of other partners. As we will hear later, this cooperation is not always smooth, because there are distinct cultural differences between the partners.

> *"But there are many many examples* [company name] *is working with PCs (public consortia) particularly in neuro. So we do not think we have all the answers and we are working with all the external partners to integrate science as best as we can, really. And not just the academics in those consortia, of course, other pharmaceutical colleagues of us from other industries, from other companies. Short answer: We rate this very highly."*

One of the interlocutors, who also participates in the IMI (Innovative Medicines Initiative) project, has readily revealed his thoughts on the subject. He told us why the pharmaceutical industry is, compared to other industries, still opposed to the concept of risk sharing and why this may is currently in the change.

> *"But now coming on to PPP. The first thing I should say, that IMI is an experiment. It is a 5 billion Euro experiment; it is not guaranteed to work. Historically the drug industry has been very bad a PPP. If you look at other industries: defence, transportation, agriculture. A lot of the R&D risk is shared by the public and private sector. When even in the USA, the Pentagon carries a lot of R&D risk for the defence. In the EU we are very used to the idea that agriculture works in PPP. For historical reasons, the drug industry is very happy to carry the entire risk of R&D on its own. And then get the entire benefit to exclusivity…in comparison to other industries that is a very unusual model. So the idea of IMI is partially based on that the exclusive model that the pharmaceutical industry historically has had might not work forever…So the idea is to try to find a way for the public and private sector to work together. This is an experiment, as you know a 100 different projects are running under IMI. And to be honest, some will be more successful than others."*

This expert indicates that these projects are searching for solutions and tools that apply to all market participants, and a significant number of different products. None of the participants has an individual interest in the development for various reasons.

> *The project… TRISTAN is developing imaging tools, which be used to predict not drug efficacy, but drug harm. And those, as you can imagine, are many different classes of drugs can cause the same type of harm. We are focusing on a number of different areas of harm. One of which is drug-induced lung disease. Now there are over 300 drugs which cause that harmful effect so that potential imaging biomarkers could sweep a wide range of drug programs. And there will be difficult to protect IP on so that the imaging companies will not develop them. Drug companies' won´t develop them, just for one drug. So this seems to be an ideal place for a PPP."*

The reasons for participating in these projects are many-sided, in principle, the participants naturally hope for an advantage in various areas such as R&D, stratification, monitoring, et cetera Imaging is only one part of it.

Relationship with Academic and Public Funded Institutions

This group was also asked how they regard the cooperation with the academic institutions. No one wanted to comment on it accurately, which is why the answer "neither good nor bad" leads again with a two-thirds opinion (67%). One interviewee deviated to another topic during this question.

Reaching consensus seems to be the most laborious task (100% consents). The answers indicate that industry has a high interest that their goals be achieved in the project.

> *"It really comes down to the common interest. We are partnering with academics who are focused on questions and developing things which are relevant to the things we need to do. And we are able to come up with an agreement, this is a specific thing that needs to be done, and there is the focused on it. People actually deliver what is needed, that works out pretty well."*

This statement can also be applied correctly to the PPPs, whereby the more significant number of participants can cause further complications. *"So it is kind of the same things with the smaller ones (partnerships), but the more cooks you have, the more complex things get."*

However, from the perspective of one interlocutor, the great advantage of PPP is that industry is in the driver´s seat and can dictate what should be developed.

> *"And the big advantage for the drug companies in there (PPP) is, that the drug companies are in the driving seat and they can say very strongly "we want you to develop a tool that looks like this because if you develop something like this, it would be very useful to us". And not just a tool, which makes a nice paper in Nature or something like that."*

III. The Radiopharmaceutical Industry´s View:

	Very good	Neither good nor bad	Very bad
Value of Public-Private Partnerships		◆	

All interviewees of this group tried to answer the question, but half of the participants had no opinion.

> *"Hm, that is difficult. I felt that I do not have enough experience to answer that, unfortunately. I have not been involved. My answer would be that they have not been particularly successful. But I would not high trust on that answer because I have not been close enough involved. But I do not believe there weren´t any big successes."*

One of the experts commented positively, but on the topic of industry-academic partnership in general, not referring primarily to the concept of PPP.

> *"I think there is a very strong role for academia. I feel that there is, and there will always be a very strong role for academia. And because especially the RP companies rely very heavily on people in the university. They have the expertise, and I think that will continue without a doubt. Obviously, big pharma companies have a large in-house, and they have large organisations, but there will always be a mixture of a private company working with a large academic [*institution] *in Europe."*

Challenges in collaboration with academic institutions

The statements are similar to the opinions of experts in the pharmaceutical industry. Among other things, it concerns finding consensus on the results you wish to achieve, the timetable, and the speed with which your projects are carried out.

> *"Well, I think fundamentally they have different goals, and you always have to deal with that. The academic institutions are not, in general speaking, not results driven, and not scheduled driven. They are knowledge driven. The businesses… they borrow it (money) from themselves, or*

somebody gave them a bunch of money, and they have a timescale, they need to go on the market, and so they are very sensitive to results. They are very focused. They want this result. The academics would be happy with almost any results, right? (Laughs)"

The academic community must also comprehend that the "*interesting data*" from their studies, is not sufficient from study design and quality perspective for filing with the regulatory agencies. The academic aspect should work in a more concise clinical trial process.

"Er, I guess the probably needs to be a better understanding in the academic community of the difference between having a technology that shows interesting data from non-prospective studies (laughs). So when, for a lot of these agents that look interesting and therapies that look interesting, getting approval for it you need to get back to the drawing board to do a proper dosimetry study."

Moreover, an interesting final argument discusses the ownership of inventions that have been developed together in a partnership.

"So once you understand that those (the participants in the partnership) have fundamentally different motivations, there can be issues about who owns the co-development. Like a product or a feature, or something that is innovative and new, which comes out of the working together. Obviously the business wants to have the right to do it and the institution, a lot of institutions especially in the US have business offices that try to monetarize their research... And they want to get a piece of that deal. So that there is this IP relation, and funding, always funding."

IV. The Molecular Imaging Technology Industry´s View:

	Strong Pro	Neutral	Strong Contra
Value of Public-Private Partnership		◆	

Due to the semi-structured style of the interviews, this questions was only answered by one interviewee. Above all, this interviewee sees a significant financial benefit in a consortium approach. However, otherwise, he is more restrained regarding consensus building in the selection of the study design or the definition of the research question. Although many academics have exciting research questions that would undoubtedly make an excellent publication, they are not very helpful from an industry perspective. To give an example: his company is involved in one of the IMI projects, and he would prefer to study designs that can prove the usefulness of the product and thus influence reimbursement issues.

"In the IMI projects, we have seen that it is difficult to design the study design to be as rigorous as one would expect from the commercial development of an imaging test."

His summary regarding the benefits of a PPP: *"…you should not screw the expectations of the industrial side too high. Well, such an IMI project may be a good way to do some research, but it is not the panacea for developing imaging tests differently."*

V. The Medical Specialist´s View:

	Strong Pro	Possibly	Strong Contra
Value of Public-Private Partnerships	◆		

From the group of specialists, all interviewees answered the question and half of the respondents are positive about the PPPs. One interviewee is against, while one has a neutral opinion. Also in this group, it is reasonable to assume that some of the interviewees talk about classic partnerships and not specifically about PPPs. Therefore, the results should be treated with caution.

For one of the interviewees the benefits is a win-win situation. On the one hand it allows clinicians to get access to a new and good diagnostic tool, and on the other hand industry could make money from it.

> *"I think that is an absolutely important part. And there's nothing wrong with that because, on the one hand, the industry has some interest in monetising it, but we also have an interest in getting a biomarker, or a diagnostic tool, that supports us and is good… So we both have the same interest."*

Another interlocutor is unconvinced because the participation of public institutions usually complicates the conversation: "*Yes, if it helps, then it is good*". However, every interviewee acknowledges the fact that academic research would no longer be possible without industry.

> *"I am extremely open-minded ... I actually get a not inconsiderable share of research funds from the pharmaceutical industry…Earlier, in the last 5-10 years, we have had IITs, we continue to try, but now it is no longer possible without support from the pharmaceutical industry."*

However, this partnership also has drawbacks, such as the industry's attempt to dominate the study design.

> *"…you have to be very critically. Because I have said it before, the sponsors determine what we do... the (research) question you would like to have answered for yourself are actually not funded, but they tell us what we have to do."*

VI. The Regulatory Specialist´s View:

	Strong Pro	Neutral	Strong Contra
Value of Public-Private Partnership		◆	

There were only two statements: First, one interviewee had no idea and could not answer the question, and for the other, it is imperative that industry and academia work together. He believes, however, that the concept of PPP works only in the non-competitive area.

> *"Now in this sense you are going into subpopulations, small, rare cancers et cetera that is normally the area where collaborations between industry and academia are stronger because really industry then needs the academic, needs centres of references, networks and all of this stuff. And perhaps those could be right, right frameworks for some of these PPP.*

> *"IMI is good at non-competitive stuff, so basic methodology, technology et cetera. Now in this phase of the CD I was not thinking immediately on something like IMI, because I thought the companies would be very interested in the certain type of biomarker, a certain type of drug. How can that be non-competitive? But I am thinking of this for the first time, so maybe the answer is a bit superficial."*

VII. Brief conclusion on the topic "Public-Private Partnerships"

	Strong Pro	Neutral	Strong Contra
Value of Public-Private Partnership		◆	

The interviews with the experts show that almost all groups have a positive attitude towards academic and industrial collaborations. We deliberately only use the term collaboration, because some interview partners may have thought during the interviews more about "classic" partnerships rather than PPPs.

However, in general the interviewees from the medical physician groups acknowledge the fact that a partnership with industry is desperately needed to drive the nuclear medicine field forward. Still, in matters of PPP, the set- up, e.g. in Germany could be challenging, as there is currently no natural process to do so.

Also the pharmaceutical industry values collaborations with the academic world in general, and the concept of PPP for tools, which are essential to many partners but does not generate a competitive advantage for a single company. It seems that reaching consensus on study design with the academic world seems to be challenging in a partnership. Due to the different motivations, working together can sometimes be provoking.

For the radiopharmaceutical industry, a PPP is neither good nor bad, also because many of the interviewees had no experience with the concept of PPP. A few challenges named by this group: finding consensus, different expectations on the timetable, the speed of research, ownership of inventions et cetera. But generally the experts speak very positively about the partnership between themselves and the academic community.

Most medical specialists also value the concept of PPP, but we must again assume that some of the interviewees had “traditional” collaborations in mind. However, they also mentioned the drawbacks of such partnerships such as the industry´s attempt to dominate the study design and -rationale.

4.5 The Focus in Research and Development and the Future Role of Molecular Imaging

We asked the stakeholders about their research focus, the industry´s mission and objective and how molecular imaging (MI) may have a role in the future of patient management. Among other things, we asked the interviewees if R&D will remain focused on PET (PET/CT and PET/MRI) and/or what role SPECT (SPECT/CT) will play. The interview partners were also interviewed on the topic "Research Focus in the area of Molecular Imaging", and individual stakeholder groups should give their opinion on where research in the field of MI has to catch up.

A Nuclear Medicine Physicist´s view:

“It is quite possible that FDG PET will continue to be a very important pillar ... but the next area where PET prevails or will solve a lot is neurology, but also in the cardio area ... "
PET vs SPECT:
"No, no, you can forget about SPECT. In this case I'm brutal. But that's very striking."

A Radiopharmaceutical Industry´s View:

"Both [SPECT and PET] *are adequate and given the cost circumstances both will remain, but PET will grow in the future. The opportunity to modify small molecules without significant influence on biodistribution is a clear advantage. With Fluorine the supply chain is already there."*

A Pharmaceutical Industry´s view:

"...From that point of view you have PET agents... at least... carbon is out of question, fluorine can be challenging because of the half-life. Technetium is much more attractive. Gallium obviously with PET is more attractive, because you can use a generator and a nuclear medicine department can make it locally. And if I were looking developing a personalized healthcare compound I would be very cautious about the fluorine agent.”

A view from the Molecular Imaging Technology Industry:

"... since then, we have focused more on Life Cycle Management and push projects in the R&D pipeline, which are already more advanced in the development stage, so in Phase II or III. And in terms of personalized medicine, we initiated a study with an “old-fashioned” product ... to see if [product name] can predict that a patient needs a defibrillator (ICD) or not."

A view from a Medical Specialist:

"So in prostate cancer, if imaging gets even better, focal treatment for prostate cancer may play a significant role. Such as brachytherapy, local photodynamic therapy, HIFU (High intensity focused ultrasound), or such treatments. I don´t see drugs in local therapy, there will always be physical energy applied, which irradiates the tumour locally.... Otherwise, at an advanced stage, the individualized target therapy will play a role.”

All statements regarding this topic are in the appendix on page 229

I. The Nuclear Medicine View:

Nuclear physicians have a relatively clear idea of what the future holds. Four interviewees believe that FDG PET/CT will continue to play an essential part in the clinical routine: “*Certainly FDG has taken its place and it will expanded here or there, and perhaps there are alternatives which will limit its use.”*

However, more and more radiopharmaceuticals will bind to a specific target structure. This will not be limited to oncology, but also increasingly expanding into neurology and cardiology.

> *"It is quite possible that FDG PET will continue to be a very important pillar ... but the next area where PET prevails or will solve a lot is neurology, but also in the cardio area ... "*

Continuing, specific drug-related targets will be developed for oncology, but the question remains as to how many of these research results will be translated into clinical routine.

> *"And of course, research is now increasingly moving in the direction of visualising and quantifying very specific, drug-relevant targets. Including modern developments such as immunocheckpoint inhibitors or things like PDL-1, PD-1. There are already compounds available*

for CXC4 or chemokine receptors. But this is the path taken in research, relatively little is translated into the clinic."

Three interviewees are convinced that the concept of Theranostics will continue to offer promising opportunities in the future. Moreover, research in this area is not limited to academic institutions, because not only some small, but also larger pharmaceutical companies have recognised the potential of this area and have initiated a clinical research program.

"There are several tendencies: ... for a while, there were doubters who thought the therapeutic application in the NUK has no future. Which cannot be said any more today... PSMA is a very promising therapy ... But there are also a lot of other companies ... that initiated controlled studies. The PSMA found its way out of academia, but there are some radioactively labelled antibodies, or some alpha-therapies, where small, but also large players in the pharmaceutical sector, invest a lot of money."

One conversation partner has already mentioned new fields of disease, where he believes that the concept of Theranostics could also be successful. He favours some promising candidates without even knowing who will win the race.

"…And in the forefront of the success of Theranostics and the therapy, of course, enormous efforts are now made to establish further target structures, which are suitable for the theranostic approach. For me, this currently covers three areas: breast cancer ... lung cancer, third is colon carcinoma and fourth ... pancreatic adenocarcinoma."

Is the future in PET or SPECT?

	PET	Both	SPECT
Future in PET or SPECT?	◆		

Also, we wished to know from the nuclear medicine physicians whether the future will solely be focused on PET technology, or whether SPECT will have a comeback. The majority (57%) see the future in PET and give the SPECT little chance.

"Clearly in PET. SPECT, that's nonsense you have to be clear. Of course, it's easier and more accessible, but it is anachronistic! You have to move to PET, that's just the rethinking. You cannot work with a "Volksempfänger" if you could have a flat screen. That's of course nonsense. If you look at it short-sighted, to get it expanded quickly, you can think about SPECT. But if you want to go to a high level, you have to push PET and not SPECT."

The remaining 43% of respondents do also see the future in PET, but would expect SPECT to still play a role.

"SPECT will definitely play a role... still purely because of capacity. If you look at it globally, SPECT has probably ten times more capacity than PET ... Of course, PET has technological advantages, such as sensitivity and resolution for certain applications. For PSMA, PET has clear advantages, because the resolution creates a benefit. But there are applications where resolution is not what matters most."

The pro PET- statements range from: flexibility in labelling, higher image resolution and thus better characterising of the tumour biology. The interviewees' don´t regard that the shorter half-life PET radionuclides to be a problem, at least not in the western industrialised countries.

"And the problem with the PET radioisotopes, which are relatively short compared to the SPECT, I consider no problem. I believe that the availability of PET is not really a problem, at least in Germany. Not even in the US, I do not think that's a problem in any industrialized nation."

Three interviewees independently belief that SPECT (SPECT/CT) will have a role in the concept of Theranostic, in specific disease areas. A SPECT scan could verify the target structure in the outpatient setting and refer the patient to the appropriate institution.

> *"If so, perhaps SPECT/CT will have a certain chance, again in the wake of substances that have already been successful in PET/CT. An example is, e.g. so-called technetium-labelled somatostatin analogous ... It is also called the PET/CT of the poor man, yes. (Laughing). The advantage is that these SPECT tracers can be billed in the outpatient area because there is an existing billing structure. The colleagues in the outpatient area can thus use the substances. The same is true for technetium PSMA... But I think a big success will continue to be PET/CT."*

Furthermore, one interview believes that the use of SPECT (SPECT/CT) has also an active political and supply-related component. SPECT is reimbursed in the outpatient setting in Germany, which does not apply to PET. Looking beyond Europe, SPECT technology has higher availability and a more competitive price compared to PET. Additionally, those SPECT RP can use technetium, which is more cost-efficient and has logistical advantages.

II. The Pharmaceutical Industry´s View

	PET	Both	SPECT
Future in PET or SPECT?			◆

The result from this group is not representative, because unfortunately there is only one statement. For the sake of completeness, however, we want to publish this answer.

This interviewee would prefer SPECT to PET. The availability of scanners and radionuclides is crucial for this interlocutor, especially when considering that a radiopharmaceutical should be used as a companion diagnostic. His view: Pharmaceutical companies think globally, and PET has disadvantages especially in developing countries or countries with currently low imaging infrastructure.

> *"When the drug company is developing the drug, it's developing it for a global market. So when [company name] is developing they are not just thinking of, certainly they think if you can sell it in the United States and EU, they are also thinking about China, Philippines, Brazil, Indonesia. These are important markets! If you going to have a diagnostic in your label you want to make sure it is available in every hospital in China, Philippines, Brazil otherwise you would not sell this drug. From that point of view you have PET agents... at least..., carbon is out of the question, fluorine can be challenging because of the half-life. Technetium is much more attractive. Gallium obviously with PET is more attractive, because you can use a generator and a nuclear medicine department can make it locally. And if I were looking developing a personalised healthcare compound, I would be very cautious about the fluorine agent."*

III. The Radiopharmaceutical Industry´s View:

We also wished to know the R&D mission and objectives of the radiopharmaceutical industry group. Two interviewees told us that their companies have specialized in the development of new diagnostic agents, mainly in the field of PET. While one of these companies is focusing on cardiology, the other company has recently successfully launched a new prostate PET diagnostic product and believes it may be useful in other tumour entities as well. So they are pursuing this idea and hoping for further possibilities.

The third company specialises in the development of a theranostic platform.

"Okay, so I would say that the mission of [company name] *is to develop theranostic platforms. So drugs, which have both a diagnostic and therapeutic component, which is shared. Not necessarily identical compounds, but they are shared. So that the personalised medicine is essential that patients who benefit from a therapeutic agent are identified by the diagnostic component."*

Is the future in PET or SPECT?

	PET	Both	SPECT
Future in PET or SPECT?			

Compared to the group of nuclear physicians, the radiopharmaceutical industry´s experts are not so sure which technology will dominate in the future. Our empirical results indicate a trend towards PET, but all interviewees also see SPECT (SPECT/CT) as a variable option.

From the point of view of an interview partner, the dissemination of the technology may depend on the costs of the respective unit of spatial resolution. SPECT´s technology has evolved over the years and is a good alternative to PET and other imaging modalities.

"I think SPECT is definitely still an option. So the difference between SPECT and PET is based around the resolution, the spatial resolution of the imaging device. Not necessarily based around basic physical properties. So if the SPECT cameras become more sophisticated, as it appears they are, then I think SPECT and PET will have a role to play. Moreover, ultimately spatial resolution for a given price will determine how much SPECT and PET, not necessarily one or the other but rather how cheap the camera is for a given spatial resolution."

The third interviewee believes that PET would be preferred, if the challenge of costs did not exist. The labelling options and existing supply chain are certainly better.

"Both are adequate, and given the cost circumstances both will remain, but PET will grow in the future. The opportunity to modify small molecules without significant influence on biodistribution is a clear advantage. With Fluorine the supply chain is already there."

IV. The Molecular Imaging Technology Industry´s View:

We have also questioned the Molecular Imaging Industry group about their current mission and objectives, as well as their assessment of which technology will play a role in the future.

Concerning their mission, an interviewee explained that there is less adaptation from the technological point of view as the market is mainly driven by radiopharmaceuticals. The only adaption from a hardware aspect may be the scope of software, as was the case with the Alzheimer tracers.

"Unlike as in CT and MRI, in MI, when you want to expand the clinical indications, it is generally tracer driven and probably requires a new specific tracer for that clinical area you want to go pursue... So and those new tracers might or might not drive something on the technology side…"

The second interlocutor, whose company recently discontinued early research projects of new RPs, sees the company's mission in the demonstration of the utility of the diagnostic tests. The goal is to get the tests reimbursed and integrate them in current patient management processes. He calls it "Life Cycle Management". However, also projects currently in Phase II and III, such as finding new applications/indications for existing products, will be pushed.

Well, I would say current mission and objective is the development of (pause) it is actually more (break) I would say the safety and efficacy is now self-evident, but the mission actually goes further in the utility of diagnostic tests. Because it is clear that safety and efficacy are not enough

to bring diagnostic products on the market, get reimbursement and integrate them into the appropriate patient management. So currently the objective is to perform much more advanced phase III studies. We have to think about utility and of course health economics in the development of such products."

Is the future in PET or SPECT?

	PET	Both	SPECT
Future in PET or SPECT?		◆	

Experts expect both technologies to play a role in the near future. However, they also agree that the most significant growth is likely to be in the PET segment.

One interviewee sees advantages for PET on the technological side, with logistical hurdles of radionuclides limiting this advantage. On the other hand, the resolution of SPECT detectors is improving and can compete with PET.

"So I would say that still ... we see future in both areas.... PET is a tough market, but has a future because certain PET tracers will rather be produced than SPECT tracers. Purely from the technical view. On the other hand, PET is problematic ... because you either need your own infrastructure ... or you work with local partners ... There are also certain countries where SPECT has, aside from the big cities, advantageous logistics compared to PET. And because of the CZT solid-state detectors, the resolution in SPECT approaches the resolution of PET."

V. The Medical Specialist´s View:

This group of interview partners was asked to evaluate new, innovative treatment options (on the technological side and pharmaceuticals) and the importance of molecular imaging in the future.

As far as innovative therapeutic approaches are concerned, experts expect a better risk stratification and consequently a more personalised therapy approach, a more widespread use of immunotherapy such as the checkpoint inhibitors, an improvement in diagnostic capabilities through liquid biopsy and improved imaging techniques. But some disease areas, such as local prostate cancer, may not profit much from new pharmaceutical innovations, but will continue to be treated with physical energy. An urologist expects that if imaging further evolves, there will be many new treatment options possible.

"So in prostate cancer, if imaging gets even better, focal treatment for prostate cancer may play a significant role. Such as brachytherapy, local photodynamic therapy, HIFU (High intensity focused ultrasound), or such treatments. I don´t see drugs in local therapy; there will always be physical energy applied, which irradiates a tumour locally.... Otherwise, at an advanced stage, the individualized target therapy will play a role."

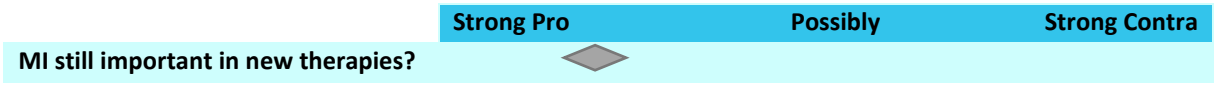
Half of the interviewees expect that immunotherapy therapeutics to enter the market since they are currently "*en vogue*". Also 50% of responders believe that diagnostic capabilities will improve due to evolving technologies.

"What is also generally en vogue is the immunotherapy ... So the keyword is PDL-1 inhibitors, et cetera. This is a brand new drug class that is just very in vogue. But I think the big keyword of the future is the topic of liquid biopsy ... but also in general, to come back to the subject of nuclear medicine, the keyword theranostic is already big in the trend, high in the class."

Two more statements should be briefly mentioned: First, one interviewee believes that in the future there will be a kind of artificial intelligence for the treatment of cancer, which will evaluate all the information and markers and suggest the best treatment option. Secondly, another interviewee finds it

worrying that millions and billions are spent for the treatment of metastatic patients, but completely disregards prevention and early diagnosis.

Will Molecular Imaging have a role in new, future therapeutic strategies?



Two-thirds of the respondents are very convinced that imaging will play an important role: *"Absolutely yes."*! For the third interviewee, it will depend on the question as to the possibility of another biomarker, such as therapy response, being able to provide a reliable answer to the question.

> *"It depends on the topic of treatment and if you have a biomarker that is good enough that the concentration of the biomarker tells us" ok, does the patient have a response or not? ". … then you could go without the imaging diagnostics. If, however, the patient has any consequence because of the localisation of the tumour … imaging with corresponding sensitivity and specificity is still indispensable."*

In general, new diagnostic options will improve treatment while also providing an advantage from an economic point of view.

> *"My assessment is that functional imaging is evolving just as well ... however, what I have seen so far is fascinating ... secondly, I think MI will continue to evolve as much as we do (In-vitro Companion Diagnostics – IVCD). Many people are probably not yet aware that we even save costs. If we can use functional imaging, and/or other methods, to save patients from unnecessary therapies, or stop meaningless and start more meaningful therapies, that certainly also makes economic sense."*

VI. Brief conclusion on the topic "The Focus in Research and Development and the Future Role of Molecular Imaging."

The stakeholder´s statements have provided a good overview on current research focus. For Nuclear medicine experts, research will continue in the field of PSMA and DOTATATE, but will increasingly address new, specific targets in other diseases. Recent success in the field of Theranostics will continue to shape research and development of academic institutions. For the two discussion partners of the radiopharmaceutical industry, focus is on the development and further development of diagnostic PET tracers for oncology and the design of a theranostic platform. The molecular imaging technology experts expect RPs to drive the market, but there will be no particular influence on the development of the technological aspect. These companies continue to focus on selling their scanners and demonstrate utility.

When asked which of the nuclear medicine technologies in the field of Molecular Imaging (PET vs. SPECT) will shape the future, the interviewees are not in agreement. The majority of nuclear physicians expect PET to be in the leading role, with SPECT still playing a (minor) role. A little contrary are the responses of the radiopharmaceutical- and molecular imaging industry, which see a balance in both SPECT and PET technology. Almost all of the interlocutors of these industry groups agree that PET has technological advantages but still has to overcome hurdles such as e.g. the availability of radionuclides and the reimbursement of the procedure. Interviewees of industry do not regard PET to be mature enough to be used as a means of companion diagnostics.

Medical specialists expect new treatment options in the future, ranging from immune checkpoint inhibitors; high intensity focused ultrasound to an artificial intelligence system that will recommend

therapy options. Mainly a better diagnosis is supposed to help them to be risk-adaptive or, e.g. better imaging will enable the treatment of local prostate cancer with new technologies. For this group, imaging will continue to play an important role. There may not be a need for imaging everywhere, especially if other biomarkers can also provide an equivalent answer.

5 Discussion:

Innovation is crucial to the future of healthcare from a business perspective but is also essential to tackle diseases, a fact which will become a social, political, economic and humanitarian challenge. All stakeholders in the healthcare sector are therefore feverishly looking for a novel application that will significantly benefit the individual, the group, or the broader society (N. Anderson, De Dreu, & Nijstad, n.d.; M. West & Faar, 1990). In *The "Theory of Economic Development"* Schumpeter imagined the cycle of innovation to be never-ending, introduced mainly by small- and medium-sized enterprises (SMEs) that will drive the technological advances (Schumpeter, 1934). A market in perfect competition, where all producers lack market power is "inferior in internal, especially technological, efficiency" (Schumpeter, 1975). He suggested that the rate of technological advances will also be better if only a few large firms, which would be more willing to finance risky R&D initiatives, dominate the market (Schumpeter, 1975). He regards market power (monopoly at its best) as a "superior method" because some large companies have the experience and the financial resources and protection to compete "against a temporary disorganised market" (Schumpeter, 1975). Unlike Schumpeter, Kenneth Arrow believes that "*the incentive to invent is less under monopolistic than under competitive conditions.*" (Arrow, 1962).

Over the decades, the pharmaceutical industry has mainly developed drugs for high prevalence diseases, with minor investments in medicines with low prevalence, which are expected to be an unproductive venture (Swoboda, 1999; Trouiller et al., 2002). Observable is that the pharmaceutical market is not a perfectly competitive market, but may behave more like a monopoly because several assumptions for the perfectly competitive market structure are violated (Rattinger, Jain, Ju, & Mullins, 2008). With their market power, the pharmaceutical industry is driving innovation in the drug market and strategically invests in new technologies. Some large pharmaceutical companies have also managed to use their market power to influence drug regulations, government decisions and influence regulatory agencies (Abraham, 2002). Even though the tightening of drug´s current marketing authorisation regulations has increased the effort for existing market participants, this more challenging and time-consuming regulatory process also serves as an entry barrier for new competitors (DeSanti & Cohen, 2001). This is also the reason we don´t see any "garage inventors" in the pharmaceutical market, compared to other industries (Carrier, 2008).

Industry has struggled in recent years with the increasing speed of new product development, the intensity of early generic competition, the exposure to loss of revenue following patent expiration and higher regulatory hurdles on top of a declining R&D productivity (Schiraldi, 2014). Those challenges have forced the industry to adjust their strategies and risk-reward ratio. Manufacturing and other operations were shifted overseas, the research pipelines were reorganised, human resources capital was notably reduced in manufacturing and research, and products from smaller, more innovative companies were acquired to fill the R&D pipeline (U.S. Department of Commerce -International Trade Administration, 2016). Also, the area of nuclear medicine has not been spared by these structural challenges, seeing big companies leaving the market or reducing R&D efforts. For this reason, new innovative ideas are almost exclusively discovered and developed in academic institutions. Some products reached the market, with the help of an industrial investor, but others have failed to pass the translation gap due to financial constraints (Clarke, 2018). However, new, but un-authorized, diagnostic and therapeutic radiopharmaceuticals have still be used in clinical routine and were administered under certain conditions on the basis of national exemptions, mainly in Europe. Over the years, the data and publications from these un-licensed applications have demonstrated the benefit of these diagnostic and

therapeutic products, attracting small and medium-sized businesses and led to the approval of at least three RPs.

So why did it take so long for some diagnostic and therapeutic RPs to receive market authorisation? Is nuclear medicine technology clinically inferior? Could it be a market failure as can be seen with the neglected diseases in developing countries?

The question of whether it is a market failure, or whether other forces are preventing the rise of these products, can only be answered by evaluating the efficiency of the technology itself. We have therefore evaluated the clinical effectiveness of two innovative radiopharmaceuticals used in the diagnosis and treatment of Neuroendocrine Tumours (NETs) and Prostate Cancer (Pc) in the first section of this thesis.

5.1 Evaluation of Clinical Efficacy

Unfortunately, the interpretation of the efficacy is not straightforward as the majority of published literature has a retrospective study design, is mainly single arm and has a variety of treatment regimens (doses and number of cycles). For NETs the most meaningful study is the randomised, controlled, comparative NETTER-1 trial (Strosberg et al., 2017). Several Phase II and III randomised, prospective trails are currently running for prostate cancer; which will better indicate the influence of technologies on overall survival and clinical benefit (U.S. National Library of Medicine, 2018).

a) Discussion of Case 1 – Clinical Efficacy of RPs in Diagnosis and Therapy of Neuroendocrine Tumours

Imaging:

NETs are frequently sporadic, unpredictable, have an unusual biological behaviour and thus the diagnosis is often delayed and the outcome poor (Modlin et al., 2008; Öberg, 2015; Ramage et al., 2005). Conventional radiological technologies such as CT and MRI have often missed or misdiagnosed some tumours/metastases (Hiramoto et al., 2001; Modlin et al., 2008; Zimmer et al., 2000), but with the introduction of PET Somatostatin receptor ligands the diagnostic quality- as well as patient management significantly improved (e.g. Geijer & Breimer, 2013; Alexander R Haug et al., 2014). Today, PET/CT with Somatostatin analogues shows a high clinical utility in terms of high diagnostic accuracy and high impact on patient management in patients with advanced disease, and therefore should be considered as first-line diagnostic imaging modality for tumours with a high expression of SSTRs, such as gastrointestinal- and pancreatic NETs (P. Sharma, Singh, Bal, & Kumar, 2014). Extensive literature on the use of these diagnostic agents exists, although most of them are retrospective and are not meeting the current quality requirements of regulatory agencies. However, recently ^{68}Ga- DOTATATE successfully passed through the regulatory process of the FDA and EMA and has received marketing authorisation. We, therefore, believe that imaging RPs can be judged to be efficient and useful, at least in specific diseases and patient groups.

Therapy:

Due to the great success in imaging, and the good binding affinity and targeting of the ligand, the next logical step was to label the biological compound with therapeutic radionuclides such as 177- Lutetium and 90- Yttrium and treat patients with advanced metastatic disease. So far the clinical results are very encouraging, and also a recent Phase III trial (NETTER-1) confirmed initial results of the academic trails and showed markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumours (Strosberg et al., 2017). More prospective, comparative studies with a standardised clinical protocol and a control

group can be expected and are needed to finally evaluate the new approach. However, based on currently available data (see Chapter 2.2.5) we would also rate the therapy with these RPs as efficient. Since ^{177}Lu DOTATATE has recently been successfully approved in Europe and the US by EMA and FDA for the treatment of patients with advanced NETs, new clinical results can be expected.

a) Discussion of Case 2- Clinical Efficacy of RPs in Diagnosis and Therapy of Advanced Prostate Cancer

Imaging:

Prostate cancer (PC) has a very complex behaviour ranging from relatively harmful to highly aggressive and thus with various options of treatment (Ferlay et al., 2014; Fuchsjäger, Shukla-Dave, Akin, Barentsz, & Hricak, 2008; Giovannucci, Liu, Platz, Stampfer, & Willett, 2007). So far TRUS (transrectal ultrasound) was the imaging modality of choice, for biopsy guidance and brachytherapy placement, but is not well suited for local staging (Fuchsjäger et al., 2008). MRI and CT improved staging, but still had challenges in advanced cancer stages, especially in biochemical recurrence. ^{68}Ga-PSMA-HBED-CC, a highly prostate specific target transmembrane type II protein used in PET, remarkably improved the sensitivity, specificity and detection rate especially in advanced tumour stages (e.g. Afshar-Oromieh et al., 2017). In some cases, PSMA PET/CT was able to detect metastases, which have been occult in CT (Lenzo, Meyrick, & Turner, 2018) and multiple studies showed the superiority to choline PET/CT (Afshar-Oromieh et al., 2014; Morigi et al., 2015). Using PSMA PET/CT also radiotherapy planning has changed in 20% to 60% of patients who received a ^{68}Ga- PMSA PET/CT prior to radiotherapy (Bluemel et al., 2016; Calais et al., 2017; Habl et al., 2017; Schiller et al., 2018; Schmidt-Hegemann et al., 2017). In a relatively short period, ^{68}Ga-PSMA PET/CT was implemented in many countries for the detection of biochemical recurrence. Based on the current available literature we would also rate this PET RP to be efficient and useful, at least in patient with biochemical recurrence and unclear metastatic status.

Therapy:

PSMA receptors have additionally proved to be an excellent target for therapy, since it is highly expressed in metastases even after multiple cycles of therapy (Pyka et al., 2016) and allows repeated intravenous applications (Rahbar et al., 2017). Several studies could show a benefit for most patients, who have already completed every treatment option available and have been running out of alternatives. In these specific patient group, several studies could show that around 30% to 100% of patients experienced more than 50% reduction in serum PSA, and >58% of patients experienced any PSA decline (Ahmadzadehfar, Eppard, Kurpig, et al., 2016; Ahmadzadehfar et al., 2015; Baum, Kulkarni, et al., 2016; Fendler, Reinhardt, et al., 2016; Ferdinandus et al., 2016; Matthias M. Heck et al., 2016; Kratochwil, Giesel, et al., 2016b; Rahbar et al., 2017; Tagawa et al., 2013; Weineisen et al., 2015; Yadav et al., 2016). Therapy with Lutetium-177 PSMA showed comparable treatment response to currently used chemotherapy agents such as Mitoxantrone and Cabazitaxel (change in PSA >50%: Mitoxantrone: 17.8%; Cabazitaxel: 39.2%), with a significantly lower rate of adverse events (Rahbar et al., 2016). Results, which have also been confirmed in a large German multicentre study with a total of 145 patients with mCRPC (Rahbar et al., 2017).

Again, based on current available literature we would also rate this therapeutic RP to be efficient and useful, with a very low probability of high-grade haematotoxicity and a prolongation of overall survival in mCRPC patients with distant metastases and progressive disease.

1) What is the clinical efficacy of Somatostatin Analogs and PSMA ligands diagnostic and therapy?

Based on the analysis of published literature, the diagnostic and therapeutic radiopharmaceuticals for neuroendocrine tumours, as well the RPs for advanced prostate cancer, can be considered clinically efficient. Meanwhile, a company has further developed the diagnostic agent ^{68}Ga-DOTATATE (NETSPOT® and Somakit DOC®) and the therapeutic RP ^{177}Lu-DOTATATE (Lutathera®) which are now officially approved for the diagnosis and treatment of patients with neuroendocrine tumours. This company has since been acquired by a major pharmaceutical company for $ 3.9 billion, most likely because of the therapeutic drug.
Compared to the Somatostatin analogues, PSMA has made a very rapid entry into clinical routine. Within a few years, the ^{68}Ga- PSMA research ligand from the University of Heidelberg (^{68}Ga-PSMA-HBED-CC) was used globally for the diagnosis of patients with biochemical recurrence. Even within a very short time, a therapeutic agent was developed and successfully applied similar to the concept of DOTATATE. This rapid entry into clinical routine is also a strong indicator for clinical efficacy. Currently a few companies have started a clinical development program for PSMA therapeutic RPs.

5.2 The Challenges and Barriers Associated with the Development and Approval of Radiopharmaceuticals

The analysis of (predominantly retrospective) clinical data suggests that these diagnostic and therapeutic RPs are at least not inferior to currently used technology. Therefore, there must be other reasons why these products are not taken up, and developed by investors. Few studies have addressed the challenges and barriers associated with the development and marketing authorisation of radiopharmaceuticals, those only consider the challenges from the point of view of a single stakeholder group and the statements are seldom based on reliable empirical data (cf. Henderson et al., 2005; Nunn, 2006, 2007a, 2007b, Zimmermann, 2008, 2012b, 2012a). In our study, which is unique from our point of view, we have used a holistic and structured approach. Since new product development is seen as an organisational activity, where it is necessary that all stakeholder groups get involved from the beginning to contribute to a successful product (Haque, Pawar, & Barson, 2000), we have integrated opinions form all stakeholders who may play a role in the process. In our case, these groups are nuclear medicine physicists (NMG), medical specialists (MSG), the radiopharmaceutical (RIG) and pharmaceutical industries (PIG), the manufacturers of scanner technology (MTIG), and the regulatory authorities (RAG). Interviewing so many different experts also allows us to rank the challenges and barriers according to their priority.

Value of Imaging:

Before we dive into the specific challenges, we should first mention that all interviewees consider molecular imaging as very valuable. The practising physicians from the NMG and MSG especially valued imaging as an indispensable technique in their treatment process. Interviewees from both groups particularly highlighted the possibility to non-invasively, localise and visualize the heterogeneity and spreading of a disease in real time (cf. Carter, Halpenny, Ginsberg, Papadimitrakopoulou, & de Groot, 2017; MacFarlane, Shah, Wysong, Wortsman, & Herphreys, 2017; O´Connor et al., 2017; O´Connor et al., 2015). Also, the pharmaceutical industry is using imaging tools regularly, almost exclusively for their R&D programs, to precisely identify target structures, quickly prove the overall concept, finding the right dose, and continuously tracking the distribution of the compound in the body. Experts of the

pharmaceutical industry confirmed that these new molecular imaging techniques are a better internal decision making tool, and helped them to speed up the R&D process, improved the patient stratification process for clinical trials and in the end saved much money. Our results are therefore in line with current statements from the literature (e.g. Lin et al., 2015; O'Farrell, Shnyder, Marston, Coletta, & Gill, 2013; Rudin & Weissleder, 2003).

Some studies briefly addressed the industry challenges with imaging biomarkers (IBMs) such as the selection of the right imaging technology for a specific question (Pien, Fischman, Thrall, & Sorensen, 2005), the validation of imaging biomarkers i.e. as a surrogate endpoint (Schuster, 2007) and the quality, validity and quantification of the imaging measurement (J. C. Waterton & Pylkkanen, 2012). So even if IBMs seem to be beneficial in the R&D process, our data indicated that the pharmaceutical industry has minor interest in commercialising IBMs or even use them as a companion diagnostic. The reasons for the low commercial interest on the part of investors are versatile, but we can use our data to categorise and describe these barriers more precisely.

The hurdle that stands out as number one among the diagnostic RPs is "**market potential"**. This issue was highest ranked by all stakeholder groups but was only partially discussed in the literature so far (Zimmermann, 2008).

5.2.1 Low Market Potential

Rising R&D costs, high attrition rates in the development process as well as shrinking revenue has put pressure on the shareholder-driven pharmaceutical industry (Kola & Landis, 2004). In effect, the industry started to prioritise those projects with the highest net present value (Stewart et al., 2001) and reduced efforts for medical innovations, which generated sales lower than $ 600 million per year (Tollman et al., 2011). Unfortunately, nuclear medicine was one of these "lower-interest" segments since the global nuclear/radiopharmaceutical market only has a total market potential of $ 4.67 billion (estimate for 2016) (Markets and Markets, 2016). The market for the diagnostic RPs is very small and thus does not seem to be attractive enough for the big pharmaceutical industry: *"…the margins are very low in diagnostics, there is more money in therapeutics..."*. This was evident in the late 1990s/early 2000s, when several large pharmaceutical companies left the diagnostics RP market. Even though new cancer therapeutics become increasingly more targeted (Habeeb et al., 2016), and patient stratification will become more important, many large pharmaceutical companies seem nonetheless unwilling to include diagnostics in their portfolio. However, radiopharmaceuticals are by no means unattractive to large pharmaceutical companies, as demonstrated by the Novartis acquisition of Advanced Accelerator Applications (AAA) in 2017. Novartis had special interest in the recently approved ^{177}Lu-DOTATATE therapeutic agent, which fits well within the Novartis oncology portfolio in the NET area (Novartis Media Relations, 2017). We therefore expect the big pharmaceutical industry to make strategic acquisitions in therapeutic (and/or diagnostic) RPs, but they will not be a primary investor for the development of new diagnostic RPs.

Thus, the development and commercialisation of diagnostic RPs may remain solely in the hands of small and medium-sized enterprises (SMEs). In fact, it seems that the development of diagnostic RPs fit very well within this segment since smaller firms are more flexible, traditionally focus more on domestic markets, create or re-engineer products or services to meet new market demands, but in general conduct less R&D compared to larger firms (Organisation for Economic Co-operation and Development, 2000). Our interviewed experts from SMEs confirmed that they have continued the development of

diagnostic RPs, which have proven to be pre-clinically or clinically effective and have a high chance of receiving adequate reimbursement in the United States. The U.S. market seems to be of special interest and was described as a "fairly big business", a "good investment" with "good growth rates". In fact, recent estimates indicate the U.S. PET RP market potential to be around $ 275 million and in connection with the "good conditions" this market is currently driving the global development of new diagnostic RPs. "Good conditions" are described to be good reimbursement values for oncological diagnostic products, and the relatively "quick" local Medicare and Medicaid reimbursement due to favourable regulation. So interviewees from the RIG and the NMG therefore see a far better outlook for the US market, since the market is very differently structured and offers more possibilities for revenue (Kuttner, 2008).

> *"PET biomarkers are a fairly big business. The PET market in the US is about 275 million a year, this year 2018. That's all PET in the US, revenue. So 275 million…"*
>
> (Manager Radiopharmaceutical Industry)

For Europe the situation is much different, maybe even worrying in the eyes of some experts. Europe has the extraordinary situation that drug applicants can apply for a Europe wide centralised authorisation for their drug, but the decision on reimbursement remains a national competence and has to be negotiated with each national health authority. The challenge: the requirements for evidence of benefit (i.e. medical efficacy data, health economic data) differ from member state to member state and application forms need to be adapted for each country. Our interviewees from the European NMG even fear that the low market potential in Europe could even become a challenge for the introduction of future diagnostic RPs. This fear was directly confirmed by an expert from the RIG:

> *"If the market for all PET diagnostics and SPECT diagnostics is payment at either a technetium bone scan rate or an FDG rate, if that is the future, from now forever, for payment for nuclear medicine, then at some point people will stop commercialise products in Europe."*

The situation in Europe is not based on strict conditions by health authorities, but also rests on the non-engagement of the industry. Typically the industry has a market access strategy and starts very early to collect data on safety, efficacy and evidence of benefits. But since the pharmaceutical industry has not engaged much in nuclear medicine, also the difficult issue of reimbursement was left with academics. Accordingly, many of the studies miss a structured process and have not met the requirements of national HTAs or the national/ international regulatory authorities. For example, the German Institute for Quality and Efficiency in Health Care (IQWIG), which is responsible for the independent assessment of the benefits of drugs and technologies, exclusively relies on the concept of evidence-based medicine. Consequently, only trials with the highest quality and for example compare option A to option B (ideally randomised) can be used for the evaluation. Patient-relevant endpoints (mortality, morbidity and health-related quality of life) need to be reached in randomised controlled trials. Also diagnostic pharmaceuticals are evaluated after the same procedure, even it is more difficult for those product group to show an existing and documented benefit on the outcome (Institute for Quality and Efficiency in Health Care - IQWIG, 2017a).

In summary, our data show that the issue of market potential, which is i.e. closely linked to the reimbursement issue, represents the greatest challenge for diagnostic RPs in Europe, and must be urgently addressed. It is to be expected that large pharmaceutical companies will not be generous in the field of molecular imaging outside of their currently running R&D efforts. This leaves the development of new, innovative products in the hands of SME and the academic community. While SMEs have a creative, quick and efficient approach to solving challenges, they often lack specific expertise and staff to, e.g. solve national reimbursement hurdles. There are currently some challenges in Europe (to be discussed in the next pages), which have a significant impact on the market potential

and eventually detain SMEs to introduce these new diagnostic products in the European market. A non-introduction of diagnostic RPs in Europe would be fatal from the perspective of patient care, which is why we believe it is urgently necessary to (1) get national/ international regulatory- and reimbursement support for SMEs, (2) line up contemporary and adequate reimbursement for innovative technologies in the DRG system, and (3) tighten the cooperation with academic institutions.

5.2.2 Reimbursement

The second most crucial hurdle (67% agreement across all stakeholder groups), which we have already briefly mentioned, is the issue of reimbursement. Reimbursement policies have a far-reaching effect on the adoption and the usage of medical technology (Office of Technology Assessment, 1982) by restricting access or supporting the spread of the drug or medical technology. In molecular imaging, especially in PET/CT, the reimbursement of procedures is globally very heterogeneous regulated and coverage policies are often variable and restrictive, especially in Europe (Fischer et al., 2016). In the U.S., reimbursement for oncological indications has increased in recent years due to "coverage with evidence development" (CED) program.

Getting a product reimbursed is time-consuming and complicated. Pricing and reimbursement is usually a national competence and countries have different approaches and processes to assess the value of a new drug and subsequently decide on the listing by public- insurance companies (Barnieh et al., 2014). Our interviewees have pointed out some critical issues that have led to the problematic reimbursement situation in Europe: Missing formal authorisation of RPs, high regulatory requirements to prove utility, and inadequate study designs/ data from academic studies. In particular, the incompatibility of the requirements outlined by the competent authority (e.g. IQWIG in Germany) and the feasibility of the academic institutions should be emphasised. Whereas doctors from academic institutions typically want to get medical questions answered, authorities also want to see evidence of benefit from a socio-economic point of view. Typically, it is the responsibility of the company which is developing the new drug to timely set up a process and collect reimbursement relevant data. But since many of the diagnostic RPs have mainly been developed by academic institutions in many European countries, the challenge of reimbursement was left in the academic sphere. A recent study evaluated the reimbursement system in five European countries and outlined the similarities and difference in their processes, showing the challenges, and revealed how much multidisciplinary knowledge is needed (Franken, le Polain, Cleemput, & Koopmanschap, 2012). The academic community has neither the knowledge nor the financial resources to cover this issue.

Even for the industry reimbursement for their products is not simply achievable, as one expert from the RIG confirmed: *„Getting past the FDA is not that bad, it takes time and money, but it is doable if you have a focused indication. But getting passed payment is a big deal.*". Medical imaging is furthermore accused of being a principal driver for burgeoning expenditures (Baker, 2001; Bodenheimer, 2005; Smith-Bindman, Miglioretti, & Larson, 2008; Sorenson et al., 2013), which may increase demands on clinical- and economic benefits data by governmental institutions.

We conclude that the reimbursement situation in the U.S. is favourable for the introduction of new oncologic diagnostic RPs, making it the currently most important market for the radiopharmaceutical industry. Even the current push by the U.S. government to decrease national healthcare spending, by forcing pharmaceutical companies to lower drug prices (Block, 2018), may not have a short-term effect on the reimbursement system in the U.S. Especially in Europe, with its state-funded healthcare system, the heterogeneity of reimbursement systems (Franken et al., 2012), decreasing reimbursement rates for imaging procedures (Merchant, 2010), and restrictive reimbursement decisions by national health

technology assessment agencies (e.g. Institute for Quality and Efficiency in Health Care - IQWIG, 2018; C. Wild, Patera, Küllinger, & Narath, 2015) will have a substantial effect on the introduction of new RPs. Due to a higher cost pressure, payers may to see more evidence, from well-designed Phase 3 trials, with clinically meaningful endpoints such as Quality of Life, morbidity and mortality (Oye et al., 2015).

On the other hand, there have been initiatives by the FDA and EMA to speed up approval for new drugs with orphan diseases status by partially lowering the approval requirements (Giannuzzi et al., 2017). Companies who may want to introduce innovative new products get free and early-stage scientific- and/or reimbursement advice by EMA and FDA (Henshall, Mardhani-Bayne, Fronsdal, & Klemp, 2011; Wonder, Backhouse, & Hornby, 2013). This initiative may particularly help small and medium-sized companies, as they usually have less in-house knowledge compared to big pharmaceutical companies (Pammolli et al., 2011). We further assume that the academic community will continue to drive the development of new diagnostic RPs. However, we believe that academics need to implement a more process-oriented, rigorous study program/-quality in order to generate more clinically and economically relevant data that can also be used for market authorisation and reimbursement decisions. We see that this understanding is already being perceived in the group of nuclear physicians:

> *"What we urgently need in academic research is industry support. So the thinking of the industry: what are the development steps of phase 0,1,2,3? What are the requirements? How can you do something like that?"* (Nuclear Medicine Physicists from Germany)

5.2.3 Regulation

Radiopharmaceuticals are possibly among the tightest regulated medicinal products worldwide and have to obey the national law on drugs, national and international radiation protection ordinance, special employment protection regulation et cetera. For all drugs, the marketing authorisation (MA) process has refined over the decades, and modern approval processes requested much more clinical data, more randomised controlled trials and more data on safety and efficacy (Woodcock & Woosley, 2008). Since diagnostic RPs are regulated similar to classic pharmaceutical drugs, they have to follow the general drug approval process (The European Parliament and the Council of the European Union, 2001; U.S. Department of Health and Human Services Food and Drug Administration et al., 2004) even diagnostic RPs do not have any pharmacological effect (Saha, 1984). Despite lacking pharmacological effect, there are cases of acute adverse events including serious side effects (~ 38%) (Laroche, Quelven, Mazère, & Merle, 2015).

However, if the product is an imaging agent some data can be waived and other additional data may be requested (radiation exposure, absorption dose of the source tissue/organ and any other tissue et cetera) (U.S. Department of Health and Human Services Food and Drug Administration et al., 2004). Extraordinary is the allowance of "extemporaneous preparation" (Article 7 in Directive 2001/83/EC) in Europe, which empowered member states to legitimate some institutions to prepare the product near the patient´s bedside and waive the marketing authorisation (The European Parliament and of the Council, 2001). But Article 7 was not transposed uniquely in all countries, and today some countries enjoy more freedom than others. In Germany, this exemption is continuously use by clinicians, who prepare their RPs in either small-scale industrial sites with GMP license or non-industrial sites such as hospital pharmacies, and nuclear medicine departments, and administer the diagnostic and therapeutic RPs to patients (§ 13.2b AMG).

Literature suggested that the topic “regulation” is highly ranked (Henderson et al., 2005; Nunn, 2007a; O´Connor et al., 2017; Zimmermann, 2013), however, our empirical data suggests that this challenge may not be perceived as of great importance to all stakeholder groups. It is interesting to note that the opinions of the experts of the NMG and the RIG are completely contrary. For both groups the regulation is a challenge, but for the NMG group it is too tight and for the RIG not stringent enough. Overall European nuclear medicine physicists perceive the regulations for diagnostic RPs to be too strict and these products should not be categorised equally as therapeutic drugs. Some European interviewees value the possibility to have quick first-in-man studies, but also half of them criticise the rapid use in humans. Their concerns are related to patient safety and uncoordinated collection of proof of utility: trial designs may not meet current requirements, data may not be efficiently used for approval or reimbursement processes and therefore create obstacles for the whole nuclear medicine field. It is the opinion of one expert that Europe will not be able to approve new RPs due to the unstructured process. However, it can be argued that European data, recorded in retrospective “individual medical treatment” cases, has been accepted by the agencies for backing up the approval of new diagnostic RPs.

> *“Germany leaves them any freedom, which I welcome. I think that's great, but the problem in Germany is that you have room to do scary things, and then, if you really want to introduce the tracer to the market, then the hurdles in Germany are even more prohibitive than they are here."*
>
> (Nuclear Medicine Physicist from Europe)

> *“I don´t think that the regulatory agencies are the bottleneck here. Actually they are doing really well. They have an interest to get this done. I am actually fairly positive about their work...”*
>
> (Nuclear Medicine Physicist from the USA)

Unexpectedly, the radiopharmaceutical industry perceives regulatory requirements to be not stringent enough, at least in some European member states. While RIG experts recognise the benefits of the administration of unlicensed products to the community and patients outside of clinical trials, the companies struggle with this “secondary market” and cannot compete from a business perspective. For the U.S. market, the interviewees are satisfied with the FDA´s cooperation and support, also because there are distinctive formulated requirements/ guidelines. Furthermore, the administration of unauthorised RPs, outside registered clinical trials and without a new drug application (NDA) status, is prohibited (Vallabhajosula, 2009).

Our interviewees from the RIG anticipate a strengthening of European regulations, with the result that the possibility of “in-house production” will become limited. Some European nuclear medicine physicists agree with this assessment, yet the field is divided. A few don´t expect any regulatory harmonisation, whereas others await a positive harmonisation and the third group fears that the regulators will change to their detriment. From today's point of view, it cannot be predicted in which direction these changes will progress. One expert told us that the lobby groups from the nuclear medicine associations and pharmaceutical industry seem to be in intensive talks with regulators to compile their statements. We can expect the radiopharmaceutical industry and occasionally large pharmaceutical companies to limit the use of un-authorised products (at least in their indications), a fact which may affect clinical practice and academic research. However, previously introduced European regulations and directives have dealt with general health/medical-legal issues (Directive 2001/83/EC, Regulation (EC) No 726/2004, Regulation EU No 536/2014, et cetera), but not specifically with a group of products. The harmonisation process may take time and could perhaps be introduced via recommendations in guidelines, code of practices or even GMP regulations.

5.2.4 Research and Development

In literature the term R&D is primarily connected to the perception of costs, but our empirical data suggests that there are also other concerns outside of costs such as speed of research, the sophistication of industrial and academic research, and research related mistakes made by academics.

Thus, while the majority of nuclear medicine physicians (57%) see R&D costs as a challenge, none of the experts from the radiopharmaceutical industry has explicitly mentioned this topic. So “R&D costs" seems not to be a provoking challenge to all stakeholder groups. Possibly physicians have little business knowledge on the development of new drugs and cannot put the millions of dollars in relation, whereas the industry is continuously calculating investments vs. expected return on investment (Schuhmacher et al., 2016). One has to say that the development of a new RP is significantly less expensive compared to a new biologically active drug. It was specified that costs for a new diagnostic radiopharmaceutical are between $ 100 to 200 million (Nunn, 2006), whereas Zimmermann (2008) estimates costs of $ 26 to 35 million (in 2017 USD) for a radiodiagnostic - and $ 52 to 82 million (in 2017 USD) for a radiotherapeutic compound. We would assume, based on the statements from our interviewees and the published financial reports from relevant companies that the real costs for a diagnostic RP would be between $ 65 million and $ 100 million. Although that sounds like a lot of investment, it is many times less than the development of a therapeutic agent (cf. R&D costs published by: DiMasi et al., 2016, 2003; Kaitin & DiMasi, 2011; Prasad & Mailankody, 2017).

The assumption that extensive basic research of academic institutions reduces development costs does not seem to be valid, at least that is the opinion of an industry expert. Academic research may somehow de-risk the investment, but has no large effect on overall costs. A reason: the quality of the data is not sufficient to meet demands of regulatory agencies:

> *“.. the Agency has an interest in using data from real clinical world experience for NDAs… however, the literature review contained no randomised, prospective trials with independent blinded image review designed for drug development. Incomplete information in the articles did not allow one to determine precise diagnostic test performance (sensitivity/specificity) or to evaluate the role if new imaging information on patient management and patient outcome… the totality of the clinical experience … may be used to support approval” (comment from the FDA in connection with the approval of a new diagnostic RP*; Center for Drug Evaluation and Research, 2016).

Surprisingly even some nuclear physicians admitted that academic studies have room for improvement regarding quality. However, this may only be achieved with the support and knowledge of the industry. It is also interesting that half of the NMG interviewees admitted possible mistakes in the development and commercialisation of new diagnostic RPs. From their point of view, some substances were too quickly used in patients, abandoning a structured and coordinated approach with the result of having weak evidence of benefits. Also, some nuclear medicine physicist’s interviewees are concerned about the speed of development in the therapeutic segment. In recent years the approval rate for drugs, mainly targeting rare diseases and sub-types of cancer, has increased in many big markets such as the US, Europe and China (Hirschler, 2018). Those new products have often used a new scientific paradigm which was developed by young biotech companies (Hirschler, 2018). Due to the lack of collaboration between the therapeutic manufacturers and the diagnostic companies or academic institutes, the development of diagnostic tests is lagging far behind. A catch up is hard to achieve and may not be feasible in some cases. For this reason, a closer and quicker cooperation with the industry may be

beneficial, although it is doubtful that the pharmaceutical industry shares their "industrial secrets" with an outside third party at an early stage.

A positive sign is the current commitment of new small and medium-sized start-up companies in R&D of new diagnostic and therapeutic RPs. So far those SMEs have proved to have a creative and innovative approach and have successfully and quickly implemented some of their R&D projects. Even those companies tend to have a less experienced development teams and fewer resources than large companies (Hay, Thomas, Craighead, Economides, & Rosenthal, 2014), but tend to take a greater risk (Hay et al., 2014). They compensate these disadvantages through tighter collaborations with academic institutions, profiting from their know-how and access to the patient population.

5.2.5 Intellectual Property Rights (IPR):

IPR is extensively discussed in connection with the development of new drugs (Dutfield, 2003; Williams, 2015), also in connection with the development of new radiopharmaceuticals (Zimmermann, 2008, 2012a, 2013). Once again, our data shows that there are significantly different opinions within the stakeholder groups. While most nuclear medicine interviewees (60%) confirmed that IPR is a challenge, the PIG and RIG did not perceive this as the primary barrier.

It has long been known that universities play an essential role in the national innovation system (Fagerberg, Mowery, Mowery, & Sampat, 2009) and contribute to economic growth and international competitiveness (Furman, Porter, & Stern, 2002). This is achieved on the one hand by the education of the students and by the creation of knowledge through university research. While Europe produces a high academic research output, European universities are lagging behind the US in technology transfer (Baldini, Grimaldi, & Sobrero, 2006; A. Conti & Gaule, 2011). Since universities have not done well in the commercialization and development of products, universities have established so-called technology transfer offices (TTO) to improve competence and secure the university´s intellectual rights (Karjala & Kiskis, 2011). The TTO´s mission is "*to evaluate, patent where warranted, and exploit faculty creativity, through licensing or the creation of new spin-off companies.*", which has worked for many U.S. universities so far but was globally not encouragingly successful (Fisch, Hassel, Sandner, & Block, 2015; Karjala & Kiskis, 2011). European universities file fewer patent applications than the U.S. and Asian counterparts, which causes those universities to lag behind technology transfer (Fisch et al., 2015).

Our data indicates an in-efficient IPR process within the university system. This can be illustrated by a story of one of the German interviewee who told us that in a (large) German medical university there is no patent attorney employed at all, but an attorney from the University takes over the responsibility. However, this lawyer, in turn, holds little of patents "*…because it does not pay off, and he does it only in exceptional cases*". In reality, however, usually not only the royalties paid to the universities, but the protection of the idea is more important to the investor as it gives the opportunity to pursue the idea in the first place. Most interviewees from the NMG have now realized that there must be some form of protection to gain the interest of the investor, with some physicians being self-critical about their approach in the development and the usage of new RPs (as discussed in chapter 5.2.4 "Research and Development").

Industry representatives regard academic research as a valuable means (not only of gaining) access to ideas and products, but also expect more engagement of universities regarding IPR. Some industrial representatives already see an improvement in some universities, but overall the situation could improve. Generally, some protection is necessary and essential for the industry, but the patent on the chemical entity is not an ultimate must (for some it is still mandatory). Thus the situation is overall not challenging as there are many possibilities of protection and industrial experts have built a protective wall around a product.

> *"So from our perspective, when we build up our IP portfolio we don´t rely on one piece of IP. We like to have the chemical entity, and then we build a whole layer of onion around it. About different IP that covers the manufacturing process for the product, how the product is being used in the field…but not having the chemical entity IP is definitely something that when we go to investors, to ask to invest in new ideas we got, the first question they ask is: "what is the IP position?" And it is a big red flag for them if you don´t have chemical entity protection…"*
>
> (Expert from the Radiopharmaceutical Industry)

Moreover, one can say that the pharmaceutical industry is very good at protecting it IPR, and extensively uses the product- and process patents in comparison to almost every other industry (Cohen, Nelson, & Walsh, 2000).

A recent example shows that IPR is not as much in the forefront of academic research as rapid publication and medical application:

> Scientists at the German Cancer Research Centre at the University of Heidelberg have quickly published results of the ^{68}Ga-PSMA HBED-CC RP in June 2012, and due to the "non-patented status" the tracer rapidly spread worldwide. Interestingly some interviewees from the NMG and RIG believed that no one had ever applied for a patent for that compound, and see this as a missed opportunity. However, the German Cancer Research Centre, University of Heidelberg assigned a patent in October 2013 (Patent application number: EP3038996A1) and other related applications followed in the years after (numbers: EP20140799340, EP3038996A1), but up to date none of these applications have been granted. Nonetheless, the patent status, the quick publication of first results in humans (Afshar-Oromieh, Haberkorn, Eder, Eisenhut, & Zechmann, 2012; Schäfer et al., 2012) has allowed a useful tracer to spread very rapidly and has since successfully influenced patient management in many patients. At present, some companies are researching new biomolecules that also have PSMA as their target, especially in the field of therapy but also in a few cases in the field of diagnosis. However, PSMA HBED-CC is currently no further research in Phase I to III trials (U.S. National Library of Medicine, 2018), possibly due to the challenges with IPRs.

5.2.6 Manufacturing, Distribution and Handling

The production, distribution and handling of radiopharmaceuticals are undoubtedly more complex, challenging and costly compared to most other pharmaceutical products (World Health Organisation, 2008). Radionuclides used in imaging and therapy typically have a short- or medium half-life, which require a well-organised production process and a secure, reliable & cost-efficient distribution network (Dash et al., 2013; Internal European Commission Ad Hoc Interservice Group, 2009). Transport costs are typically substantially higher for medical isotopes compared to conventional drugs (World Nuclear Association, 2017) and country-specific higher requirements could further increase effort, time and technical and financial resources (Internal European Commission Ad Hoc Interservice Group, 2009).

This is definitely a deterrence for the pharmaceutical industry since this industry branch thinks and sells globally and must ensure that everyone has access to the product. Global access is hardly achievable using PET radionuclides, SPECT with technetium could be a better option. Zimmermann (2013) has considered this point of manufacturing and handling in more detail, divided challenges into the areas of radiochemistry, selection of radionuclides and costs of infrastructure. From our data, we can only say that the selection of radionuclides and access to this technology is crucial for the pharmaceutical industry.

For the NMG and RIG the manufacturing process, distribution and handling is nothing new. Therefore, these interviewees have not recognised this as a "special" obstacle. However, what was described as a challenge in literature, especially for the self-producing academic institutions, was the requirements of good manufacturing practice (GMP) introduced in recent years (Deutsches Bundesministerium für Gesundheit, 2009). In Europe it is up to the national authorities to decide whether the production and quality control of RPs in non-industrial institutions should be GMP-compliant, but we have seen that this was implemented in many European countries. GMP production is more demanding as it requires unique infrastructure, equipment, training for employees, documentation and a detailed labelling process, which in turn results in significantly higher costs (Gerrits, Woerdenbag, Luurtsema, Hooge, & Boersma, 2017). However, after none of the respondents from the NMG has identified this as a challenge, it looks as if the academic institutions have come to terms with the new requirements.

Short Excursion- Therapeutic Radiopharmaceuticals

Compared to diagnostic RPs, many interviewees from all groups see a bright future for therapeutic RPs. The successful introduction of the theranostic concept in NETs, and most likely also in prostate, will lead to more discoveries and developments in diseases areas with high market potential such as breast cancer, lung carcinoma, colon carcinoma and also pancreatic adenocarcinoma.

Therapeutic RPs have significantly better commercial- but also product-relevant premises, which makes it more attractive to large pharmaceutical companies. With the acquisition of AAA already a big investor´s showed interest, primarily in the therapeutic drug Lutathera® and the already advanced developments in the therapeutic drug for advanced, metastatic prostate cancer. A primary reason is the significantly better **market potential** compared to the diagnostic RPs. Even though the number of patients who benefit from this radiopharmaceutical therapeutic approach may be small (compared to block buster drugs), the current reimbursement rates are comparable or even higher than currently available chemotherapeutics drugs in many international markets (National Institute for Health Care Excellence (NICE), 2017). Just for comparison, the global monoclonal antibody therapeutics market was valued at approximately $ 108 billion in 2017 (Zion Market Research, 2018), whereas the total global radiopharmaceutical market was valued at US$5.2 billion (Transparency Market Research, 2018). From a **regulatory** point of view, therapeutic RPs pose no big challenges to the pharmaceutical industry as they are treated the same as other medicines and this knowledge is sufficiently available. Also, the **development** of therapeutic RP does not pose a significant challenge to the companies, the unique concept of theranostics may open up new avenues. For example, it would be conceivable that the companies trawl through their "biomolecule libraries" and identify targets with high binding affinities, which may not have been developed further due to little or no therapeutic effect. However, labelling these highly selective molecules with a therapeutic radionuclide may result in a useful, inexpensive new product. In the context of diagnostic RPs we have also discussed the challenges of **manufacturing and distribution**, which, however, are not of concern in the therapeutic field. Due to the significantly longer half-life of therapeutic radionuclides they can be distributed over long distances without significant

problems. For example, the short-range therapeutic beta-emitter Lutetium-177 has a half-life of 6.7 days, while the diagnostic beta plus emitter Fluor-18 only has a half-life of 109 minutes.

Therapeutic RPs, therefore, have good prospects to be increasingly developed and approved in the future. It is also likely that larger investors will invest in this area more often, fuelling the field of nuclear medicine. Some nuclear physicians have expressed the hope that diagnostic RPs can also float in the success- wave, giving rise to more diagnostic products with marketing authorization. However, in our view, this would only be the case if the whole theranostic concept would be applied: mandatory use of the diagnostic test, in the sense of a companion diagnostics, before the application of the therapeutic agent. However, based on available empirical data and our assessment, companies will avoid this approach as much as possible.

2) What are the biggest challenges of diagnostic (and therapeutic) radiopharmaceuticals and why are they mostly developed in public research facilities and have not received a marketing authorisation?

Our analysis and empirical data suggest that the **low market potential**, in combination with the currently challenging European **reimbursement rates,** are the main barriers for successful commercialization and introduction of new diagnostic radiopharmaceuticals. Furthermore, also the **availability** of short-lived radionuclides is especially provoking for the pharmaceutical industry. Small and medium-sized enterprises (SMEs) therefore take on this task and engage more and more in R&D activities. The currently active SMEs in the RP business have proven to have a creative, fast and effective approach in recent years and managed to get several new products approved. They will likely continue their research and development program in disease areas with a slightly bigger market size, but will not engage in the development of companion diagnostics by itself. Our data also suggest that some of the challenges, which have been extensively discussed in the literature, may be important to a single stakeholder group, but not for others. **Regulation** is such a challenge, which is highly ranked within the nuclear medicine stakeholder group but not so important to others. Some nuclear medicine physicists believe that the regulatory requirements are too high and diagnostic RPs should not be regulated similarly to therapeutic drugs. Contrary, the radiopharmaceutical industry experts request a tightening with the aim to limit self-production of public institutions. The great divergence of these statements may be explained by the regulatory intensification regarding production, quality control, clinical trials et cetera. in recent years, which especially targeted the academic community. Also, over the last decade the academic institutions have increasingly engaged in R&D of new RPs, but due to higher regulatory requirements for clinical trials, missing knowledge on how to conduct proper clinical trials and tight budgets, it has become increasingly difficult to carry out these studies. Also the topic **Intellectual Property Rights** popped up regularly in the literature, and our data suggests that it is important but not a big challenge. From an industry perspective, IPR is essential and the patent on the chemical entity is desired, but they also made clear that there are several ways to protect a product. It turned out that nuclear medicine physicists increasingly acknowledge the importance of protecting ideas and admit that this mistake is more likely to be on the side of universities, which often have not implemented an efficient process.

Therapeutic radiopharmaceuticals are less likely to face these challenges, as the main challenges "**market potential**" and "**reimbursement**" have much higher values, and also the "**manufacturing**" and "**distribution**" of therapeutic RPs is easier. The reasons for the previous lack of interest may be based on the fact that there have not been any new, useful examples of success. With the successful introduction of Lutathera®, we may see other big players entering the market. Further promising disease fields such as mammal, lung-, colon- and pancreatic adenocarcinoma are already being researched.

5.3 Diagnostic Radiopharmaceuticals used as Companion Diagnostics

Since the topic of personalized medicine and the associated use of biomarkers is so up-to-date, we asked our expert about the general value of companion diagnostics (CDs). Additionally, whether molecular imaging can take on the task of a companion- or a complementary diagnostic, and what challenges would be associated with it.

Benefits and Challenges Associated with Companion Diagnostics in General

As already discussed in the theoretical part, a CD is a diagnostic test that provides essential information on the safe and effective use of a similar drug or biological product (U.S. Food and Drug Administration, 2018a). Intensive research on the cellular and molecular biology level allowed us to differentiate cancers based on their molecular aetiology, the natural course of the disease and also their reaction on therapeutic interventions (Cheng, Koch, & Wu, 2012). The great hope is to stratify patients according to their specific (molecular) characteristics and administer the targeted therapy only to those patients who are more likely to benefit (Trusheim & Berndt, 2015).
In our study, there is substantial agreement among stakeholder groups regarding the benefit of these diagnostic tests in general, ranging from more targeted therapies, improved outcome, better patient stratification, and superior clinical trial outcomes. Keywords that can also be found in the current literature (cf. Kalia, 2013; Mansfield, 2014; Papadopoulos, Kinzler, & Vogelstein, 2006; Simon, 2008).

The groups are less united when it comes to the challenges of CDs. For medical specialists the discussion is around efficiency generation, validation and standardisation. They also believe that the successful introduction of these tests will be complicated since there is no commercial benefit for the industry. On the contrary, the market will be cut off. This could explain the slow and disappointing adoption of CDs (M. Hughes, 2013; Meckley & Neumann, 2010) with divergent interests of the stakeholders regarding a (fast) implementation of these CDs (Satanove, 2016). We can also support this testimony by three statements from our experts:

i. An expert from the pharmaceutical industry indirectly confirmed that they would generally prefer to introduce a product without a CD. For example, in two pivotal studies, they successfully used a CD for patient stratification, but in some cases a pre-selection via a CD would not have been necessary. "*And in the advanced lung cancer patients… you did not need to enrich it with the diagnostic…So that kind of set us back for a little bit…oh, Jesus look what we have done. We have anchored ourselves…*"
ii. The second statement is from a medical specialist, whose group was working on a biomarker for the stratification of patients with advanced prostate cancer. He also confirmed that the industry had little interest in supporting his research group: "*… we have been trying to develop biomarkers. That costs money and the company… hold us back for a long time, but I knew from the beginning that they would not give us any money.*"
iii. Another interviewee from the PIG describes the stalemate when the CD delivers a positive result but also those patients, who should not belong to the preferred group according to the test, respond to the therapy.

    The lack of interest of the industry to offer appropriate diagnostic agents (CD) to their therapeutics can be illustrated by a real case: The FDA recently approved the in-vitro assay (Ventana® PD-L1) to assess the PD-L1 status on patients with metastatic urothelial cancer (mUC), who are considering treatment with the monoclonal antibody atezolizumab (Tecentriq®). The assay was used in the Phase III registration trial and showed a higher objective response rate in patients with higher PD-L1 expression, but also a response rate in patients

with minor PD-L1 expression (Rosenberg et al., 2016). Ventana® was therefore not registered as a Companion- but a Complementary Diagnostic and thus is no prerequisite for the administration of the therapeutic agent.

Our data suggests that PIG experts are well aware that CDs could restrict patient access to their therapeutic drug. Thus these group is not so keen to move ahead quickly, even payers would be happy to see a quicker implementation since the market gets more restrictive and costs are reduced (Danzon, 2014). From the CD developer perspective, CDs may also not be a big commercial win. They would face limited applicability of the diagnostic test, and our experts even envisage the danger of the entire development being in vain if the therapeutic drug fails in a (late) stage. In combination with the low prices for the test, this could be very unattractive for the diagnostic companies (Jerel, Ma, & Sutaria, 2010; Satanove, 2016), which is why it probably will not succeed without the financial support of the pharmaceutical entrepreneur in the sense of a compensation payment (Jerel et al., 2010).

Radiopharmaceuticals being used as Companion Diagnostics?

We were particularly interested if radiopharmaceuticals would be a suitable CD? Based on the statements of the interviewees from the NMG one could assume that molecular imaging becomes the CD of choice. The responders are convinced that imaging biomarkers have much higher accuracy and higher value in monitoring and staging than in-vitro assays. The statements correlate with those from the predominantly nuclear medicine literature: more precise localisation (M. D. Farwell, Clark, & Mankoff, 2015), real-time and non-invasive procedure (Pauls et al., 2007; Weissleder & Pittet, 2008), depiction of the heterogeneity of the target tissue et cetera (Abramyuk et al., 2009; Bleavins et al., 2011; Krause, Beck, Souvatzoglou, & Piert, 2006).
In principle, medical specialists agree that molecular imaging is an essential tool in patient management but they would not generally prefer imaging biomarkers over in-vitro assays. What they want is any biomarker with high sensitivity, specificity and selectivity. In their mind, the future will most likely be a reasonable combination of imaging- and in-vitro tests, with some interviewees expressing great hope in liquid biopsy. So far, literature on the subject of CD deals mainly with in-vitro tests (Agarwal et al., 2015; Alix-Panabières & Pantel, 2012; Crowley, Di Nicolantonio, Loupakis, & Bardelli, 2013; Jørgensen, 2013; Mansfield, 2014; Scheerens et al., 2017; Ziegler, Koch, Krockenberger, & Großhennig, 2012), only a few studies show the advantages and disadvantages of imaging biomarkers (Idée, Louguet, Ballet, & Corot, 2013; O´Connor et al., 2017; Scheerens et al., 2017; Van Heertum et al., 2015)

We understand the desire of nuclear medicine doctors to get more diagnostic RPs approved via the concept of CD, but we generally do not see the chance of success as great. The main reason: for our interviewed pharmaceutical industry experts imaging biomarkers lack global availability, low prices, convenience and easy application, high accuracy, detection of multiple mutations, simple use in Phase I to III trials, natural patient segmentation et cetera.

> *"And I believe that is because the pharmaceutical companies' don´t want a potential market limiting step on the way using their drug. I had some conversation with the imaging teams inside big pharmaceutical companies, which gave me that hint, not as an official policy but they believe, that MI is used widely in their clinical trial process, but they never wanted it to be a mandatory step underway using their drug. Because unlike a blood test driven tissue test, they still looking at MI as a complex, expensive hard to find the thing that would limit their market for their drugs. So even if it could lead to a better patient population that take the drug, they view that as market limiting and unless the regulatory body or payer absolutely*

required it, they try to find a way to get the drug approved without it." (Expert from the Molecular Imaging Technology Group)

Moreover, our interviews suggest that even for the radiopharmaceutical industry the development of an imaging companion diagnostic is currently not attractive. In their opinion, the market for a CD is too limited (cf. Kulkarni, Ma, Furstenthal, & Evers, 2013; Satanove, 2016), the commercial risk is higher compared to classic diagnostic products since there is a chance that either the therapeutic will fail or a new development will replace the therapeutic agent or that the test will not be reimbursed (cf. Moore, Babu, & Cotter, 2012). Since the CD is just a vehicle of the therapeutic drug, and the pharmaceutical industry has a great interest to keep it cheap and simple, the developer may not receive much revenue for of the imaging biomarker (Conti, Veenstra, Armstrong, Lesko, & Grosse, 2010). Amongst other things, these considerations have led AAA to register ^{68}Ga-DOTATATE as a stand-alone diagnostic test and not as a CD of Lutathera® (^{177}Lu-DOTATATE).

To summarize, our data suggest that it will be difficult for RPs to be accepted as companion diagnostics. Experts of the pharmaceutical industry describe the disadvantages as too numerous, which is why they will continue to use imaging biomarkers for R&D purpose with no intention of getting it commercialized. Unfortunately, even small and medium-sized radiopharmaceutical companies would currently not engage in the development of CDs themselves since the profit margin and market potential are low.

Should biomarkers be mandatory?

Latest figures show a steadily growing CD market (Agarwal et al., 2015) with one-third of the newly developed therapeutics have a connection to a genomic or proteomic marker (Kulkarni et al., 2013). However, other experts mention that the development is slower than expected (Towse, Ossa, Veenstra, Carlson, & Garrison, 2013), the potential is not yet realised (Trusheim et al., 2011), the utilisation is constrained (Luo et al., 2016) and the pharmaceutical industry does not prioritise the development of CDs (Jerel et al., 2010). Therefore, we wanted to know, if CDs should be mandatorily requested, especially for expensive therapeutic approaches.

Again, opinions differed between the group of physicians, industry and the regulatory authorities. The majority (83%) of nuclear medicine physicians can well imagine that some biomarker tests could be required by regulatory authorities in the future, with the main argument being the cost burden for particular therapeutics. Also, medical specialists envision that CDs possibly be mandatory: 75% of responders from this group expect the test to be undoubtedly mandatory, but it will take some time to be implemented. There is no explicit answer from the pharmaceutical industry's experts just a hint through the testimony of an interview participant: he believes that biomarkers will not be compulsory, at least not for all medications, but the decision will be made on a case-by-case basis. Moore et al. (2012) claimed that in several recent guidance documents some regulatory organisations have already required the use of a companion diagnostic (in some instances) before the administration of a personalised therapeutic.

On the other hand, we have the testimony of two experts from an international medical agency who think that the mandatory development of a CD for every new drug is not the right concept. In their opinion, evidence of benefit for newer, very specific therapeutics, which target a very specific patient subpopulation, will no longer be readily available without Companion Diagnostics. So specific

biomarkers/CDs will most likely enter the market, the decision on how to prove the benefit, how to stratify the patients, and which products therefore need a CD should remain by the industry.

3) What are the Benefits and Challenges of Companion Diagnostics in general, and are Radiopharmaceuticals suitable for the use as a Companion Diagnostics?

There is strong agreement among the interview partners on the **benefits** of companion diagnostics and the associated better patient stratification, more targeted therapies, and possibly better outcome. But there are also numerous **challenges** that have been mentioned by different interview partners. On the one hand, the physicians are thinking of proof of efficiency, i.e. validation and standardization, and currently, don´t believe that the pharmaceutical industry will drive the CD development forward since it will downscale their drug´s market. This was indirectly confirmed by a pharmaceutical industry expert who´s company has used a biomarker in the development of a therapeutic agent, although it probably would not have been necessary "*…oh Jesus look what we have done. We have anchored ourselves…*". Also from the point of view of the diagnostics industry, a CD is not extremely lucrative. The direct link to the therapeutic drug limits the use of the test, and currently, these CDs are poorly reimbursed. Furthermore, there is a risk that the therapeutic fails in the development phase or is replaced by a more effective (competitive) therapeutic drug. In both cases, the CD would be almost worthless.

With regard to the question of whether **molecular imaging could be a useful CD**, the nuclear medicine doctors have a obvious answer: **YES**. In their view, the method is clearly superior to the in-vitro test in many questions that are important for the treatment of patients. And also the representatives of the industries (PIG, MITG, RIG) have a clear answer: **NO**. For the pharmaceutical industry, imaging biomarkers cannot meet the needs of the industry which are: global availability, low priced, convenience and easy application, high accuracy, detection of multiple mutations, simple use in Phase I to III trials, etc. The radiopharmaceutical industry complains about the market size, which is even smaller than for stand-alone diagnostic tests, the additional commercial risk that the linked therapeutic drug fails and thus also the CD, the restrictions in pricing, and the currently low reimbursement rates.

And because the benefits of CDs are highly praised, but the introduction is progressing hesitantly, we also wanted to know whether CDs should be **mandatory** requested? Nuclear physicians and medical specialists are very fond of this idea and believe by the majority that CDs will become mandatory in the future. The pharmaceutical industry has not given a clear answer except one interview participant who assumes that it will be a case-by-case decision. From the perspective of the experts of the regulatory authorities, CDs will not become mandatory since it does not seem to be the appropriate concept. However, from their point of view, there will be no way around the development and use of CDs since newer drugs target sub-subpopulations and the proof of benefit can only be achieved by a precise stratification of patients.

5.4 Alternative Drug Development Process for Diagnostic Radiopharmaceuticals?

Over the decades, the regulatory requirements for the approval of new drugs has become more stringent, although due to extraordinary events such as the thalidomide scandal with severe side effects in pregnant women in the late 1950s (Hilts, 2003). As a result, these stricter regulations also increased the company´s R&D expenses and subsequently shifted the focus on diseases with a high patient population (Haffner, Whitley, & Moses, 2002). However, as a result, there has been little development in diseases with low prevalence and governments decided to implement specific laws such as Orphan Drug Act (1983) in the US and the Regulation (EC) No 141/2000 in Europe, to provide an incentive for companies to invest in such R&D activities. Subsequently, the number of approved orphan drug indications has risen continuously over time and has been called a success in America and Europe (Lanthier, 2017; The Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat, 2011).

Currently approved diagnostic- (^{18}F-Fluciclovine, ^{68}Ga-DOTATATE) and therapeutic RPs (^{177}Lu-DOTATATE) have also benefited from this orphan drug status in the U.S. and Europe. With higher reimbursement rates and more significant market potential for therapeutic RPs, it is likely that investors will continue to develop these drugs to market. For diagnostic RP, our empirical data and experience suggest that these products will continue to struggle to find an investor. We, therefore, evaluated, if there could be an alternative to the "traditional" pharmaceutical drug development process, which may support the development of these products. For rare disease medications, the concept of public-private partnerships (PPPs) have been suggested as an alternative (Buse & Walt, 2000a, 2000b; Nwaka & Ridley, 2003; Trouiller et al., 2002; Yildirim et al., 2016). The principle idea of such a partnership is that for-profit institutions from the private sector (e.g. pharmaceutical industry) meet with institutions from the public sector (e.g. academics, international organisations, governments) and share their knowledge, expertise, resources and investment to work on complex challenges, which may not be accomplished by a single institution (Trouiller et al., 2002). Numerous studies have evaluated various projects and described the advantages and disadvantages of PPPs (e.g. Amiri & Michel, 2015; de Vrueh & Crommelin, 2017; Laverty & Goldman, 2014; Vaudano, 2013; Wellenreuther, Keppler, Mumberg, Ziegelbauer, & Lessl, 2012), the structure (competitive and non-competitive area), the types of participants, and the scope and duration of the project (Yildirim et al., 2016). An example in the private sector would be a collaboration by two private parties to develop a companion diagnostic (Fridlyand et al., 2013) but more common are collaborations between private and public institutions or multi-partner consortia such as the "Innovative Medicines Initiative (IMI)". IMI is currently the largest PPP worldwide in the field of life science, supported by the European Union and the European Pharma Association (EFPIA) (Yildirim et al., 2016).

The majority of our interviews with all stakeholder groups (NMG, PIG, RIG) see a high value in the concept of PPP, two partners (RIG, MITG) have a neutral view. However, we believe that some interviewees were less familiar with the concept of PPP and we assume that some responses are based on their experience with a "normal" partnership/ collaboration. Both groups of physicians (NMG, MSG) valued the concept very highly, probably because these stakeholder groups appreciate the access to funding and knowledge to conduct their research. At the same time, some interview partners criticise the industry for trying to dominate the study design: *"…you have to be very critical. Because I have said it before, the sponsors determine what we do."* This asymmetrically distributed power has already been identified in other studies (e.g. Singh & Prakash, 2010) and is also a result of the short-term projects,

which usually involve small amounts and are mainly focused on applied research or development projects (Blumenthal, Causino, Campbell, Louis, & Seashore, 1996). Another challenge mentioned by the academics is the creation of such partnerships, especially meeting the legal- and partner´s requirements and still having a win-win situation. Khanom (2010) confirmed conceptional constraints in his study and showed that governance, management and policy design is important, as well as the nature of cooperation, inter-organisational arrangements, financial relationships, commitment, roles, the purpose of the PPP et cetera. Concerning "purpose" and "arrangement" the pharmaceutical industry seems to have a clear opinion: *"Moreover, the big advantage for the drug companies in there* [the IMI project] *is that… the drug companies are in the driving seat, and they can say very strongly "we want you to develop a tool that looks like this because if you develop something like this, it would be very useful to us"*.

The interviewees made clear that the big advantage of a PPP is the cooperation with various partners, which allows them to address issues that are important to the whole field, but no one has the resources to do it themselves. The industry sees some stumbling blocks when it comes to working with the academic institutions: (a) consensus-building, which even gets worse the more stakeholders are involved, (b) speed and (c) the "not results driven" attitude. Nonetheless, universities are a vital source of innovation, knowledge and new ideas, which is why all major pharmaceutical companies have close relationships with prestigious academic institutions (Perkmann & Walsh, 2007).

In our opinion, the concept of PPP may be too difficult to implement for the development of new diagnostic RPs. Diagnostic markers cannot usually satisfy the needs of many partners, which is the primary motivator of PPP. However, after the assessment we even believe that the traditional development process is suitable for the approval of new diagnostic RPs. What may be needed is closer co-operation and coordination within academic institutions, as well as a co-ordinated approach with small and medium-sized enterprises (SMEs). SMEs are the backbone of the European economy and key for future economic growth, innovation, job creation, and social integration within the EU (The European Commission, 2018). To further support SMEs, also in the development of new drugs and medicinal technology, the European Commission and the European Medicine Agency have introduced special programs in the field of regulatory work, scientific advice and support in the marketing authorisation process.

From our point of view, SMEs are best suited to drive the development of new diagnostic RPs since they have a good understanding of pathology & human biology, close collaborations with academic institutions, a flexible and rapid decision-making process and they are willing to take risks (Love & Roper, 2015; A. Moore, 2003). Collaborations usually built on a bidirectional flow of knowledge, training, skills and expertise where every partner has the right to provide input regarding the course of the project (Ross et al., 2010). This ideal is rarely achieved in reality since there is usually a partner with more influence, who uses that imbalance to impose unfavourable conditions on the others (Essabbar, Zrikem, & Zolghadri, 2016). This power imbalance may lead to an increasing commercialisation and dependence of research in the medical field (Ajai Singh & Singh, 2005), which contradicts with the fundamental interests of academia to pursue free, long-term, disinterested, fundamental research (Lee, 1996). In general, academics are more focused on the question rather than the answer (Cutright, 2000) and publications are a way to receive recognition and thus enhance job prospects and other beneficial goods and services (Committee on Responsibilities of Authorship in the Biological Sciences, 2003). Something which can also be seen in the field of nuclear medicine, where several study groups and individuals have gained considerable recognition with their quick first-in-man, theranostic trials.

So in future, both partners need to adjust their behaviour and approach in the partnership to allow more ideas to become final products:

i. In order to level the balance of power, and to assess the benefit and commercial profitability of university inventions (Siegel, Veugelers, & Wright, 2007) it is wise to set up a national and/or international technology transfer offices (TTOs). These independent TTOs should pool scientific, regulatory, legal and economic expertise and evaluate research ideas, use their network to attract investors and subsequently enter into negotiations at eye level. Since the majority of university-TTOs are non-profitable and funds even cannot cover operation costs (Abrams, Leung, & Stevens, 2009) the focus should be on national and/or an international TTOs on the level of nuclear medicine associations. For example, the Society of Nuclear Medicine and Molecular Imaging (SNMMI), *a "nonprofit scientific and professional organisation that promotes the science, technology and practical application of nuclear medicine and molecular imaging"* has already set-up councils and centres of excellence to facilitate the development of new molecular imaging discoveries (Society of Nuclear Medicine and Molecular Imaging, 2018). The SNMMI has successfully supported two SMEs in designing their clinical trial program and launching new diagnostic- and therapeutic RPs.
ii. The academic challenge is to realise that some of their (applied) research may have a higher likelihood of technology transfer and these ideas need to be protected to increase the interest of an outside investor and allow more patients to have access to the new technology. This may delay publications due to the time frame of the IPR process and increase the risk that other study groups may overtake them.
iii. A simple and efficient IPR process, which is controlled either via the university or the TTO, should be available. It is necessary to have a clear strategy and make sure that "*IP is clean, well defined, and protected before trying to raise commercial interests. This involves costs regarding recruiting sufficient expertise or paying for external advice. The ownership of IP needs to be resolved. The IP and patent strategy should thus consider what technology is proprietary to the department, which is licensed on an exclusive base, and which parts are licensed on a non-exclusive basis.*" (Siegel et al., 2007).
iv. Academic trials need to meet the design requirements of the regulatory authorities to allow the usage of the data for the application process. This would result in increased quality and further decrease the investor´s investment risk and the total investment. This could further attract more investors with the chance to have an increase in R&D investments due to higher competition (Aghion, Bechtold, Cassar, & Herz, 2014).

4) What are the Challenges and/or Success Factors of Public- Private Partnerships (PPP) in Context of the Development and Marketing of Diagnostic (and therapeutic) Radiopharmaceuticals? What could be an alternative to the traditional development process?

The concept of PPP has entered the healthcare sector in various forms to finance, provision, and research the health care market (Baru & Nundy, 2008), to help governments coping with increasing healthcare costs and decreasing governmental budgets (Blanken & Dewulf, 2010). The concept of PPPs has some advantages and some risks compared to "classic" collaborations (Akintoye, Beck, & Hardcastle, 2008). We wanted to know, if this concept may be an alternative to the traditional pharmaceutical development process and if it would be suitable to push the development of new diagnostic RPs?

However, based on our evaluation we believe that a PPP may not be the right concept, at least if the investor is from the pharmaceutical industry rather than a patient support group, pressure group or public institution. Typically, PPP projects are non- competitive, deal with fundamental methodology and technology and are important to more than one institution. A possible field of application: the development of a new tracer, which for example would be able to accurately monitor therapy success in a variety of diseases. FDG-PET is already a very good tool that can fulfil this task in many oncological issues. The strength of future diagnostic RPs is likely the high selectivity, binding affinity and this sensitivity for very specific diseases (even in subpopulations with specific receptor expressions). The intersection with other companies is therefore likely to be very low, thus also the interest and engagement of these companies in such PPP projects. Also for therapeutic RPs this concept seems not to fit.

Questions as to the challenges such collaborations entail, the interviewees addressed consensus-building (all stakeholder groups), the complicated legal framework to set-up a PPP (nuclear medicine physicist), asymmetric balance of power in favour of industry (physicians), speed and non-result-oriented work by academics (industry), the complexity to agree on goals and study designs in large PPPs (industry) and the quite different general motivations and goals between the stakeholders (industry).

We therefore believe that there is no need for a new development process in the field of nuclear medicine, but that cooperation between academic institutions and the SMEs should be promoted. Lived reality should be modified and supported by independent national and/or international Technical Transfer Offices (TTOs). Academic researchers should protect certain ideas more regularly, clinical trials should more often meet current regulatory requirements, and universities should set-up a simple and efficient IPR process. To assess these ideas from a scientific, legal and economic point of view, we suggest national and/or international technology transfers offices (TTOs) which can support researchers/universities with their expertise. Having central TTOs could improve efficiency since many TTOs have problems in funding and generating enough revenue to cover operating costs (Abrams et al., 2009). SNNMI is already a well-established non-profit organization, which has already successfully assisted SMEs in the implementation of their clinical trial program, the submission of regulatory dossiers and the approval of the products.

5.5 Future Outlook of Molecular Imaging

With the push towards personalised medicine and the associated development of more targeted, specific target structures for therapeutics, molecular imaging will continue to have an essential role in daily clinical routine and research & development (Kircher et al., 2012). Literature suggests that both PET/CT and SPECT/CT will have a share in the detection, staging & restaging, monitoring of therapy response, and prognosis of various diseases (e.g. Farwell, Pryma, & Mankoff, 2014; Hoffman & Gambhir, 2007; Pysz, Gambhir, & Willmann, 2010; Sinusas et al., 2011).

Interestingly, our experts from the NMG see the future of molecular imaging primarily in PET/CT. SPECT/CT & SPECT will still play a role, but may not experience the growth of PET / CT. PET/CT will continue to be dominant in cancer, especially in the visualisation and quantification of specific drug relevant targets, but will also find widespread use in neurology and cardiology.

> *"Clearly in PET. SPECT, that's nonsense you have to be clear. Of course it's easier and more accessible, but it's anachronistic! You have to move to PET, that's just the rethinking. You cannot work with a "Volksempfänger" if you could have a flat screen."*
>
> (Nuclear Medicine Physicists, Europe)

Of course, the radiopharmaceutical- and medical device industry also believes in a bright future for molecular imaging, but does not commit itself to one or the other technology. Particularly advances in SPECT detector technology has improved the resolution significantly (Niimi, Nanasato, Sugimoto, & Maeda, 2017), and there is still a cost advantage for users (e.g. Chua, Gnanasegaran, & Cook, 2009; van der Wall, 2014; van Waardhuizen et al., 2016). Based on our evaluation we assume that both technologies take their share, with SPECT/CT remains an important pillar in specific indications in developed countries and having technological advantages in less developed countries. Anticipating a more widespread use of the theranostic approach, the PET/CT availability of scanners and infrastructure, the cost per scan and the capacity could be possible limiting factors. In this case, SPECT/CT could take over the validation of the target structure, stratify patients and assigning them to the relevant competence centres. As already highlighted, our experts from the pharmaceutical industry have expressed little interest in using imaging biomarkers as a stratification/companion diagnostic tool, but if, then they would undoubtedly prefer SPECT (/CT) due to more comfortable handling and global extension. Anyway, advice from a pharmaceutical expert to the academics would be: "*…not to try to develop new tracers for drugs for tumour mutations, but look at other types of cancer drugs such as tumour immunologic, hypoxia et cetera. And develop good imaging biomarkers for tracking therapies, and you also may be much more successful in developing CDs for other diseases.*"

Our medical specialists expect new therapeutic approaches, initiated by a better stratification, with e.g. a more widespread use of immunotherapy, improved diagnostic capabilities through liquid biopsy, more precise and new radiotherapy approaches due to improved imaging. The majority of these interviewees expect molecular imaging to continue to play an essential role in this process, a statement also current publications support (Jung Kyung-Ho Lee Kyung-Han, 2015; Sinusas et al., 2011; Society of Nuclear Medicine and Molecular Imaging (SNMMI), 2018). In particular, some specialists place high hopes in the liquid biopsy, which, if successful, could challenge some molecular imaging applications. Blood-based biomarkers will undoubtedly play an important role in predicting tumour progression, response to therapy, therapy resistance, or even early diagnosis (Quandt et al., 2017). However, liquid biopsies will not merely replace PET/CT or other molecular imaging technologies, but will preferably have a guiding role, indicating when imaging is needed and help to interpret the imaging results (Wong, Tothill, Dawson, & Hicks, 2017). However, as also mentioned by a specialist from the MITG, molecular imaging needs to position itself and elaborate the advantages of the technology. The challenge, molecular

imaging must tackle against large PPPs in the EU and US, which are explicitly working on the further development of in-vitro assays/ liquid biopsies, with substantial financial support (Neumann, Bender, Krahn, & Schlange, 2018). Currently, the majority of the interviewed experts, from all stakeholder groups, recognise the advantages of molecular imaging over in-vitro biomarkers. However, molecular imaging needs to be further engaged in building high- quality evidence of the benefits of imaging in clinical routine, and in allowing technology to be reimbursed.

6 CONCLUSION

The radiopharmaceuticals (RPs) DOTATATE and PSMA can already be named as a clinical success story since those RPs have considerably changed patient management in patients with advanced Neuroendocrine Tumours (NETs) and metastatic castration-resistant prostate cancer (mPc). Extensive research of academic institutions has enabled both diagnostic compounds to become the method of choice in diagnosis, and have shown the potential of these high-affinity receptor ligands in treatment using the radionuclides Lutetium-177 and Yttrium-90. With the current engagement of the pharmaceutical industry in the development of new therapeutic RPs, there will be more and more prospective, randomised data showing the benefit of this Peptide Receptor Radionuclide Therapy (PRRT) approach in new areas of disease. The first successful prospective, randomised trial (NETTER 1) has already enabled the establishment of PRRT in international guidelines.

In contrast to therapeutic RPs, diagnostic RPs experience little interest of the large pharmaceutical industry, and R&D is performed primarily by small and medium-sized companies (SMEs). Our data indicate that this is due to the fact that diagnostic products are confronted with low market potential, a problematic reimbursement situation, intellectual property rights issues and much more. Whereas the US has a more favourable situation for diagnostic RPs, and thus currently drives the industrial development of new oncologic diagnostic RPs, Europe is fighting against the non-authorisation status of the products, negative health assessment reports and thus non-reimbursement by health insurances in some member states. However, some physicians in European member states profit on generous national exemptions permitting them to administer these products to patients in the clinical routine, which have led to a world-class research position. From the industry´s perspective, i.e. this allowance is a great challenge, creating a secondary market and therefore further decreasing the market potential in Europe. As a consequence of the low reimbursement rates, the SMEs active in the radiopharmaceutical industry may even be considered stopping the commercialisation of diagnostic RPs in Europe, if reimbursement rates for new products are in the same order of magnitude as current rates for PET and SPECT RPs. However, most industrial experts, as well as some nuclear medicine physicians, expect the regulatory requirements in Europe to traverse through a process of harmonisation, which in the end will reduce the possibilities to use unauthorised products in clinical routine and research activities, especially in currently “liberal” European markets.

With the general push towards personalised medicine, we may also anticipate increased use of diagnostic tests, which help to stratify patients, monitor therapy response and make a prediction on the outcome. In contrast to the opinion of the majority of nuclear medicine physicians, the pharmaceutical, radiopharmaceutical and medical technology stakeholders see an increased role of logistically more favourable SPECT RPs for targeted diagnostics based on the recent advancements of technology. Although this could be a chance to attain approval for more diagnostic RPs, unfortunately the pharmaceutical companies currently show little interest in imaging biomarkers being used as companion diagnostics. Responses from interviewees suggest that imaging biomarkers cannot meet the pharmaceutical industry´s needs such as global availability, low priced, convenience and easy application, high accuracy, detection of multiple mutations et cetera. And for the radiopharmaceutical industry, the market is not attractive enough, which means that these companies would not register a diagnostic test as a CD. The companion diagnostic market is therefore expected to be dominated by in-vitro molecular diagnostic tests, with increased use of a liquid biopsy. An increased role of imaging biomarkers may only be triggered if regulatory bodies would request the mandatory use of imaging

biomarkers in patient selection. However, our interviewees from the regulatory stakeholder group did not favour a mandatory selection by imaging (although they regard this as a valuable option).

Due to the low interest of potent investors, we have evaluated whether the concept of public or private partnership (PPP) may be beneficial to accelerate the approval of new diagnostic RPs. Unfortunately, we must conclude that this concept is not very helpful. However, from our point of view, it does not provide an improvement to the current approval/development concepts.

Recent developments in diagnostic RPs are primarily driven by the US market, which is very attractive regarding size and revenue for SMEs. The European market also has the potential to become more attractive, if well- designed trials can show that the benefit and reimbursement can be resolved in significant markets. Currently, the regulatory environment and legal framework in France, Spain and Italy is more favourable for the introduction of new RP by the industry compared to Germany. In Germany the self-production based on § 13.2b AMG is seen as a major obstacle, although the potential of innovation is recognised by all stakeholders. Data derived from § 13.2b AMG application, however, do not produce sufficient evidence from the point of view of the regulatory authorities and national Health Technology Assessment Centres to justify authorisation and reimbursement. This is mainly based on the inadequate study designs of the academic studies conducted so far. However, the academic community is not to blame for these inadequate study designs since the financial resources by far exceed their financial capabilities and in many cases the in-depth knowledge on how to conduct a clinical study program is limited. The academic community makes the best use of the legal possibilities and has contributed significantly to recent advances in molecular imaging and therapy by providing valuable information on diagnostic accuracy, toxicity, dosimetry et cetera. From empirical data derived from the interviews, we anticipate a more structured process for investigational substances in Europe due to the regulatory harmonisation process, we hope that more of the academic clinical trials will be conducted in accordance to current regulations outlined by the FDA and EMA. Moreover, even without a possible regulatory harmonisation process, new diagnostic ligands should follow the official marketing authorisation track to give patients and the community the highest possible access.

Given the current situation, a higher rate of approval for diagnostic RPs can only be achieved through close cooperation between SMEs and the academic/public institutions since large pharmaceutical companies do not show interest in this limited market, and PPP are not suited for this approach. Collaborations between academic institutions and SMEs, should be more rigorously supported by national/ international technology transfer offices (TTOs). These TTOs have already been successfully implemented in the US, where traditionally there is a closer interaction between the industry and the academic institutions. The function of these TTOs would be the assessment of academic discoveries concerning their scientific and economic benefits by a team of experts, help to set-up a well-structured clinical trial program, and use their network to get access to private- and public funds. This organisation usually pools expertise on, e.g. intellectual property, manufacturing, radiochemistry, clinical trial programs et cetera. We believe that it is necessary to execute projects, regarding RPs with high clinical potential, at the national/international level since university TTOs are primarily unable generate sufficient funds, and good nuclear medicine knowledge in these unspecialised institutions is rare. A positive example, is the Society of Nuclear Medicine and Molecular Imaging (SNMMI) which has already set-up specific councils and centres of excellence, shared valuable expertise as a partner to the industry and serves as an interface on an industrial level to established universities and research organisations. We assume that such a national/ international TTO has faster access to funding, professional negotiations could increase the chances of fair royalties for the universities, and (hopefully) more academic discoveries will be developed further and may skip the problem of a translation gap.

Limitations:

Our study has some limitations which have to be pointed out. The low number of interviewees in some stakeholder groups such as the pharmaceutical-, radiopharmaceutical industry, the national regulatory experts, and the missing experts from health insurance group may restrict the informative value in some research questions. Since we considered third-party recommendations and personal descriptions from job portals in our expert´s selection process, we cannot exclude a subconscious bias. And while we also tried to eliminate the bias of the author in the evaluation and interpretation of the data as far as possible, we would recommend further studies with a quantitative and qualitative research approach to validate the data and pinpoint the exact motivations of stakeholders in the development and commercialization of innovative diagnostic RPs.

Abstract

Objective The dissertation evaluates the current status of radionuclides in diagnosis and therapy of Neuroendocrine Tumours (NET) and Prostate cancer from (I) a medical perspective by reviewing existing medical studies and (II) the identification of current challenges in the development, authorisation and commercialization of these radiopharmaceuticals (RPs). Furthermore the intention of this study is to evaluate if molecular imaging, such as diagnostic RPs, can be used as biomarkers to stratify patients, monitor therapy response and make a prediction on the outcome. Finally we evaluate if an alternative drug development process may solve some barriers and increase the authorization of new RPs.

Design The study uses a quantitative research methodology for the evaluation of the medical efficacy of DOTA compounds in the diagnosis and therapy of NETs, and PSMA ligands used for diagnosis and therapy in advanced prostate cancer. The qualitative research part includes twenty five expert interviews with interviewees from different industry branches (pharmaceutical, medical technology and radiopharmaceutical), medical specialists from the nuclear medicine and oncology field, as well as interview partners from national and international regulatory bodies.

Results Based on the analysis of published literature, the diagnostic and therapeutic RPs for NETs, as well the RPs for advanced prostate cancer, can be considered clinically efficient. Concerning challenges in the authorisation of these radiopharmaceuticals our analysis and empirical data suggest that the low market potential, in combination with the currently challenging European reimbursement rates are the main barriers for a successful commercialization and introduction of new diagnostic RPs. Other factors such as availability of short-lived radionuclides, regulation, intellectual property rights and manufacturing & distribution are important to some, but not all stakeholder groups. Molecular imaging may also not be an ideal companion diagnostic in the view of the representatives of the industry since imaging biomarkers cannot meet the needs of the industry in regard to proof of efficacy, validation and standardization. Finally the qualitative data suggest that there is no need for a new development process in the field of nuclear medicine, but that cooperation between academic institutions and the SMEs should be promoted, supported by national/ international technology transfer offices (TTOs).

Conclusion The radiopharmaceuticals (RPs) DOTATATE and PSMA can already be named as a clinical success story since those RPs have considerably changed patient management in patients with advanced NETs and metastatic castration-resistant prostate cancer (mPc). With the current engagement of the pharmaceutical industry in the development of new therapeutic RPs, there will be more and more prospective, randomised data showing the benefit of this Peptide Receptor Radionuclide Therapy (PRRT) approach in new areas of disease. But there is currently a lack of interest for diagnostic RPs since these imaging biomarkers cannot meet the pharmaceutical industry´s needs and there are significant commercial barriers. The companion diagnostic market is therefore expected to be dominated by in-vitro molecular diagnostic tests, with increased use of a liquid biopsy. Given the current situation, a higher rate of approval for diagnostic RPs can only be achieved through close cooperation between SMEs and the academic/public institutions, clear benefit data from well- designed trials and solving reimbursement issues in the main markets. These collaborations between academic institutions and SMEs, should be more rigorously supported by national/ international technology transfer offices (TTOs).

Zusammenfassung

Ziel In der Dissertation wird der aktuelle Status von Radiopharmazeutika (RP) in der Diagnose und Therapie von neuroendokrinen Tumoren (NET) und Prostatakrebs aus (I) medizinischer Sicht, auf Basis der Evaluation von aktuellen medizinischen Studien und (II) den aktuellen Herausforderungen bei der Entwicklung, Zulassung und Vermarktung bewertet. Darüber hinaus soll untersucht werden, ob die molekulare Bildgebung (z. B. diagnostische RP) als Biomarker zur Stratifizierung von Patienten, zur Überwachung des Therapieansprechens und zur Vorhersage des Outcomes verwendet werden können. Eine weitere Fragestellung ist, ob ein alternativer Arzneimittelentwicklungsprozess einige Hindernisse lösen und die Zulassung neuer RP erhöhen kann.

Design Die Studie verwendet eine quantitative Forschungsmethode zur Bewertung der medizinischen Wirksamkeit von DOTA-Verbindungen bei der Diagnose und Therapie von NETs, und von PSMA-Liganden bei der Diagnose und Therapie des fortgeschrittenen Prostatakarzinoms. Der qualitative Forschungsteil umfasst 25 Interviews mit Experten aus verschiedenen Industriezweigen (Pharmazeutische Industrie, Medizintechnik und Radiopharmazeutische Industrie), Fachärzten aus Nuklearmedizin und Onkologie, sowie Interviewpartnern von nationalen und internationalen Aufsichtsbehörden.

Ergebnisse Basierend auf der Analyse der veröffentlichten Literatur können die beschriebenen diagnostischen und therapeutischen RPs für NETs, sowie die RPs für das fortgeschrittene Prostatakarzinom als klinisch effizient angesehen werden. In Bezug auf die Herausforderungen bei der Zulassung dieser Radiopharmazeutika legen unsere Analysen und empirischen Daten nahe, dass das geringe Marktpotenzial in Kombination mit den derzeit herausfordernden europäischen Erstattungssätzen die Haupthindernisse für eine erfolgreiche Vermarktung und Einführung neuer diagnostischer RPs darstellt. Andere Faktoren wie die Verfügbarkeit kurzlebiger Radionuklide, gesetzliche Bestimmungen, Rechte an geistigem Eigentum und Herstellung & Vertrieb sind für einige, aber nicht alle Interessengruppen wichtig. Die molekulare Bildgebung ist aus Sicht der Branchenvertreter möglicherweise auch kein idealer Biomarker/ Begleitdiagnostikum, da bildgebende Biomarker die Anforderungen der Branche hinsichtlich Wirksamkeitsnachweis, Validierung und Standardisierung nicht erfüllen können. Schließlich legen die qualitativen Daten nahe, dass im Bereich der Nuklearmedizin kein neuer Entwicklungsprozess erforderlich ist, sondern dass die Zusammenarbeit zwischen akademischen Einrichtungen und klein und mittelgroßen Unternehmen (KMU) gefördert, und von nationalen / internationalen Technologietransferstellen (TTOs) unterstützt, werden sollte.

Schlussfolgerung Die Radiopharmazeutika DOTATATE und PSMA können bereits als klinische Erfolgsgeschichte bezeichnet werden, da diese RPs das Patientenmanagement bei Patienten mit fortgeschrittenen NETs und metastasiertem kastrationsresistentem Prostatakrebs (mPc) erheblich verändert haben. Angesichts des gegenwärtigen Engagements der Pharmaindustrie in der Entwicklung neuer therapeutischer RPs wird es zunehmend mehr prospektive, randomisierte Ergebnisse geben, die den Nutzen der Peptidrezeptor-Radionuklid-Therapie (PRRT) in neuen Krankheitsbereichen belegen werden können. Derzeit besteht jedoch ein Mangel an Interesse an diagnostischen RPs, da diese bildgebenden Biomarker die Anforderungen der Pharmaindustrie nicht erfüllen können und es erhebliche kommerzielle Hindernisse gibt. Es wird daher erwartet, dass der Markt für Begleitdiagnostika von molekulardiagnostischen In-vitro-Tests, mit verstärkter Verwendung einer Flüssigbiopsie, dominiert wird. Angesichts der gegenwärtigen Situation kann eine höhere Zulassungsrate für diagnostische RPs nur durch eine (I) enge Zusammenarbeit zwischen KMU und den akademischen / öffentlichen Institutionen, (II) neuen Daten zum Nutzen dieser Produkte aus gut konzipierten Studien und (III) der Lösung von Erstattungsproblemen in den Hauptmärkten erreicht werden. Die Kooperationen zwischen

akademischen Einrichtungen und KMU sollten von nationalen / internationalen Technologietransferstellen (TTOs) vermehrt unterstützt werden.

Appendix:

i. Statements made regarding the Value of Imaging/In-Vivo Imaging Biomarkers (Chapter 4.1, The Role of Imaging, page 103)

Item	Manifestation	Example of literal expressions
Category Nuclear-Medicine Physicists „The Role of Imaging“	***Statement made regarding the value of imaging/in-vivo imaging biomarkers***	• “The differences are clear, a blood sample indeed characterises the patient as a whole, but imaging can precisely characterise individual regions and individual organs…” • “And the therapeutic goal is usually not the treatment of the entire organism, but the treatment of a certain target region. In such a case, imaging is the more accurate biomarker method compared to an in-vitro assay taken from the blood. “ • "Because what is used so far are indeed methods that rely on biopsy or local tissue samples, or just on primary tumour preparations. But certainly, in the course of pre-treatment, the tumour pathology already changed. That means we have in principle no real-time procedures, which represent the biology of an entire tumour.” • “…in real time you can visualise and quantify, in a realistic and non-invasive way, […] the entire body, so all lesions and not just part of a tumour." • “So the localisation succeeds of course only with imaging, not with blood tests. That is basically how it is." • "You know Imaging people usually are quite limited in their understanding of medicine… they believe that you will be able to have, for any drug, a biomarker, an imaging biomarker. That is, of course, total nonsense. So you have to focus on the stuff that is really needed."
Category Oncologist/ Specialist „The Role of Imaging“	***Statement made regarding the value of imaging/in-vivo imaging biomarkers***	• “My estimation, functional imaging will further develop… what I have seen until now is fascinating… probably it will also save costs; many people have not recognised this yet. If we have the chance to avoid therapies in patients, stop a pointless therapy and start with a more sensible therapy, by using functional imaging or another method, this would definitely be economically meaningful.” • "Yes, a huge one [role of MI in new therapeutic strategies]. Imaging will get better and already got better. If you look at the pictures, a magnetic resonance tomography delivered ten years ago… we now have a new 3 Tesla device, one of the most modern generations. 'It looks like a CT; it is crazy. It will go on, I am sure.” • "It depends on the problem! I would say that if it is just about verifying therapy response, and you have got a biomarker that's so good that the biomarker's concentration tells us “ok, the patient responds or does not respond to therapy? And everything else is not from interest” then you could wave imaging. But if the patient has any consequence from the localisation of a tumour, which cannot be shown with Liquid Biopsy, then it is of course just a question of a tumour “yes” or “no”. Or what kind of genetic alteration or mutation does the patient have. … Moreover, if this results in any kind of consequence… imaging with the appropriate sensitivity and specificity is still indispensable.” • “And I think that will be more in combination (Note: in-vivo and in-vitro biomarkers). I do not think that one will replace the other. However, a combination of both will then be able to represent the best possible status of the patient."
Category Pharma-ceutical Industry „The Role of Imaging“	***Statement made regarding the value of imaging/in-vivo imaging biomarkers***	• "The primary reason we developed this imaging agent was as a research tool." • “But the motivation for us to develop it is, what we want to do is, to see how that changes in time over treatment. And how does it change when you treat…” • “So we want to look at that kind of research questions and see to understand what changes... we are also trying to develop tracers for CD8 and other aspects of the immune system. To really use it as a research tool." • “One of the most telling slides the pathologist in our group likes to show is... he shows two different slices, and one of them has very, very, just a ton of PDL-1, the other has nothing. And he shows on the next slide/imaging that they are both from a same tumour.” • “…the nice things about imaging is, you cannot just look at one tumour, you cannot just look on parts of the tumour, you can look at the whole tumour, and at more tumours throughout the body. And the hope is that this would

		be more valuable and it would do a better job in predicting patients response, but this is true or not time will tell." • "...we tried to use imaging, and would say we have tried to use imaging to generate, maybe more inclusion/ exclusion kind of criteria for the enrichment of our trials." • "…we are using it for internal decision making." • "In fact, we are developing a number of these molecular markers with academics. But I think the real question is "Are we really developing to use it all the way into a CD?" and "Are we using, are we developing it all the way to make a business?" The answer to the last two is: probably no. Because this is not our primarily stream business." • "Now, imaging has some advantages: you can look at all the lesions, your metastatic lesions, some have mutations some don´t, some … there are a lot of academic reasons why imaging might be nice to have. But really for tumour mutations has a very hard struggle. It is also the true, the case that the imaging tools we have are not as precise as the free circulating DNA tools." • "Of course drug companies use imaging biomarkers a lot in their research and development as pharmacodynamics biomarkers, proof of mechanism, proof of principles, and proof of concept, set the dose in phase II." • "They are asking the question: Does the drug reaches the target, does it engage the target, does it modulated the downstream physiology, and so on… " • "But in terms of an internal decision making we are using a number of these molecular ligands, and we have a very extensive back program where we are trying to develop ligands…. So we are using it for R&D decision making right now, for proof of mechanism on tissue markers, understand the distribution, understanding dosing there are a number of ways we are using radiopharmaceuticals…. So we have a lot of interest in this field, in some cases, we have the product in some cases we have the decision making criteria internally."
Category Radiopharmaceutical Industry „The Role of Imaging“	***Statement made regarding the value of imaging/in-vivo imaging biomarkers***	• "MRI and CT see the disease in about 15% of cases, [our product] sees the disease in about 70% of cases. And for that particular disease, the location of the disease had quite an impact on patient treatment… radiotherapy is expensive and hurt patients and some are getting inappropriate radiotherapy because actually the disease is already in the bones." • "There is huge opportunities still in cardiology, tend to think that cardiology and neurology are better"

ii. Statements regarding the Challenge of “Reimbursement” (Chapter 4.2.1, Issue with Reimbursement, page 108)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicist „Reimbursement”	***Statements regarding the challenge of reimbursement***	• "Yes, reimbursement is a huge problem, clearly. Reimbursement of costs is one of the main limitations for PET overall." • "The non-authorisation and the reimbursement goes hand in hand. So under our current legislation, the admission is not fundamentally the problem, but due to the lack of admission, there is no refund. You can turn as you want, ultimately it's about that: it has to be paid in some way." • "…today we have a considerable range of tracers that can be used clinically. And then also in the aftermath, we have been relatively successful to get these tracers reimbursed by the health insurances [country outside the EU]. And that is a catastrophe in Germany because you have to make special contracts with every health insurance company." • "Yes, that is clearly the financial aspect. So PET-CT imaging… is unfortunately not cheap. And the substances that are mainly used at the moment are Somatostatin analogues and PSMA ligands. They are still not authorised in Germany, so they are also not reimbursed in the outpatient practice and not in the clinic setting. So you can do the imaging, and we do it, but it is not paid. And in the outpatient setting certainly not … only FDG in two indications…" • "…and based on the German Social Code V PET-CT is actually a compulsory service of the statutory health insurance, in the pre-stationary area…. But the health insurance companies simply refuse to pay the costs, and this sometimes leads to difficulties. So the patients have to file applications, the health insurance companies reject that in part, then contradictions are filed. This is sometimes a bit of a hassle, but it's just a relatively small part of the patients we're now looking after. But it could be easier. It would also

		make things easier, especially if the federal committee, which is responsible for approving or payment of RPs, would work a little faster."
Category Radiopharmaceutical Industry „Reimbursement"	***Statements regarding the challenge of reimbursement***	• "I think getting products reimbursed is the biggest challenge in Europe. Governments like to pay, just from a PET scan basis, governments like to pay for PET scan as an FDG rate. And so this is true for SPECT as well." • "If the market for all PET diagnostics and SPECT diagnostics is payment at either a technetium bone scan rate or an FDG rate, if that is the future, from now forever, for payment for nuclear medicine then at some point people will stop commercialize products in Europe." • ".. I think they will not receive the reimbursement of a therapy… I think diagnostics will be appropriately reimbursed [in the US], unless there are major changes in the structure of the US market. However, for Europe, it is probably the case [reimbursement issue]. The average price of an oncology drug is in Europe 30% of the price in the USA. And … reimbursement of SPECT and PET scans are in most European countries … under pressure. In fact, in some countries, there is no reimbursement of the pharmaceutical part. It is only reimbursed of the cost of the actual scan, the imaging part. And that is a problem. So two parts for that: No, not worldwide but yes in Europe." • "The greatest barrier to get a commercial biomarker is payment. Because the government agency, that pays for it, has a specific non-payment rule. In other words, if you develop an oncology diagnostic agent, there is a pass to payment. If you develop a neurology or a cardiology PET diagnostic agent, there is no reimbursement. You have to go through the TED trial [Coverage through evidence discovery trial]. For example, Amivid, Neuraceq, and Vizamyl are three PET biomarkers for amyloid, right? All approve 2012 or 2013. None of them has reimbursement, none of them will have reimbursement for years. So those companies who brought that forward, have paid for the trials, paid for the filing and have been struggling to make a business out of it ever since. " • "Getting past the FDA is not that bad, it takes time and money, but it is doable if you have a focused indication. But getting passed payment is a big deal." • "...the other major consideration: "what price can you get?", "Is it reimbursed?" But an awful lot of the RPs are not reimbursed. This is a big issue for a lot of companies." • "We need to get pricing, reimbursement which allows us to make a profitable proposition. We are not there yet; we are not there yet." • "So there are insanely conservative countries like England, which is perhaps 20 years behind Germany. There are advanced countries such as Denmark, where almost all indications are reimbursed, or France where FDG is relatively broadly reimbursed. Italy, for example, has 6 times more PET-CT examinations per million inhabitants than Germany. Because simply the reimbursement is better regulated. That is extremely different."

iii. Statements regarding the topic "regulation" (Chapter 4.2.2, Challenge with Regulations, page 113)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians „Regulation"	***Statements concerning the topic "regulation"***	• **"**So in Germany, it is not a problem that is part of our success that we can work with non-approved drugs. But we are very much dependent on the German framework conditions and if at some point, in the course of internationalization / globalization, these whole rules are standardised and the same everywhere, then we get a problem in Germany. " • "And that is actually a problem … that we in Germany tend to administer the substances very quickly in the patient and do not worry about how we can create sustainable evidence of benefits." • "I hope! There is also the hope for the EU that we can still find a more reasonable standard. Because Germany is very restrictive, strict. Also, as far as the EU regulations are concerned, it would be nice, I have some hope ..." • Interviewer: "*But in comparison to other countries, a tracer can also be used in Germany via the national exemption, where other countries also ..."* Interviewee: "Yes for first-in-man applications, that's right. But in the end, we are very limited. In principle, we can do a lot of experimental things, but officially very little ... It is amazing how much research comes from Germany, although we fight so hard with the reimbursement. It's a huge problem." • "Sure, it's an advantage that you can have first-in-man studies very quickly! But even there, you would have to find a rule that allows it so synonymous because the risk is indeed very low. That is in itself completely excessive,

		the fears which are discussed, especially in view of the fact that nothing has ever happened. So it's a total hysteria. The guidelines are far too strict, and we just cannot compare PET Tracer with a new therapeutic drug. That's a completely different order of magnitude. And the huge advantage of PET that one can work with molecular quantities is obviously not understood." • "…that in principle it would be easier to obtain approval for the PET Tracer and to obtain a first-in-class approval, rather than with the caveats of a full AMG study. That's certainly nonsense. That's not rational." • "And the problem we have in the legislation, and I assume that this is more or less the same all over the world, that you have laws for medicines and that PET tracers are classified as medicines. And on the other hand, you have the legislation for the radioactivity, the tracers are radioactive! Now, these legislatures are always made for, for important, for just. .. I say heavy duty, and heavy duty means that if I give a medicine, of course, that should be pharmacological effective and if it has a pharmacological effect, it can kill the patient as well. " • "It's just that the approval of a new PET tracer, a diagnostic tracer, is very complicated because it's a medicine." • "I don´t think that the regulatory agencies are the bottleneck here. Actually they are doing really well. They have the interest to get this done. I am actually fairly positive about their work... I think the study design is an issue that has to be done right, and for the treatment trials of course there you have to be, they are concern about pharmacology and toxicology. So you have to provide them with some data." • "In Germany, this is definitely the case that the challenge is too high, yes. So you can also see that in comparison to other countries, e.g. France ... the whole approval process took less than 1 year for all oncological indications. It already takes 12 years in Germany. And as I said we have only 3 indications in which this has been confirmed, and still no billing rate. This is simply a political catastrophe, but the political will. Because the health insurance companies just see millions or hundreds of millions of costs approaching them if there is a wide-scale approval. That, of course, more effective control of the therapy is possible, and above all, unnecessary operations are avoided in many cases, the health insurance companies just do not want to see." • "... the regulations are extremely heterogeneous. It is rather that the interpretation of the regulations is very heterogeneous ... I put it this way now: There are developments that barriers will decrease in countries with high barriers. But there is also the tendency that for countries that have barely known barriers that new barriers will open up. So there are certain tendencies for harmonisation at the most diverse level. So on the one hand, on the side of the regulations themselves ... then, of course, also from the law enforcement authorities. The authorities…, whose knowledge partially increased in this area." • "But there is the recognition of the regulators that certain rules should be there, that they should be reasonably consistent, and that certain rules simply do not fit. And there should actually be simplifications."
Category Radiopharma-ceutical Industry „Regulation"	***Statements concerning the topic "regulation"***	• "We think that we think the market will get more regulated. Er, we don´t think the market will get less regulated, so er so we think there is a fantastic opportunity. Ah, and it looks like a good place for investment. I think, so we think the regulation will kick in at some point. (Laughs). And it will become a more regulated market. Lots of markets are quite regulated in this area, so in the US, France, Italy, there are countries that follow the regulation process and so there is still a great opportunity in those markets." • "So now what is the very debatable point, which requires an ongoing unfolding discussion with all the parties' concerned, which includes regulators (FDA and EMA). Two things: the first thing is relating to dosimetry … and the second thing involves the future design of clinical trials and the use of real-world data to perform the full personalization of full theranostic platform." • "I think the opportunities [self-production of RPs] will decrease because as the drugs are commercialized, the large pharmaceutical companies will no longer tolerate the use of unlicensed products in the same indications. Even as they are different compounds. So I think the opportunity of home production will decrease, and that means that RP will be competing on a level playing field with the other modalities. And it is cost." • Interviewer: "*Do you expect that the regulation globally will meet at a specific level and that some countries, such as Europe, may get stricter regulations?*" Interviewee: "Yeah, I do think that. Yes definitely."

iv. Statements regarding the topic "Market Potential" (Chapter 4.2.3, The Issue with Market Potential, page 116)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians	***Statements concerning the topic "Market Potential"***	• "Well, I believe that in diagnostic tests, unfortunately, the profit margin that one has with the commercialization of a diagnostic test so that just is not as high as having a therapeutic substance." • "... I, therefore, believe that the connection between diagnostic substance and therapy, which on the one hand must be natural and on the other hand also forced a bit, then the new diagnostic test can be successful." • "Well, we are partly to blame ourselves, because we do it ourselves. Then it is often not patentable, and thus there is no one who wants to invest because there is no money to earn." • "If you look at the list of companies that have entered the imaging market it is quite stunning. There are a quite bunch of companies that come in. And also pharmaceutical companies are attracted to theranostics because that is the market. There is a big big need. AAA will charge 47.000 Dollars per cycle DOTATATE. So that's four times what it saved in the US so that accounts for 80.000 $ or so per patient. Let´s have 10.000 patients, 40.000 cycles so you can calculate the significant amount of money. Now if you think in prostate cancer you suddenly have, conservatively estimating, 40.000 patients for 160.000 cycles. And each of them is 20.000 $ or 25.000 $ or 30.000 $ than you can calculate, that this is multi-billion Dollar business. So that's we are talking, now they are coming in and like that stuff. Money being made." • "…there is not enough money especially with the Gallium compound." • "And, for example, in the field of outpatient care, only a few indications (PET/CT) have been added, and even in EBM PET-CT is still not anchored. So that's a big obstacle, for the industry, I think that's, of course, not so nice. But they are of course targeting the US as a market, which is a very large market and where the approval of new RP has recently increased significantly in speed." • "One thing is for sure, that with a ... diagnostic product ... it is difficult to generate returns. If I think of Fluor-18 marker now, for Fluor-18 I need infrastructure around that ... and writing pharmaceutical profits is very difficult ... plus, because it's just diagnostic, you can, of course, charge a lot less .... with Ga-68 kit markings, I do not have the problem of logistics, but ... the margins are still worse and all reimbursement systems ... are never ready to pay as much as for therapeutic drugs."
Category Pharma-ceutical Industry	***Statements concerning the topic "market potential"***	• "…the margins are very low in diagnostics, there is more money in therapeutics, and we focus on the diagnostics we need to get the therapeutics approved and to people." • "There are companies out there, which are in business developing molecular diagnostics and they have the same problem. They have very small margins, that´s a tough business. And in fact what happens, we didn´t develop the PDL-1 tracer, but we paid the company to develop it. Every penny they needed for it because we needed to have that test." • "In fact, we are developing a number of these molecular markers with academics. But I think the real question is "Are we really developing to use it all the way into a Companion Diagnostic?" and "Are we using, are we developing it all the way to make a business?" The answer to the last two is: probably no. Because this is not our primarily stream business." • "As you know in drug development, in every hundred projects the industry starts, if they are lucky one becomes a medicine. So you have huge, you have huge attrition. And of course you have attrition in the diagnostic, so for the academics working on Etarfolatide the tracer and indeed for the company developing it, they got nothing out of it. Even it was a great tracer, when the therapeutic died the market for the diagnostic died as well. So it is a very unattractive place to be in."
Category Radiopharma-ceutical Industry	***Statements concerning the topic "market potential"***	• "The reason why AAA is worth 4 billion is not because of the Gallium diagnostic, is because of the Lutetium therapy." • "We think there is a fantastic opportunity there. We think there is a fantastic opportunity in molecular imaging." • "We think that we think the market will get more regulated. … and it looks like a good place for investment."

		• "Novartis, one of the major players in oncology, has acquired AAA and have started a radiopharmaceutical platform insight Novartis. And that includes searching, as they said publicly, for other compounds. So PET tracers that have useful prognostic information for a therapy. And also they made it publicly clear that this does not necessarily only relate to oncology, also in other areas of medicine, it might be useful to have a diagnostic targeting moiety, which if diagnostic and prognostic insulation and then has associated therapy, which can produce a therapeutic benefit. Even if the disease is not in cancer. It would be in other disease areas, in cardiovascular, in orthopaedics, not necessarily wherever radiation destroy tissue in a targeted way." • Interviewer: "*What do you think about the market potential, is it a problem for diagnostic RP to compete?"* Interviewee: No, I don´t think so. I think they will not receive the reimbursement of therapy, the levels of reimbursement for innovations will, as we see with fluciclovine in the USA. So certainly the USA market, I would say no. I think diagnostics will be appropriately reimbursed unless there are major changes in the structure of the US market. However, for Europe, it is probably the case. The average price of an oncology drug is in Europe 30% of the price in the USA. And the regulations of reimbursement of SPECT and PET scans are in most European countries, meaning the reimbursement of the pharmaceutical part, is under pressure. • "So then you can use Axumin. Well, that was a very strong unmet need, and dose sells have been very good. They are small, relatively to FDG. FDG is used for oncology, up to 1.8 million doses of FDG are sold a year, 20.000 maybe 40.000 of Axumin. But Axumin costs 40 times what FDG costs. So from a revenue standpoint, it is significant, so we are seeing... If you brought another biomarker to replace FDG, for example, you would never make a business case for this. Because FDG is good enough and it is cheap. But if you have a very specific unmet clinical need, you can find basically a niche market. That is what Ga-68 NETSPOT/ Ga-68 DOTATATE did, that is very specific. Very small market, but they charge 5.000$ a dose. So it is a business!" • "PET biomarkers are fairly big business. The PET market in the US is about 275 million a year, this year 2018. That's all PET in the US, revenue. So 275 million, and PETNET has about half of that. Er, and if you operate your business profitably, it can be a good business. You have high fixed costs, you a lot of cyclotrons, chemicals labours, people, but you can still make a good margin on that. " • "The growth is projected to be fairly dramatic, the new biomarkers that are coming out are extremely er, well the revenue is much more as the revenue from the majority, which is FDG. So FDG in the US is about 150 Dollars a dose, picking just an average. Where for example the new prostate drug on the market is 4000 dollars a dose, it is like 30 times more expensive." • "Highly competitive market, very low margins and actually it wasn´t good business. As a consequence, huge consolidation in the market." • The market opportunity for such a product is a niche compared to a therapeutic drug… A pharmaceutical company would say "Actually it costs me a significant amount of money and the market opportunity is low." The other major consideration "what price can you get?" Is it reimbursed? But an awful lot of the RPs are not reimbursed. This is a big issue for a lot of companies." • "The return on that investment! Return on investment … and revenue is smaller than in therapeutics."
Category Molecular – Imaging Technol. Industry	***Statements concerning the topic "market potential"***	• "... that you have a relatively specific patient group and develop something with a very specific target and you have to do the full phase I, II and III studies. That will cost 100 to 150 million, the development. And then, in the end, that's not necessarily a huge market commercially. Then it's just a big problem. As already mentioned, in PET imaging, of course, the margin is not nearly as big as with contrast media or with SPECT nuclear medicine tracers. Due to the need to create your own local infrastructure, or to work together with companies that locally produce the PET molecule and then deliver it accordingly." • "And then… there is even limited commercial interest in the ones which do have IP protection because we don´t have a great track record of success stories here. … So ever since that acquisition (Avid being bought by Elli Lilly because of their Amyloid imaging RP), they have been struggling and not been successful achieving reimbursement for the amyloid imaging agents for PET."

v. Statements regarding the topic "Research & Development" (Chapter 4.2.4, The Issue with Research and Development, page 120)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians	***Statements concerning the topic "Research & Development"***	• "And that is actually a problem; I think that is a problem of our system that we in Germany tend to go with the substances very quickly in the patient and do not worry about how we can create sustainable evidence of benefits. So somewhere there should be a compromise… Although it is possible in Germany, but the global success is held back by the regulations." • ".... that we begin very early, still in the field of preclinical research, with our diagnostic tests and work together with the experts in the development of therapy." • "And, of course, research is now increasingly moving in the direction of visualizing and quantifying very specific, drug-relevant targets, including modern developments like immunocheckpoint- inhibitors or things like PDL-1, PD-1 ... But this is the path taken in research, and relatively little is translated into the clinic, one has to be very clear. " • "So there's a number (of challenges) and also keeping pace with the rapid development of new therapeutics. We cannot keep up with the development of diagnostics that would fit for therapeutics." • "Well, we are partly responsible for that! Because we do it ourselves, thus it is not patentable anymore. And therefore nobody is investing, because there is no money to earn. " • So if we want to use a new tracer today ... just for research purposes, I just have to spend 100,000 CHF to do a toxicology study. This will stifle any research project immediately. So that's the problem with the PET tracers. " • "The problem with therapeutic tracers is a completely different one ... when you start to treat (with therapeutic RPs), you have a pharmacological effect. And if you have a pharmacological effect, then you need to prove that using this medicine will benefit the patient more than it harms him. That requires Phase III studies ... " • "You know what the major issue is really cost too, who pays for it. If you don´t have stakeholders like in the pharmaceutical industry, which is now changing a little bit with Novartis having bought AAA. That changes the game, but as long as you don´t have stakeholders with a lot of money who is paying for it? That is really complicated, who is paying for the development." • "... what we urgently need in academic research is the support from the industry. So the thinking of the development steps of phase 0,1,2,3, what are the requirements, how can you do something specifically." • "And then everyone starts again to re-invent the wheel, and there would have to be better cooperation. Just a promotion from the side of politics, indeed from the ivory towers of the University to bring the research then really directly into the industry." • "And in my opinion, there would have to be a lot more going on to translate the results as quickly as possible into practice, well as you say from Bench to Bedside. So to implement preclinical research or early clinical research quickly into practice. And to implement the clinical trials, there is a great shortage there." • "(Academic research must) make more clinical trials, and a clinical trial is called in accordance with current EU regulations, as notified drug trials. These studies need to generate data that is really usable for approval. And that's not as difficult as it's often portrayed. Of course, it takes money and time, yes. And it will not work for everything that you would like to have….and there is already pressure from the authorities and also (the nuclear medicine doctor) see the reason. There are already more controlled studies! For example, where, in the simplest case, one can accurately portray safety and say it is a registered study whose primary objective is safety. For example, this is something you never did for the DOTATOC." • "..not without anyone (investor) to the "ready for the market" phase. But for early first studies quite well, where then possibly an investor is even more interested."
Category Radiopharma-ceutical Industry	***Statements concerning the topic "Research & Development"***	• "Yeah, I think the really shared challenges with other therapeutic platforms is the cost of exploiting them. So I think the advantage currently in the RP world is that there is a recent history of home production and of clinical use of RPs." • "I think people forget about the costs of development and they also forget about the actual costs of commercializing RPs… So there is a really large cost infrastructure about getting products approved. And there is a large cost infrastructure about maintaining products in the market."

		• "Er, I guess the probably needs to be a better understanding in the academic community … so when, for a lot of these agents that look interesting and therapies that look interesting, to get approval for it you need to get back to the drawing board to do a proper dosimetry study. You need to do the rat model to show; you need to still got through Phase I, II, III process in lots of these instances. Because the FDA and the EMA wants to have properly designed clinical trials in this area. I think either the academic community works in a more followed clinical trials process, so when they develop agents, they actually got data ready for regulators or that it got an understanding that even you got interesting data in people, you will, actually for the regulators, still have to go through this proper regulatory process. So effectively those initial data what they have done is they de-risked the chance that the therapy works, but they haven´t decreased the total investment you have got to make the product into ah, something the regulator will approve." • "From a discovery point of view, the one big advantage of RP will have, it will be possible to go back over the back-catalogue of large pharmaceutical companies and find compounds with very high specificity, but don't have a therapeutic effect. So I think that will be an interesting and less expensive development of the next couple of years. Things that have failed and have been written of, because basically they didn´t work. But nevertheless, they accumulated in a target; they might be of use if they can be labelled with radiation." • "I just wanted to stress that Siemens was in the biomarker development business in the US for a decade, spend a tremendous amount of money. Hundreds of millions of dollars and got out of it because it was such a drill hole. Yeah, so we are willing to let other people develop the biomarkers and proof the clinical utility and then they have to come to us because we are half the market in the US anyway." • "So effectively those initial data what they have done is they de-risked the chance that the therapy works, but they haven´t decreased the total investment you have got to make the product into ah, something the regulator will approve."
Category Molecular – Imaging Technol. Industry	***Statements concerning the topic "Research & Development"***	• "Well, I would say the problem, especially in oncology, is that you have a relatively specific patient population, you develop a very specific target, and you have to do the full phase I, II, and III studies. This costs you 100 to 150 million, and in the end, there is not necessarily a huge market commercially." • "So we agreed on watch status, because ... (the new product) may continue to be interesting, but the development of (product X) depends on how you expect it, but it has to do with the $ 100 million and has not yet paid off, and (the company) has no interest in repeating that with the (new) imaging molecule." • "We probably do not do enough, in my opinion, because we could basically do more. Of course, that's always a matter of money, and I still see a lot of academic interest in developing new molecules. We internally decided not do discovery and early phase research anymore, but in principle, we should try to be a little bit more active. This would allow us to license promising projects at a later time. So the pipeline is no longer internally but externally, but so we can also boost research through collaborative research. Thus that would be a logical consequence of deciding that we do not do so much by ourselves. " • "So we are not actively in the discovery phase anymore, but I am sure A. mentioned, we do quite a bit of clinical trials for others, but we don´t charge them for the costs of things. It is sort of a small side business for us with the hope to get some more tracers on the market. And then we do investments in like we gave support to the SNMs clinical trials network on getting the Gallium PSMA project moving. So we do funding of others we think it is worthwhile, help to accelerate to get these tracers done." • "… there are some very interesting RPs they don´t have IP protection anymore. Even they have never filed for a patent in the first place, or they have been around so long that the patent has effectively been expired. And those are interesting, but a company have not really get behind it because that would spend all the money on clinical trials and the approval process and then anybody could make a generic."

vi. Statements regarding the topic "Intellectual Property Rights" (Chapter 4.2.5, The Issue with Intellectual Property Rights (IPR): page 124)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians	***Statements concerning the topic "Intellectual Property Rights"***	• "I think the challenge is more on the university side, that such patenting can be done efficiently, unbureaucratically and standardised. Nowadays, if you have something new and you have not patented, then it's not worth anything to the industry." • "They only get an industrial partner, if they really have a patent on their academically developed product. This has to be accelerated, and again it is important that this is simple to implement for the academics." • "Intellectual property is always a problem; you just have to define it beforehand ... Researchers are also beneficiaries in my view because you have the same partner as during exploitation and you do not completely lose the patent. … as a researcher you can be happy to participate financially. This is also just an advantage." • "This is always this tightrope walk, I see that extremely relaxed (concerning the negotiations of IPR in a partnership)." • "I do not think that's a problem (concerning the negotiations of IPR in a partnership)." • "Well, we are partly to blame ourselves, because we do it ourselves because it is not patentable often." • In the end, the problems are always related to patents. You have to own a patent so you can make money in the pharmaceutical industry. And if the regulatory hurdles are extremely high, then you have a patent, and so you can use all the crap it may take 10 years. Then half has already expired." • "And when they (the university) starts to say:" I have to care that the university earns a stupid amount of money", then this patent can again have prohibitive / negative consequences." • "I'll give you a very specific example now, the Gallium PSMA-11 tracer. Which can now be named as the second most used clinical tracer, after FDG. If Gallium PSMA-11 would have been patented, it would not be there today. Because it would have taken much longer for this to be implemented." • Of course, it helps if something is protected, but it must have happened before the clinical trial anyway. On the other hand, it is not like many people think. In my opinion, it is not true that only products that are protected will be developed. It can also be a certain protection exclusivity of other things, for example, from a certain time advantage you have. Or I know a company that has a patent on a particular marking technology. It marks an unprotected product with its marking technique and then is a little exclusive in the case, not?
Category Pharmaceutical Industry	***Statements concerning the topic "Intellectual Property Rights"***	• "Well, IP is very broad. So if you have a tracer you can develop IP on the composition of matter, if you have an imaging biomarker which is based on a CT signature or we talked about Ferriscan, so the MRI R2* that is not a tracer that is relaxation time. You don´t get IP on the relaxation time because it was discovered by physicists 50 years ago or more. Where you can develop IP on is in copyright and business processes. So with Ferriscan the IP there is on the copyright of the software, the business process, the whole procured for validating scans and giving the physician validate R2* measurements. And again I would urge you to think... Imaging is not just out proprietary tracers, even in PET FDG has a very important role to play, and even there is no property to secure on that anymore. Many other PET tracers don´t have a composition patent; there are other good uses for them."
Category Radio-pharmaceutical Industry	***Statements concerning the topic "Intellectual Property Rights"***	• "That was a big move for Heidelberg around Ga- PSMA PET, for instance, they didn´t patent it. And now there is a good technology that is available so could have a relevance in prostate cancer. But there isn´t really a company who wants to invest in it. Because Heidelberg failed to patent it." • Interviewer: "So you wouldn´t go if there is no protection for you? Interviewee: "Yeah I think it is difficult to do that because because you can have a generic competitor. And it costs a lot of money if you think... I think people forget about the costs of development and they also forget about the actual costs of commercializing RPs." • Interviewer: "So you also tried to gain IPR through these collaborations, is it a goal for you? Interviewee: "Yes, yes. I think that is the cause of everything we do, is having a strong IP position. So you know, if we had an academic

		collaborator coming to us and say that is great technology and it is not patented, that would be just a really big red flag for us." • "I know AAA effectively has a generic product and they have invested, er which is fantastic but er from our perspective we would have looked for a reason with strong IP position." • "And academic need to think about that IP and protecting it. So there is an asset worth investing in. (laughs)." • "Academic institutions are very variable in their approach to IP. And you know there are some really smart about it, and they understand that they need to protect it and protect it well, and there are others. But I think, maybe the academic community understands that more every year (laugh)." • "So from our perspective, when we build up our IP portfolio we don´t rely on one piece of IP. We like to have the chemical entity, and then we build a whole layer of onion around it. About different IP that covers the manufacturing process for the product, how the product is being used in the field. So you can build, but not having the chemical entity IP is definitely something that when we go to investors, to ask to invest in new ideas we got, the first question they ask is: "what is the IP position?" And it is a big red flag for them if you don´t have chemical entity protection, from an investor perspective. But the [pharma] guys also know that there are ways to get around it. But there aren´t always ways to explain that to investors (laughs)." • Interviewer: "What about the IP- rights issue? Is it a problem for you as a company to go ahead in the development of such compounds?" Interviewee: "Er, no I don´t think so. I think the market will determine the price, so IP…. In terms of the royalty percentage for the IP, I think that is only market forces. Some universities take a very reasonable approach and have 3-4 % royalties. Others insist of a much higher percentage, and I think the market will just determine, so I don´t think that is a problem." • "Again, from our business we are not going to reach out to an academic in Europe and pay for their development. So somebody stepping in who is in the biomarker developing business is necessary and they won´t do that unless there is, unless they can get patent protection on their investment." • "One thing that mitigates in the USA a little bit: if you bring what is called a "new chemical entity" to the FDA and the FDA defines that this is a chemical that they have never approved for any utilization … you get 5 years of exclusivity. Independent on any patent, the FDA will not approve another application with that biomarker for 5 years. So you have 5 years basically to try to recoup your investment. So even you don´t have patent protection, so somebody could bring Ga-68 PSMA to the market in the US, then you are for 5 years the only entity to make it. " • "So the patent is not too important." • "I think it depends on the intersection of that. IP pops out of public institutions. There are clear-cut mechanisms where the industry can interact. "
Category Molecular-Imaging Techn. Industry	***Statements concerning the topic "Intellectual Property Rights"***	• "Yeah, there is, if I can I will break that in two categories because there are some very interesting RPs they don´t have IP protection anymore. Even they have never filed for a patent in the first place, or they have been around so long that the patent has effectively been expired. And those are interesting, but a company have not really get behind it because they would spend all the money on clinical trials and the approval process and then anybody could make a generic."

vii. Statements regarding the topic "Manufacturing, Distribution and Handling" (Chapter 4.2.6, The Issue with Manufacturing, Distribution and Handling, page 129)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians	***Statements concerning the topic "manufacturing, distribution and handling"***	• "And the problem with the radioisotopes, which are relatively short compared to the SPECT with technetium, I don´t consider this to be problematic. I believe that the availability of PET is not really a problem, at least in Germany, not even in the US. I do not think this is a problem in any industrialized nation." • "... these therapeutics typically have half-lives in the range of days and not in the range of hours. This changes the whole logistics. So they can produce Lutetium DOTATATE in Holland, and from there they can flood the world."

		• “Now, when I think of 18- Fluorine 18 labelling, for F-18 I need infrastructure ... and (pause) generating typical pharmaceutical profits is very difficult.” • “... there are developments like the Ga-68 kit labelling. Now I do not have the problem of logistics, but ... the margins are still worse in comparison ... to therapeutics."
Category Pharmaceutical Industry	***Statements concerning the topic “manufacturing, distribution and handling”***	• "When the drug company is developing the drug it's developing it for a global market… they are thinking if you can sell it in the United States and EU, they are also thinking about China, Philippines, Brazil, Indonesia. These are important markets! … If you going to have diagnostic in your label you want to make sure it is available in every hospital in China, Philippines, Brazil otherwise you would not sell this drug. From that point of view you have PET agents... at least..., carbon is out of the question, fluorine can be challenging because of the half-life. Technetium is much more attractive. Gallium obviously with PET is more attractive, because you can use a generator and a nuclear medicine Department can make it locally. And if I were looking developing a personalised healthcare compound, I would be very cautious about the fluorine agent." • “… drug companies develop drugs for global markets, and so the imaging also needs to be available in that global market. And that are really difficult problems, the academics often miss."
Category Radio-pharmaceutical Industry	***Statements concerning the topic “manufacturing, distribution and handling”***	• "And what we are doing now is rolling out the manufacturing infrastructure to make the product available... That gives us an opportunity to provide a product that is Er, the same in all markets effectively." • "So [the company] is sort of, not a R&D organisation, we are a biomarker production and distribution company. We are the market leader in the US, we have 43 pharmacies, we have about 48% market share, we do about 1 million doses a year, and we supply these doses to about 1 million patients a year… work with other partners, other businesses that are in this field and need a commercial outlet for the biomarker." • “You have high fixed costs, a lot of cyclotrons, chemicals labours, people, but you can still make a good margin on that." • “Hospitals have been producing their product and also supplied several hospitals around them. For years that was under the radar, the regulation got tighter on the national level and controlled.”
Category Molecular-Imaging Techn. Industry	***Statements concerning the topic “manufacturing, distribution and handling”***	• “Then already mentioned, in PET imaging, of course, the margin is not as good as with contrast media or with SPECT nuclear medicine. Due to the need to create their own local infrastructure or to work together with companies that locally produce the PET molecule and then deliver it accordingly. " • “And in principle, especially as far as PET imaging is concerned, the question is how big reimbursement has to be to cover costs of the test… SPECT is much simpler. And especially technetium-based products, even reimbursement is not that high, you can still cover costs, which is much more difficult in PET." • “On the other hand, PET is problematic because you need PET centres to make the tracers locally and thus the margin is always worse than in SPECT. And that's unlikely to change. Either you need your own infrastructure, which will increase base costs, or you'll be working with local partners who manufacture PET tracers. Of course, they also want to have some of the profit, so the margin will always be worse than with SPECT. There are also certain countries where, apart from the big cities, logistics in SPECT is easier than in PET imaging.”

viii. Statements concerning the definition of a “Companion Diagnostic” (Chapter 4.3.1, The Stakeholder´s Definitions of a Companion Diagnostic?, page 133)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians	***Statements concerning the definition of a “Companion Diagnostic”***	• "A diagnostic test that directly influences the therapy decision, a key test that describes whether a patient is eligible for therapy or not. Later the results tell us if the therapy was successful or not." • "Companion Use is a methodology to overcome these general limitations of conventional diagnostics, and there are several possible models for this: On the one hand, for example, it would still be possible to identify specific target structures based on therapeutic results, i.e. Immunohistochemistry,

		but also tissue-based or genetic- or proteomic analysis. But one could also imagine getting this information out of the blood since liquid biopsy is such a cue. But you could also use nuclear medicine techniques to get information on the expression of the target structure. It is only a companion use if the RP based diagnostic can identify the therapy-relevant target structure or any other method. Only then one should be able to treat these target structures with these specific therapeutics." • "I would also add, now that Artificial Intelligence, bioinformatics is taking over, I would also add radiological procedures that do not identify target structures, but where machine-learning algorithms predict the probability of target expression." • "Basically, CD is the idea of better utilization of therapeutic drugs, by using imaging tests to identify patients who are firstly eligible for the procedure and secondly responding to the procedure. So you could summarize this briefly. Which in itself is a very good idea, under certain circumstances could improve the outcome of therapeutics, if substances are used only in patients where the appropriate target is available." • "Especially with many new oncological therapies, but also with neurological therapies, where one increasingly relies on individual therapies. With a CD you could just optimise that. Bronchial carcinoma is not just bronchial carcinoma, but one could individualize it with imaging." • "For me, the CD is medical imaging that stimulates follow-up. In a way, that compensation for a therapeutic drug are made if the CD test has been performed… So a practical example: … one would perform an FDG PET or PET after 2 months to show that the tumour is actually responsive." • "Interviewer: That means we speak on the one hand of prognostic biomarkers, but also of predictive biomarkers? Interviewee: De facto it is the same. So if I make a prognosis, then I'm making a prediction. " • "Well, there are two terms that you can connect with it. One is in-vitro testing, which has been in use for over 20 years now. In part, the immunohistochemical methods, e.g. Herceptin diagnostics.... The second term, which of course is close to us as a nuclear medicine physicist is in-vivo molecular imaging diagnostics with PET tracers. For example, before a planned therapy, in the sense of theranostic imaging, or for the follow-up of therapeutic procedures.... But a true companion diagnostic means that the diagnostic agent and the therapeutic agent are identical, except for the radioisotope." • "... starting from the regulatory definition, it is actually the parallel development of a diagnostic procedure. But that can be very broad, that can be a genetic marker, a laboratory parameter or just an imaging biomarker... And the idea behind it that it will be included as part of the regulatory approval. It does not really come from the radiopharmaceuticals. The radiopharmaceuticals may well be CD, the easiest case may be FDG ... But it does not just have to be PET, it's SPECT too."
Category **Pharmaceutical Industry**	***Statements concerning the definition of a "Companion Diagnostic"***	• "So what I think of a companion diagnostic is something that is proven with some certainty that certification against that is showing a therapeutic advantage and those are not stratified against that do not have that certified advantage… So it is not good enough just to say it is positive in my essay and get a better response, you also have to show those you are negative and therefore calculate the exact specificity and sensitivity of an assay. And that's the high bar too often clear with an imaging readout simply because of logistics and large patient populations that are required… Right now I would say if you look at the imaging assay, right any imaging assay is very rare to find anything which is mature enough to call companion diagnostic. Unlike the ICD (In-vitro companion diagnostic field." • "So to my mind a companion diagnostic is a subset of a predictive biomarker that specifically developed in conjunction with a therapeutic." • "The first thing to say is you really need to understand the difference between a prognostic biomarker and a predictive biomarker. Many cases people failed to understand that, and two literature is full of papers even from people who should know much better. Who think they have discovered predictive biomarker whereas in fact, they have discovered prognostic biomarkers." • "So the idea of a prognostic or predictive biomarker … can forecast the clinical outcome… On the other hand, a predictive biomarker is one, and I think occasionally you see the term prescription biomarker, which is rarely used, what is a much better term. So that forecast whether the patient responds to a specific treatment, the forecast of benefit or harm. A purely

		predictive biomarker does not improve your forecast up to the patient outcome unless you specified the treatment." • "When we got our first line NSLC we again we went again for the highly enriched population we had shown a clear benefit, whereas [the other company] didn´t do that. They went for a much lower bar, they didn´t look for the higher population, and their NSLC was a complete failure. So obviously this was a big win and all of a sudden, wow Juhu the diagnostic is really is critically important." • "In the US we have these terms companion diagnostics and complementary diagnostics. A companion diagnostic means that you must give the diagnostic test done and have positive results to be able to use the drug. Complementary means there is a diagnostic that adds information to make a decision, but you don´t need to use it."
Category Radio-pharmaceutical Industry	***Statements concerning the definition of a "Companion Diagnostic"***	• "I think that the idea of a diagnostic that selects the patients to the relevant therapy is er probably the relevant bit… So I think the CD should be probably selecting the appropriate patient for that particular therapy. There are quite a few people talking about CD for a therapy monitoring perspective, and I think that is probably a mistake in the community, because er from a regulatory perspective, regulators don´t really like you to have the same target for a therapy monitor as a therapy provider." • "Yeah, so I think the regulatory definition for a CD is one which again [our company] would tend not to support. In other words, [our company] doesn´t see the value of calling its product a CD. Which gives it potentially a more restrictive application. Clearly, the diagnostic product will have an indication, or requests for indications from the regulators, based on the data that is in the file. And if that data involves diagnostic or prognostic, as well as therapy, then it will essentially be registered as a drug by in its own right. Not as a CD. So that is an important distinction." • "So my definition of a CD agent would be one, so there are two levels. One level would be, it is actually only approved label for the therapy. So the FDA would approve a therapy, and on its label, on its official use, it would say: you can only use the therapy once you have done this test. This would be a completely tied and connected CD. The other, maybe more practical version, is the payment. So insurers would say, I am not going to pay for this therapy until you have done this diagnostic test that shows me the application. So there.. I have not seen a true FDA labelled CD, the FDA is not really supportive of that. But insurers always require testing, proofing, especially for therapy which is expensive. " • "Companion biomarker and complementary biomarker, but understanding the difference importance. Complementary biomarker provides information on how they threated, a tool to monitor progression, monitoring the success of the therapy. Companion diagnostic is a mandatory element in the therapy measure. So the companion is necessary if it is not part of the therapy."
Category Molecular Imaging Techn. Industry	***Statements concerning the definition of a "Companion Diagnostic"***	• "For me, it's a diagnostic test that's linked to therapy and helps as a companion in the therapeutic management ... So it may mean that, for example, the diagnostic tests can help determine which patients are likely to respond to certain therapies and therefore should receive or not receive the therapy. And, of course, in the course of therapy, it can also provide information about how successful the therapy in a patient is and what interventions should take place ... So that would be the high-level definition." • "Sure, the companion diagnostic in general in my view qualifies a patient for a certain therapy and also monitor the patient on that therapy. The examples are in widespread use are very kinds of tissue markers, before put on a cancer drug like HER2, before getting Herceptin. And many many examples like that even if they are blood-based or tissue-based test before being put on cancer chemotherapy. And because this is all about diagnostic imaging, there has been some general lack of companion diagnostic using molecular imaging as that qualifying test before being put on a drug. And even though we keep holding out that is potentially very interesting, we have some emerging areas that would probably fit the definition."
Category Medical Specialist	***Statements concerning the definition of a "Companion Diagnostic"***	• "Among CD's, I would also see PET. It helps us to make therapy decisions on some lymphoma entities, in Hodgkin's, at least in clinical trials. We really value having PET-positive findings, which we then treat accordingly such as irradiation. Otherwise, my lab is doing a lot of research on biomarkers, but we are far from seeing this in clinical use. One lab is looking at genetic markers, especially gene mutation in molecular lymphoma because there is nothing stratified about what as a clinician has long bothered me."

		• "For me, that's the combination of imaging and the most specific tumour labelling possible. That's what we want to achieve… The biggest challenge is that they really have to be tumour-specific, or at least tissue-specific." • "Yes, we have several, I would not call it a companion diagnostic, but a diagnostic agent that one uses in certain indications, because you cannot use everything for everything. But one has to know exactly which investigation is best. Of course, what I've been busy with lately is the PSMA scan." • "With the CD tool, I have to be able to select patients who have the disease. Furthermore, I have to identify in which stage the patient is... both with certain prognostic relevance. Er, and thirdly it would be desirable that I can use the diagnostic as a predictive marker, i.e. as a marker for treatment response."
Category Regulatory Specialist	***Statements concerning the definition of a "Companion Diagnostic"***	• Okay, so when you ask about the definition I mean at the moment there is no agreed definition, at least in Europe. Obviously there is a definition around the FDA providers, but in the regulations, I am sure you read it, the definition going forward it terms of CD is very similar, but not identical to the FDA definition. You are aware of the new regulation that will come into effect in 2022, correct? • "I think it's part of the definition, it should be essential to identify the patients in which the drug will work. That is the main one, for oncology. Or where you can identify patients are particularly susceptible to certain side effects." • "I think in the future the CD will have to be, well certified. Meaning that there will be an assessment biomedicine if it meets the definition of a CD… PET RP they wouldn´t fall into the new regulation, only if they work in the device regulation…. But pharmaceuticals should not be affected." • "So a companion diagnostic, so what I know. One is the diagnostics you have, the choline or FDG, where you just check every now and then as a tumour develops. And on the basis of that one can treat again, develop or cancel depending on the results. And the latest thing I've heard: if there are antibody therapies, those antibodies are connected to a chelator with a nuclide and can make something visible. Of that second group, I have only heard something so far, no application has been on my desk so far." • "God oh god. For me, a CD in the narrower sense is a diagnostic procedure, in the sense of a yes / no answer, which is linked to a drug via a registration document. So actually, CD's are just the diagnostic tests that are required according to the registration, which are really defined in that document. So it is not optional, but a must-have criterion that needs to be performed so a drug can be administered. After all, drugs are classically approved for a tumour mutation, and then it's clear that I can prove these tumour mutations with a biomarker. "

ix. Statements concerning the topic "Benefits and Challenges associated with Companion Diagnostics in General" (Chapter 4.3.2, The Benefits and Challenges associated with Companion Diagnostics in General, page 137)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physician	***Statements concerning the topic "Benefits and Challenges associated with Companion Diagnostics"***	**Benefits:** • "Treatment would be more restrictive but more targeted." • "That means we need methods that predict the presence of treatment-relevant targets with greater accuracy." • "…which is a very good idea in itself and could possibly improve the outcome of therapeutics if substances are used only in patients where appropriate target exists." • "..and if this companion biomarker really identifies patients, they really benefit from this treatment..." • "On the other hand, it is the case that the therapeutic substances ... are targeted only to hit the tumour cell, i.e. targeted therapy. And if they treat the same 100% again, then in many cases they will get a negative result. The conclusion would be: the therapeutic substance is not effective. Now, if you identify and treat the right 30%, then they will see the therapy is highly effective. If the industry really wants to make tumour-specific substances, targeted therapy, and want to obtain approvals, then they are extremely interested in the CD." **Challenges:**

		• "Biggest obstacle: there is no financial gain for those who offer a therapeutic agent." • "It's not a good incentive for the industrial side to implement such diagnostic tests in our system right now, but we academically have an extreme interest in it, but the industry partners are not necessarily." • "So the biggest challenge is certainly the availability, it needs methods that are available on the spot, i.e. where the therapy is performed." • "Er, secondly the evidence has to be proven of course ... So there are trials that show that it works well and others that are more critical. In Phase 3, there are prospective, randomised trials that show different results. So the evidence that these procedures and I do not mean imaging yet, but generally biomarker-based target identification methods, does not work out that way." • "The snag is that it sounds good, but it's often not so interesting for the pharmaceutical companies that are supposed to be the driving force. Because of course, in a nutshell, they have a commercial interested that their substances are broadly applied and not in selected cases." • "With the many different individual forms of therapy, it will not be explainable with a single biomarker. You might have to do different imaging tests to find out which factors are expressed in the patient. " • "The other is the situation that there can be multiple positives, positive for breast cancer, but still for another factor. That would require multiple imaging procedures, which is certainly difficult." • "The other problem is the follow-up because the biomarkers that allow the choice of therapy is not necessarily suitable to evaluate the response of the therapy because it is often the case that the good old FDG PET can be used meaningfully again." • "They have to show high positive and negative predictive value! So Outcome." • "That is clearly the financial aspect. So PET-CT imaging, as in-vivo biomarker / CD is not cheap, unfortunately." • "Well, from the industrial side, this also has two medals. So, if you have a diagnostic procedure, which could be done theoretically by the 100% of the patients, but you push away 70% ... then, of course, this is a loss for the industry." • "The Nuclear Medicine Community can show in various studies how good FDG is or ... that is more difficult now, someone who has an approved drug says "okay we'll add this because we have a benefit". But there must be a benefit, and that must be reflected in a somewhat broader application, ultimately in more money."
Category Pharmaceutical Industry	***Statements concerning the topic "Benefits and Challenges associated with Companion Diagnostics"***	**<u>Benefits:</u>** • "…if the mutation isn´t there they have no chance to responding. If the mutation is there, they have a good chance to respond. But there is not black and white with the checkpoint inhibitors. Which makes it complicated." • "When we got our first line [disease] we again we went again for the highly enriched population we had shown a clear benefit, whereas [the other company] didn´t do that. They went for a much lower bar; they didn´t look for the higher population and their [product] was a complete failure. So obviously this was a big win and all of a sudden, wow Juhu the diagnostic is really is critically important." • "…certainly yeah, there is no doubt about the evidence." • "There are 4 disease areas where predictive biomarkers and companion diagnostics, personalised medicine, has really had an impact historically. 1. Cancer, 2. Infection, 3. Rare diseases and 4. Drug metabolism… And as you know many cancers are driven by tumour mutations, and so you can identify, by the right mutation, you can choose the right drug. It is less true that predictive biomarkers/ CDs had an effect on major diseases like asthma, myocardial infarct, diabetes, dementia, depression, psychosis. " **<u>Challenges:</u>** • "… using that method, we had a limited population that we could have the drug available for. Because we selected, have pre-selected, to have the enrichment to be able to get approval. Whereas [the other company] has spent the program for several years and they will be able to show that it worked in all the patients…. So that kind of set us back for a little bit, and there was a lot of... you can use imaging… oh Jesus look what we have done. We have anchored ourselves…" • "However, even if you don´t see [the target], also these patients respond. So it is in the interest of the dynamics between the oncologists, who want

		to make certain that the patients have any chance to benefit from the drug that could help them. And the payer who are saying well wait a minute, this is an expensive drug, and we can´t give it to every patient, who might be... We have to focus on the patients who do benefit. So the way it plays out varies from country to country." • "As you know in drug development, in every hundred projects the industry starts, if they are lucky one becomes a medicine. So you have huge, you have a huge attrition. And of course, you have attrition in the diagnostic. So for the academics working on Etarfolatide and indeed for the company developing it, they got nothing out of it. Even it was a great tracer, when the therapeutic died the market for the diagnostic died as well. So it is a very unattractive place to be in."
Category Radio-pharmaceutical Industry	***Statements concerning the topic "Benefits and Challenges associated with Companion Diagnostics"***	**Benefits:** • "…if you select, for HER2 for instance, HER 2 and HER receptors you know, Herceptin does not work unless you got HER receptor breast cancer. So that is a fantastic combination of patient selection…" **Challenges:** • "I guess part of it is how broad the indication is… By the time you come out at the end of there, you don´t actually have a really big patient pool to sell to. Because you can only sell it to patients in that cancer (laughs), with that therapy. And there is always the risk that a different pharmaceutical company … finds a different therapy that is better in that cancer. Er, the whole linking to pharmaceuticals is really difficult from a commercial perspective because your market potential is quite small." • "When pharma uses RPs, they can end up with a really small indication, and your return is even harder to get. Where a broad indication in a diagnostic is much better because you have many more opportunities to sell you scan." • "… [the company] doesn´t see the value of calling its product a CD, which gives it potentially a more restrictive application." • "Pharma has recognised that biomarkers and imaging are critical in the disease development. 15 years ago Merck walked away to a very promising therapeutic play, there is no biomarker marker. Today the recognised the use of biomarkers in the drug development."
Category Molecular Imaging Techn. Industry	***Statements concerning the topic "Benefits and Challenges associated with Companion Diagnostics"***	**Benefits:** • "... the diagnostic testing partly helps to decide which patients are likely to respond to certain therapies and therefore should or should not get this therapy." • "And in the course of the therapy give information on how successful the therapy is and which interventions should take place ... So to get confirmation that the therapy is effective and can be continued." • "I think that is a very interesting step into Theranostics that will get a lot of things opened up." **Challenges:** • "The challenges of both technical and scientific nature. First, you really have to develop this CD so that the test itself works as a CD." • "But on the other hand, of course, there are the economic challenges, because the diagnostic test is linked to the success of the therapy." In general, the success chances of a diagnostic test is greater than the chance of success of a new drug. So the chances to launch a product on the market decreases for the developer of the CD. " • "Of course, the third challenge is the regulatory side ... obviously there is no way to submit the diagnostic test and therapy as a package to the BfArM, EMA or FDA. One has to negotiate with each authority, so there are also challenges." • "And I believe that is because the pharmaceutical companies' don´t want a potential market limiting step on the way using their drug. I had some conversation with the imaging teams inside big pharmaceutical companies, which gave me that hint, not as an official policy but they believe that MI is used widely in their clinical trial process, but they never wanted it to be a mandatory step underway using their drug. Because unlike a blood test driven tissue test, they still looking at MI as a complex, expensive hard to find the thing that would limit their market for their drugs. So even if it could lead to a better patient population that take the drug, they view that as market limiting and unless the regulatory body or payer absolutely required it, it tried to find a way to get the drug approved without it."
Category Medical		**Benefits:**

Specialist	***Statements concerning the topic "Benefits and Challenges associated with Companion Diagnostics"***	• "With the current therapies, we are able to control the disease in many, many patients. But there are approximately 20 to 25% of patients who have a rapidly progressive course, which die very early… We must stratify these patients early for other therapies, experimental therapies. We have access to these therapies, but we only use them when the standard therapies have failed. But if we could predict that the standard therapies would not work in the first place, we would help a lot." **<u>Challenges:</u>** • "Well, biomarkers have to be first established, validated so we can use them in clinical routine. It needs to be robust, reproducible, which also means harmonization and standardisation." • "The biggest challenge is that they really need to be tumour-specific, or at least tissue-specific. Which is probably the case with PSMA (PET/CT). The even greater challenge, of course, is that detection should also be possible, especially in relapse patients, in the 1mg PSA range and below. You have to move the limit down, the detection limit." • "The interest of the clinicians is of course there, but they will wait, I think, for a long time. Because such a development is similar to a development of a drug. That costs millions, you have to say that very clearly." • "To simply validate them, that's the tricky thing ... and of course the price for the patients or for our health care system. Very often additional markers like that PCR3 or PHI are partially not paid by the health insurance companies." • "And we've got a relatively large lab, and we've been trying to develop biomarkers. That costs money and the company, I do not name them, that sells [the product] ultimately gave us no money. Understandably, why should they sponsoring a biomarker that says, "Okay, in this case, you should not give this drug". They hold us back for a long time, but I knew from the beginning that they would not give us any money. So I would say the development of these biomarkers will be difficult."
Category Regulatory Specialist	***Statements concerning the topic "Benefits and Challenges associated with Companion Diagnostics"***	**Challenges:** • "So probably we need to distinguish broad categories of drugs where say the more traditional, even if not very clearly targeted drugs, where the biomarker simply means a restriction in indication. So you try to avoid to develop it too specifically, to target a bigger population that could be the industry´s interest. But I think the whole other bunch of drugs, which unless you are very specific and fish out what is the right population, they will simply not work. " • "But that also means that in order to be successful you must have both components functional. So if the drug does not work, then there is no result and if the test picks the wrong people, then, of course, the study fails. And that makes it relatively difficult." • "And the second reason why there are not so many CDs, because the world of industry is set up differently. There were and are classic drug manufacturers, they were just looking after therapeutics, and on the other hand, there are diagnostics manufacturers, who only took care of diagnostics. And yes, only in the last 10 to 15 years has there been this realization that with molecular oncology, it is actually necessary that the industry there work much closer together to bring successful products to the market." • "The difficulty, of course, is that these subgroups get smaller and smaller. So in tumour mutation, there are two or three mutations that cover most of the patients, 80% maybe 90%. For the last 20% I need a lot more tumour mutations, and I have to take a closer look. These are rare mutations and, of course, relatively small subgroups remain at the end, which is difficult to study and of course are not that lucrative." • "So I have to do a lot of screening work, in clinical trials, until I find the patients." • "And a third problem may be in the end in the application of these therapies. Sometimes it happens that the actually high-quality CD is replaced by a simpler test ... It cannot be that we have a great drug with more than 8 years of patent protection, which is really expensive and in the selection, you use a copied test or a test which is tinkered by the hospital laboratory itself. And you have a significantly worse test quality than the underlying, and from the regulatory agencies approved test procedure."

x. Pros and Cons of In-Vivo Imaging Biomarkers vs In-Vitro Assays (Chapter 4.3.3, Pros and Cons of In-Vivo Imaging Biomarkers compared to In-Vitro (molecular) Assays, page 143)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians	***Statements concerning the topic "Pros and Cons of in-vivo imaging biomarkers vs in-vitro assays"***	**Pro:** • "The differences are clear! A blood sample will characterize the patient as a whole, but imaging can accurately characterize individual regions and individual organs. At least with our nuclear medicine techniques, we visualize the whole body and we can look at individual regions. You cannot do that with a systemic marker, and the main goal of therapy is not to treat the entire organism, but to treat a certain target region." • "In such a case, imaging is the more accurate biomarker method compared to an in-vitro assay taken from the blood. It is a bit different when we speak about biopsy data. Then the problem would be that the biopsies need to come from the right regions, but you just do not know it as well as you know it with imaging." • "Because what has been used so far are methods that rely on biopsy or local tissue samples, or even on primary tumour preparations. But the tumour pathology changes in the course of pre-treatment." • "In other words, we do not have [relating to in-vitro assays] any real-time procedures there that can represent the biology of an entire tumour. And, of course, this is the strength of imaging techniques, especially biomarker-driven imaging techniques. Because you can basically visualize and quantify in real time, realistic, non-invasive the entire body, so all the lesions and not just part of a tumour." • "So the big advantage (note: the imaging biomarker) is evidence of heterogeneity. In principle, one can prove if a patient has a large number of metastases and he may be positive for any biomarker, but one does not know where it comes from. So the localisation only succeeds with imaging, not with a blood test. That's basically how it is." • "The second is the scale of the disaster: Alzheimer's disease has a biomarker for detecting amyloid pathology, but ultimately it's difficult to say how far pathology has progressed. You can only do that with imaging markers in this form." • "So in many cases, imaging will be superior, but I think the ideal form will be a combination. Cheap gatekeeper tests in the form of blood tests that can be easily and quickly used to screen. In case of positive findings, imaging should be supplemented." • "Of course, imaging is important in many situations: if a tumour disseminates in the body and extracts a substance, then ultimately an integral value, which is the tumour marker, really does help us a lot. It may be that certain clones respond to the therapeutic, but others do not, and so you cannot treat them specifically." • "In principle, you can have a patient with liver metastases, or lymph node metastases in the lungs and the metastases in the lungs respond to the therapeutic drug, but the liver metastases continue to grow. Thus [with imaging] you can specifically tell if you need surgery or not. " • "There the question is really, is the target expressed, and is it uniformly expressed at it is prostate cancer, where 90% will have high expression of PSMA. That is not the case for Somatostatin receptor. There are of course in-vitro biomarkers also, but you know to survey the whole body where you can have a mixed expression in different lesions, is quite important. If you have lesions that have low or no expression of you target, then the patient will not respond in the long run." • "While eventually, the cost of taking the blood and analysing the blood is low, but validating the marker is going to be as expensive as by imaging. So what the blood biomarker does not tell you… let's say it is circulating cells or circulating DNA … or you just take some urine marker, you never know where it comes from. You never know if it is homogeneously expressed..." • "Yes, well, the in-vitro assays, you have to say brutally, almost exclusively focus on the primary tumour. So the tissue that was removed during the primary tumour surgery will be used, at a later time if there is a recurrence, to decide on the further therapy. Of course, it is often the same, but if you look for example at breast cancer, then you know that in about 30% of women, who express Herceptin receptors in a primary tumour, the status will change. • "In-vivo imaging shows, at the time of therapy decision, what the patient's actual receptor status or antigen status is." • "… the value of in-vivo companion diagnostic is certainly much higher than in-vitro diagnostics. But of course, it is considerably more expensive."

		• "So the advantage is the picture, and in the picture, I have more information than in a generalized blood biomarker. • "An important topic is certainly oncology. When I do a response evaluation, I often have metastatic patients and see if he may respond to individual metastases or not. And not just a general response, that's certainly the general advantage." **Neutral:** • "It's not always just in-vitro biomarkers, but it does not matter which biomarker, the biomarkers as such are still under-used." **Con:** • "You know Imaging people usually are quite limited in their understanding of medicine. They are tunnel blinded … Because they believe that you will be able to have, for any drug, a biomarker, an imaging biomarker. That is of course total nonsense. So you have to focus on the stuff that is really needed." • "…for instance if you have an intermediate endpoint biomarker, so you want to know if the patient responds to the prostate cancer, there I don´t think I need imaging. There I just want to have a PSA. Take blood and show me that this PSA is going down, I am quite happy. If the PSA is going up, all the stuff does not work. Imaging people tend to think that everything can be solved by imaging that is of course not true." • "The main disadvantage is the co ... that it is much more laborious and comes with costs ... I would not develop a PET biomarker for a cold medicine. Because if a snuff preparation costs 20 €, then I cannot make a PET scan for 500 €. But if that is a new generation immunotherapeutic for € 100,000, then perhaps a PET is indexed."
Category Pharmaceutical Industry	***Statements concerning the topic "Pros and Cons of in-vivo imaging biomarkers vs in-vitro assays"***	**Pros:** • "But the motivation for us to develop it is that we want to see how that changes in time overtreatment … one of the reasons you have a higher response rate with chemotherapy and checkpoint inhibitors [product name is that in those patients the chemotherapy killing of cells, you got all kind of DNA, and the immune systems is activated trying to clean things up. Then you get the checkpoint inhibitor in there, and it can really just finish it off. So we want to look at that kind of research questions and see to understand what changes... we are also trying to develop tracers for CD8 and other aspects of the immune system. To really use it as a research tool." • "So when you do IHC (immunohistochemistry) you have a limited sample of a tumour... so what the nice things about imaging are, you cannot look at just one tumour you cannot just look of parts of a tumour, you can look a whole tumour and at more tumours throughout the body. And the hope is that this would be more valuable, and it would do a better job in predicting patients response, but this is true or not time will tell." • "Now, imaging has some advantages: you can look at all the lesions, your metastatic lesions. Some have mutations some don´t, some … there are a lot of academic reasons why imaging might be nice to have." **Neutral**: • "The primary reason we developed this imaging agent was as a research tool." • "There are people who are interested, not [company name]. But there are other companies that are interested in developing immune-oncology tracers…" • <u>Interviewer:</u> "So from your mind and your company, do they build on imaging as a CD or would they prefer a simple blood-test also from regulatory and reimbursement perspective? <u>Interviewee:</u> I think to have it before an imaging assay, yes…. So I think yes if we look at some companion diagnostic phase today I would say 99% is probably some receptor status IVCD (in-vitro companion diagnostic). We don´t have many good examples of an imaging assay that is a companion diagnostics." **Cons:** • "There are examples, like if you look at the Oncosite test. It is a genetic panel test, right. In genetic panel tests are increasingly going in that same direction, imaging should be no different except that I think imaging has a higher challenge." • "Imaging has the entire business of radiopharmaceuticals and its maturity in the clinics. Right, if something that is in my view more relevant in terms

		of therapeutic diagnostics. So something which is established, like a perfusion scan with technetium, those I can still see as clinical criteria for treatment and maybe reference criteria, but I don´t think there is any example outside of oncology that is using it as a CD." • "In oncology, imaging has a different burden, imaging is more like a clinical workup scenario… You do use imaging a lot, readout and protocol itself….they are not really a stratification or something in diagnostic use." • "The other side, one of the lessons I learned working on the IHC diagnostics... Firstly I see it is much more of an issue in Europe, where there is a lot more cost consciousness. There are hospitals given a certain amount of resources to take care of the patients, and that's it. In the US there is no control, the only control is that the label says you cannot administer this if you don´t have the test. So you get the test done, the same thing can happen in Germany. The German government was tough for us and with our organisation, they are going to say "yeah ok, so you need to have that test done, but 125 Dollars is too much. We don´t have the money in our system to pay 125 Dollars for this test. So, we need to get that test for 45 Dollars." • "And so tumour mutations has been a very productive area for cancer research, and in that area, you have to accept that imaging has a very difficult battle to fight. Because in many cases you can see these mutations in circulating free DNA. Ham… if the mutation is there, you can begin to prescribe the drug." • "But really for tumour mutations (imaging) has a very hard struggle. It is also the truth, the case that the imaging tools we have are not as precise as the free circulating DNA tools. In the MICAD [Molecular Imaging and Contrast Agent Database] database there are hundreds of eGFR tracers, but remember there are many many mutations, such as mutations which yet are discovered. And ideally, you would need to profile every molecular imaging tracers against all mutations, known and unknown. Which is almost an impossible thing to do." • "And they won't be clean; different tracers will have different binding to different mutations. Whereas you just look on the free circulating DNA, you have the mutations status straight away." • "So I think, what I am going to say is far from strong. But you could argue that academics are wasting their time with yet another eGFR tracer. I think, what I would say to the academic community is that cancer research moves on. We will come to an end... We will get good drugs for all of the tumour mutations or the important ones. The good drugs will go generic, they already are. We will develop drugs for 2nd and 3rd mutations, minor mutations, but eventually, we will come to that stage where that space is well covered." • "In order to get the regulatory dossier for registration, you need to have your patient's segmentation done right from the beginning of phase II or even phase I in oncology. And that is actually quite easy to do if you have a blood test. But it is very very difficult to do it with an imaging test. To get an imaging test logged in before you have seen any patient. That is the challenge." • "When the drug company is developing the drug it's developing it for a global market. So when [company name] is developing they're not just thinking of, certainly they think if you can sell it in the United States and EU, but they are also thinking about China, Philippines, Brazil, Indonesia. These are important markets! Places like China and the BRIC have a growing middle-class, they have western diseases and certainly want to have access to western medicines, and they can't afford it. If you going to have Diagnostic in your label you want to make sure it is available in every hospital in China, Philippines, Brazil otherwise you would not sell this drug."
Category Radio-pharmaceutical Industry	***Statements concerning the topic "Pros and Cons of in-vivo imaging biomarkers vs in-vitro assays"***	**Pros:** • "There are some companies convinced. I don´t know if you know [Diagnostic RP Company]. [Diagnostic RP Company] developed a CD for patient selection for ovarian cancer. That got the attention of [Big pharma company], and I worked with [Diagnostic RP Company] during having clinical studies in Europe. And [Big Pharma Company] acquired the license for 800 million, which was a big deal a couple of years ago." • "There are huge opportunities still in cardiology, I tend to think that cardiology and neurology are better." • "Pharma has recognised that biomarkers and imaging are critical in the disease development… Today they recognised the use of biomarkers in the drug development, using imaging biomarker as inclusion criteria. Pharma companies are clearly coming to us with the intention of appropriate

		patient selection. They are very interested in researching biomarkers, in the development point of view." **Cons:** • "…I think the problem that pharma companies always had with PET is the availability of the product. And so if you were to compare testing the Cerebrospinal fluid, with PET then effectively anyone, who can do a lumbar puncture, can get cerebrospinal fluid… If you used CFS testing then maybe you therapy get access in 90% of the available patients, if you got a PET/CT scan in front of it then you go to reduce the access of your therapy to patients." • "So pharma has got to that point …I don´t think that they are looking at nuclear medicine and RPs as an actual choice. And I think that ties into that availability, I think that they are worried that they could predict gate in front of their therapy. That meant it would slow the adoption of the therapy in the long run." • "…And not everyone thinks that amyloid imaging is that relevant, there are some people who do, but generally, the regulators don´t believe it."
Category Molecular-Imaging Techn. Industry	***Statements concerning the topic "Pros and Cons of in-vivo imaging biomarkers vs in-vitro assays"***	**Pros:** • "In oncology, with secondary diseases such as metastases, the involvement of lymph nodes, and so forth, you can see that imaging can provide more information than a PSA test ... Hopefully, imaging can deliver much more information such as localisation or spreading of the disease. You really have to find the sweet spot of molecular imaging. Show that the test as such also makes sense and provides the information that contributes to the management of the patients." **Neutral:** • "Well, I would say, one thing we have not discussed so much yet, which is very important to me. What are the disrupters, what is threatening molecular imaging? ... As you can see on the amyloid side, there is already the CSF test, and there is intensive research on blood-based tests. And the disruptive innovation for molecular imaging is if a test exists which is much simpler and has the same amount of information. In the end, the question arises: "Why do I have to image?" • "Basically, it's not about living on the island of imaging, but you have to see what's happening around you and what other tests are being developed." **Cons:** • "Well, in oncology, where imaging is really needed to plan the intervention, the surgeries, you need the imaging information. So in oncology, you can see that imaging has its value. But I'm not so sure about amyloid plaques or Tau ..." • "However, if the CSF test, and the future blood tests, can provide information that is equivalent to the information of the imaging test, then I can well imagine that at least the use of imaging will decrease and you will first perform a cheap blood test. And for those who need an additional imaging test, for whatever reason, the imaging test will be performed in certain groups." • "Now one of the challenges is: should we calculate patient-specific dosimetry in each case? That could be very complex; this is what I mentioned at the beginning of the call where pharma companies did not want to have a potentially complicated step like a PET image before using their drug! I think there is some disincentive to do patient-specific dosimetry for all these new emerging RPs because it adds complexity and more procedure steps." • "Because unlike a blood test driven tissue test they (pharmaceutical industry) still looking at MI (Molecular Imaging) as a complex, expensive, hard to find the thing that would limit their market for their drugs." • "The added value of imaging must be established in comparison to the blood test, the CSF test. Otherwise, it's just an even more expensive test. And we also asked ourselves how to differentiate the PET imaging test from the CSF test. And imaging allows us to do staging by region. A one-value test per patient may not work as well as an imaging test."
Category Medical Specialist	***Statements concerning the topic "Pros and Cons of in-***	**Pros:** • "Previously, we wondered if we have local recurrence or distant metastases. We assumed it's more likely to have a local recurrence if the PSA rises slowly or just rises after 2, 3 years. If the value increases faster, it is a systemic recurrence. It was not very well-grounded. In individual cases, that helped little. People have always been irradiated, and still, the PSA

	vivo imaging biomarkers vs in-vitro assays	value has continued to increase. Then they got a systemic therapy. This was not a targeted treatment, but shooting into the forest with a lot ("Mit viel in den Wald schießen"). " • "The diagnosis of high-risk prostate cancer has improved because a much more accurate clinical diagnosis of the spread can be made. So if someone has diagnosed a highly aggressive prostate cancer by punch biopsy, then we now perform a PSMA PET / CT." • "We have a much better chance of diagnosing lymph node metastases. This means that the field of lymphonodectomy at surgery, or the field of lymph node irradiation during initial radiotherapy, can be modified individually." • "Imaging has created diagnostic added value! To what extent this affects the survival of the patient is too early to say, there is no data available yet." • "But we're already fishing out more patients with a low PSA score, who show either local recurrence or lymph node recurrence or distant metastasis. This is particularly important because it has been shown that at a lower PSA level, the secondary irradiation works better. The clinical advantage for the patient is a more targeted therapy than in the past." **Neutral:** • "And I do not think that one will replace the other. I believe the added value in the reasonable combination of both." • What we are currently doing with lymph node biopsies is to define the targeted molecular fingerprint of a tumour before initiating therapy. And then to make the best possible prediction about the further clinical course. We use LB (liquid biopsy) to better understand therapeutic response and functional evolution because a tumour is a dynamic tissue. But especially in this area, imaging plays an important role. Especially in the case of Hodgkin, not so much in molecular lymphoma. But in other aggressive lymphoma entities, the American guidelines request a PET. So one thing does not exclude the other ... Functional imaging is actually used to detect the clinical course at an early stage. " • "No, whether that's liquid biopsy or something else, actually, I do not really care. Because we've been looking for a better marker than the PSA value for years. PSA is not a good marker in primary diagnosis, but it's the best that we have, and one we have learned to deal with." • "And I think there will be a combination. I do not think that one will replace the other. But a combination of both will be able to represent the best possible status of the patient." **Cons:** • "The PSMA PET / CT test was primarily praised, many studies have been done with insane sensitivities and specificities. That very well may be, but we have checked surgically if the cells illuminating are really a tumour. And thus the sensitivity of the PSMA scan drops under 60%... " • "The big cue of the future is Liquid Biopsy. That one gets the molecular information about a tumour by markers in the blood, be it circulating tumour cells, exosomes or something similar. You get a prognostic or predictive marker."

xi. Statements regarding the topic "Mandatory Prescription of Biomarkers by Regulatory Authorities" (Chapter 4.3.4, Should Biomarkers Be Mandatory Prescribed by Regulatory Authorities? page 149)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians	***Statements concerning the topic "Mandatory Prescription of Biomarkers by Regulatory Authorities"***	• "I think that would be ... so it would be very good, it would be desirable. But if they manage to include the appropriate regulations in the licensing mechanisms? I do not think that will happen fast." • "Let's put it this way, in order to first initiate such a mechanism politically, there are very very expensive therapies needed, which lead to such great costs that they can no longer be controlled. And let's face it, then the

		regulatory authorities need to see the reason that better diagnostic tests could reduce costs accordingly. " • "... the way we really have to go! Whether it's easy to walk, I vaguely doubt it. But that's the only true way." • "Yes, they will be demanded, definitely. It's just the question which tests required. Of course, the pressure and commitment of the industry will be crucial in terms of which detection methods and biomarkers are required. But that will come as surely as that Amen in the church! It is already happening now. " • "I do not know if it will be prescribed, but it will all be a matter of cost. Saving money should be more a reason to convince the authorities. Rather than the pharmaceutical companies, which would want the drugs to be used broadly." • "We might even have allies in health care if they would understand this. But one does not always have the impression…" • "Yes, I think everything else makes no sense in my view. Whether the authorities think wisely is another matter. (Laughs)" • "So, you would have to do a precise cost analysis. We know the cost analysis. For example, when you look at bronchial carcinoma in PET, you just know that PET does not save lives, but it saves money. Because between 15-20% of patients receive an upstaging to stage N3, which prevents them from having surgery. One would have to do an additional PET in 10 patients, but in 2 or 1.5 patients you spare surgery! And a neat cost analysis would show that these 10 PETs are actually well-used money." • "I think there should be CDs; I think there should be biomarkers to select patients appropriately. Yeah absolutely, because there are two ways in oncology. There is one way that you try something and treat, and you got six cycles of chemotherapy, and in the end, you may know if it worked or not. To me that's unethical, especially after one or two cycles you could do a simple FDG glucose metabolic imaging and see if the treatment works or doesn´t… that would be my first biomarker requirement. Is your glucose metabolism going down? If not, stop the treatment. But we have not reached that point." • "Yes, I think that will happen more and more. Because our health care system is already groaning enormously under the current costs. And in the future, the new therapeutics will certainly not be cheaper but rather more expensive. If you compare the costs of new therapies such as KART cells, ranging from € 200,000 to € 300,000 or more per treatment cycle, and costs of therapeutic agents such as 5-fluorazil, which have been developed in the '90s and' 80s and have total lifetime costs of less than 100 D-Mark or Euro per patient have, than you just see the gigantic difference." • "And all new substances, whether they are antibodies or kinase inhibitors or whatever, are all very expensive. The compulsion to select just the right patient clientele, which also really benefits from the therapy, the coercion will increase extremely. In the future, you will not be able to afford to treat patients, do a CT scan or MRI after three months, and then say, "Well that did not work". But what we really need is this theranostic approach, which means that we perform an in-vivo imaging scan just before the therapy and prove "the antigen, our target structure that we want to achieve via therapy, is available". And thus the patient is a suitable candidate for the relatively expensive therapy. So the necessity will definitely increase."
Category **Pharmaceutical Industry**	***Statements concerning the topic "Mandatory Prescription of Biomarkers by Regulatory Authorities"***	• "I don´t think it going to be mandatory for every drug; it's going to depend from drug to drug, indication by indication." • "What benefit does the diagnostic have? …If you can show in all common population, right, without a diagnostic that the benefit to the patients is substantially more, without the diagnostic, the existing therapy, right, so if you can improve the outcome significantly, they will approve the drug. Certainly, outside the US, they approve the drug, but the payers are not going to pay for it. So I think the way the diagnostics come in, the primary driver for that is there are two drugs. The one is "do you need to select that population to show a significant benefit", right, that´s the one. And the second one is "if you don´t have the diagnostic to show a significant benefit, is that given the costs of the drug, is that significant benefit enough to not have to use a diagnostic"." • "And I think outside of the US; generally if there is a diagnostic that can help to make that decision, the payers are going to be pushed to use it." • "Er, I think personally think over time.. the need to really find out which patient gets the right drug will become more and more important. Right. So whether it is the nuclear authority who asks for it or the spheres, the

		insurance companies ask for it. It is still an open question in my view. … if it is available, some people can set that up. It is probably useful." • "Interviewer: Will they (regulatory authorities) demand a CD maybe an imaging CD for like very expensive therapeutic drugs?: Interviewee: So yeah, very short: it could become important, it does not say it is right now, but it could become important either by the regulatory agency or by the sphere (e.g. insurance companies). And the sphere could be a big driver/ player here. • "Well, the regulators are not concerned about the cost of the drug. That is a different question for the healthcare systems." • "So I think regulatory authorities are very interested in stratifying patients so you identify as many as possible who benefit and as few as possible who will have harm. … You could stratify patients with purely clinical observation, stratify them on the basis of standardised biomarkers you have in any lab: PSA, lung functional. Or you could stratify them on the basis of brand newly developed biomarker which is approved at the same time, in other words, a Companion diagnostic. But don't think the regulatory authorities care how you do it, all they care about it is whether you maximise the number of patients who benefit and minimize the number who have harm. • "The payers have a similar view because they want to maximise the cost-benefit in terms of patients who benefit and minimize the cost of harm." • "No (MI as a CD), as far as the costs are concerned of molecular imaging tracers in cancer research. The 3 things you need to look at 1st, the assay needs to be locked down before you start and that is extremely difficult; 2nd, if you are competing with a 50$ blood test that could be done in a lab it is hopeless, and 3rd, drug companies develop drugs for global markets, and so the imaging also needs to be available in that global market. And that are really difficult problems, the academics often miss."
Category Medical Specialist	***Statements concerning the topic "Mandatory Prescription of Biomarkers by Regulatory Authorities"***	• "But I personally think we are always talking about investing a lot of money. In Germany you have huge difficulties getting PET reimbursed, that's a nuisance. Our sequencing analyses are not cheap right now, but they are vanishing compared to the cost of experimental therapy. I am firmly convinced that if you show the clinical benefits ... that these measures are required by the authorities. As it is already the case with acute leukaemia, where a detailed molecular diagnosis is carried out. This is also required according to the WHO classification, and there is no reason that this should be different in my area of research. This will almost certainly happen with lymphoma." • "So it's not going to happen that fast in Germany. Or there's not even such a thing in Germany that something is required for any kind of treatment. But there will be guidelines and possibly it will find an entry into clinical practice via guidelines. It assumes, of course, that the method is widely available and that is not the case with the Ga-PSMA." • "If there were biomarkers that would be fine. I can imagine that it will be required." • "That's a good question. I can imagine, I can just imagine it. Right now, of course, it's fictional, because there's no marker that's so good that it could justify that. But I could imagine that the health insurances say: "yes only this and this patient we will cover costs". It also depends a little bit on the fact that biomarkers driven clinical trials need to be performed… And that something is prescribed by law is absolutely conceivable! The question is, of course, this is contrary to the interests of the pharmaceutical industry. That will be interesting to see. Of course, they want everyone to get it."
Category Regulatory Specialist	***Statements concerning the topic "Mandatory Prescription of Biomarkers by Regulatory Authorities"***	• "Interviewer: Right, it reduces the market a little bit in this area. Interviewee: Exactly, exactly and because they have to conduct the studies.... So that's interesting. But if there are any ground-breaking results, then I could imagine that (it will be required). Not in the foreseeable future, but in principle." • Well, I mean such would not be the right concept. But if a CD would be required to identify a patient population that benefits from the drug in some way, yes. Because if you need a test to identify the right patient population for your drug, I think in an indirect way you could, you know someone would use the word mandatory, but you know the company would need to show the evidence and that is sort of in an indirect way. They would need to have the evidence to support that." • "…the likely scenario is that they will be mentioning the biomarker, or whatever marker that the test or a test a CD is supposed to identify, and then there will be a description of what test has been used. Rather

		performance characteristics of the test it has been used for example in the clinical trial." • "No, no under no circumstances, under any circumstances ... If the company says they would need it in combination, we will look at it. And if the company says they will go without it, then we will also look at it." • "Yes, I think that's very real. This is a situation where a positive study shows that a drug helps in marker-positive patients. And the approval would say that it can be used in these marker-positive patients. Now the Joint Federal Committee (GBA) is facing the decision, what to do? So you have to join this dichotomy in marker -positive and marker negative. The alternative either would be that you do not reimburse the drug, which would be a disaster! Because the drug also has a benefit. And vice versa, the other alternative would be that the GBA releases the drug for all patients, regardless of marker status. This would also be a disaster because that is a charter for non- complying use of approved drugs. So that does not work either, so there is no way around it…"

xii. Statements regarding the topic "Benefits and Purpose of PPPs" (Chapter 4.3.4, Should Biomarkers Be Mandatory Prescribed by Regulatory Authorities?, page 149)

Item	Manifestation	Example of literal expressions
Category Nuclear Medicine Physicians	***Statements concerning the topic "Benefits and Purpose of PPPs"***	• "In principle, I think that makes very much sense. In Germany, this has often failed due to the extremely strict regulatory framework. It is not simply a PPP to the mutual benefit; it should be a win-win situation for both. From my experience, putting this on a solid legal basis so it can be a success is the biggest problem. Because there is so much bureaucracy associated with it, it also looks daunting. I think that needs to be greatly simplified to be successful. " • "The industry partner wins because he gets better diagnostic tests, or tests in general, for his therapy and the area of application. And on the other side, the academic partner wins because he has a better sense of where, in the future, the things he or she is dealing with scientifically, could have a clinical relevance on a broader spectrum." • "So the value is tremendously high, PPP is basically what drives the bulk of the research. The otherwise publicly funded research, so by DFG or EWIF, consists of 90% mechanistic research, which is also important, but has nothing to do with the whole issue of implementation… PPP research is exactly what drives the field, which we are extremely interested in." • "In the RP field, we are fortunate enough to find medium-sized companies that are very active, increasingly active. Because big pharma jumps in and buys up such companies. So I expect a lot from this financing branch for the future. Also associated with the hope that one is able to set up multicentre trials or something to generate evidence." • "I heard about it, but I cannot rate you because I do not know the details. (Interviewer explained PPPs on the basis of the IMI initiative, and maybe the interviewee thought to comment on this specific project)" • "I think government agencies are not well suited to invest. The reason is that then the whole story starts, what is the payback? That is something even the NIH never tried. Because the NIHs provides grants for all kind of stuff, so then you could get IP which was in part funded by taxpayers. So, therefore, money should go back to the NIH also to the FED. That has never been done, because then it gets so complicated. That you cannot ask the Americans to do that. The American philosophy is more we support you, you make money and then taxpayer revenue comes in anyway. " • "Maybe something that works in Europe, it would be strongly politically by most, at least by the current crazy administration. But I think it would not score very well on either Democrats or Republicans, because you can knock the American way doing business. • "Yes, I think they are extremely useful. Er, there are many more approaches possible, not so much in Germany. In the United States more often, where they are trying to create a PPP between industry and certain university research institutions or even public research institutions. So I think that makes extraordinary sense." • "Yes, in principle, this is definitely an instrument that does no harm. Er, but like everything in life, there are some advantages and disadvantages. Basically, there are certain divergent interests between the industry and the public sector. The researcher wants to publish, of course, he wants to become rich, while the industry wants to get rich, or at least does not want

		to become poor. But yes, it can work, and it is safe (pause; take a breather), it is certainly a path leading to the goal, but not the only one." • "There are other examples, where this was purely driven by academic, and only at the very end someone has put it on a commercial track... The IMI is something special, which always had the constraint ... an instrument where the industry forces the others what to do… The EU has initiatives where it promotes cooperation with companies, where companies can join, but the academic side is stronger. These is normally areas where the industry is not interested. There are federal instruments that provide incentives to participate. For example, we participate there."
	Statements concerning the topic "Collaboration with the industry to develop a Biomarker"	• "No! That would be a PPP; we do not have that. What we do is we collaborate in research collaborations with other departments that develop therapeutics and then have them patented. And there we are trying to test the effectiveness of these substances at a preclinical level, just as early as possible. The diagnostic tests do not always have to be new, that could also be an established test which just needs to be brought together with the new therapy to show that it can help to predict the effectiveness of this therapy, or even to judge later when you perform it." • "The bulk of our third-party funding is exactly that. We also have large institutes, such as the Ludwig-Boltzmann Institute where there is [amount] for four years and so on. Those are all PPP or so FFG, K1 projects or something, or Christian Doppler laboratory, these are all extremely well-sponsored projects in Austria… I also have a lot of board work, and for us, the political component is extremely important to gain the interest of the industry in doing such things." • "Yes, we do that ... we were once part of a study where a companion diagnostic was evaluated, but then, unfortunately, it failed ("ging in die Hose"). That was not necessarily a success story." • "So there are companies who tried to do that... I don´t see this, maybe there is something, like contracting manufacturing. I find it; I hate it because it is so complicated and it takes so long. And if you think about it, for every drug you have to come up with an imaging biomarker, the drug is already there, and then you have to come up with a biomarker. You will never catch up. That's why I think; the mechanism is different. It comes from a clinical need and then it can be a probe that happens and then by coincidence the probe also potentially gets your insight about the drug target. And you start with a drug that would make sense to me. So the other way round." • "I cannot think of anything."
	Statements concerning the topic "How the collaboration with the industry works."	• "It varies from company to company, but I could not say that everything is good or bad ... It depends a lot on the companies because we have partners from the technology industry who do not have that much money. That's a whole different order of magnitude, so you cannot expect Siemens Healthcare to be able to fund big clinical trials. They do not have budgets for those things. They are trying to support us, but not in a huge way. Also because we in Germany are no longer the largest market." • "As far as the pharmaceutical companies are concerned, we have the problem, in some cases that the pharmaceutical companies do not realize that they need to talk to the nuclear medicine doctors. • "Yes, of course. Yes, there are quite a number of companies interested in, for example, labelling their cold products in order to achieve better patient selection for the therapy. Or also, what I already said at the beginning, therapy response, therapy control. How to dose the substance, so many questions of pharmacokinetics, pharmacodynamics, et cetera."
Category Pharmaceutical Industry	***Statements concerning the topic "Benefits and Purpose of PPPs"***	• "All do, all the companies can do that, and all the companies do that. I think the biggest benefit of PPP or any partnerships is that putting the resources together and focusing on issues that are ... that no company can solve. " • "No matter what the context, the main value of that is, it allows us to address issues that are important for the field as a whole, but none of us has the resources to do ourselves. Of each of us is trying to do it ourselves, it is completely inefficient. And there no competitive advantage to doing that. So that is the biggest value: bringing all these people together, focusing on issues of common problems that cross the border to move the field forward to give us the tools we need to." • "[Company name] labs has about 10.000 to 14.000 people, something like that….Most of that in clinical development and regulatory, and all that sort of stuff. …most of that expertise you are pointing out is the critical piece we need for drug development, drug discovery and drug development. And

we are never going to have the expertise of the academic world. So absolutely to be able to tap into the cutting edge expertise which is out there in the academic world is extremely valuable in the PPP. "

- "We don´t have all the expertise internally, so we need to be able to partner as a company... Partnerships are absolutely critical. You cannot do anything without them. That is not something which is unique to PPP. You don´t need PPP for that, that is my point.
- "The kind of things that can be much more difficult is, the (break) they can work out, and there are examples where they do work out, both in the US and Europe. But when there are large groups of companies and academics working together in these PPP (IMI in Europe, FNIH in the US). Those things can work out really well, and those works can also work out that you don´t get much out of it at all. And I think in the end what determines how well it works, how well the academic and private partners their vision is aligned in the important things that have to be done. So it is kind of the same things with the smaller ones, but the more cooks you have, the more complex things get."
- "So I would say we value this very highly. We are very very open to this particular concept of open innovation. We have certainly worked with a number of PP consortia, with IMI in Europe other consortia in the USA as well. And it caused very pharmaceutical areas like liver, brain, number of things we are actually sponsoring. Our time, our resources to really get into the consortia and work with them extensively. ""
- "But there are many many examples Novartis is working with PCs (public consortia) particularly in neuro. So we don´t think we have all the answers and we are working with all the external partners to integrate science as best as we can really. And not just the academics in those consortia, of course, other pharmaceutical colleagues of us from other industries, from other companies. Short answer: We rate this very highly."
- "I co-lead two IMI projects… so this is an area I'm very interested in, and I think there are a lot of misconceptions, mistakes in this area even from people who know a lot better."
- "But now coming on to PPP. The first thing I should say, that IMI is an experiment. It is a 5 billion Euro experiment; it is not guaranteed to work. Historically the drug industry has been very bad a PPP. If you look at other industries: defence, transportation, agriculture. A lot of the R&D risk is shared by the public and private sector. When even in the USA, the Pentagon carries a lot of R&D risk for the defence. In the EU we are very used to the idea that agriculture works in PPP. For historical reasons, the drug industry is very happy to carry the entire risk of R&D on its own. And then get the entire benefit to exclusivity…in comparison to other industries that is a very unusual model. So the idea of IMI is partially based on that the exclusive model that the pharmaceutical industry historically has had might not work forever…So the idea is to try to find a way for the public and private sector to work together. This is an experiment, as you know there are a 100 different projects running under IMI. And to be honest, some will be more successful than others.
- "There are huge cultural challenges in working together between industry and academia. But the idea is to produce tools that everybody can use. So it might be the example that there is a role for generic predictive biomarkers, which could support a number of different drugs. The project I just started, TRISTAN, is developing imaging tools, which be used to predict not drug efficacy, but drug harm. And those, as you can imagine, are many different classes of drugs can cause the same type of harm. We are focusing on a number of different areas of harm. One of which is drug-induced lung disease. Now there are over 300 drugs which cause that harmful effect, so potential imaging biomarkers could sweep a wide range of drug programs. And there will be difficult to protect IP on, so the imaging companies won´t develop them. Drug companies' won´t develop them, just for one drug. So this seems to be an ideal place for PPP."
- "So what we are currently thinking is, that we should develop the tools and then we would expect small business to be commercial it on a non-exclusive basis as services."
- "Different IMI projects there are different reasons for companies to be involved… In other areas companies are working on patient stratification, so they have a better sub setting of patients, and that will support all of their drug development. Sometimes they are developing better clinical assessment tools, again for more precise clinical trials. In other cases, they are developing better assays for toxicology…There are many reasons, why

		drug companies are engaged in IMI, which has nothing to do with imaging at all. "
	Statements concerning the topic "Relationship with Academic and Public funded Institutions."	• "It really comes down to the common interest. We are partnering with academics who are focused on questions and developing things which are relevant to the things we need to do. And we are able to come up with an agreement, this is a specific thing that needs to be done, and there is the focused on it. People actually deliver what is needed, that works out pretty well." • "There are things we appreciate we cannot do alone. Large Datasets… tools and devices we are not going to invent, but maybe someone else is going to invent, and we have to use them. That are those things that work well. What doesn´t work: Maybe the ability to build consensus. What we want to do exactly, across a number of different layers. It is often a difficult thing to achieve. By design, because we all are doing somehow different things… Being clearer about the valuables, and a consensus agreed faster. Because some of these taking four, five, six years." • "The kind of things that can be much more difficult is, the (break) they can work out, and there are examples where they do work out, both in the US and Europe. But when there are large groups of companies and academics working together in these PPP (IMI in Europe, FNIH in the US). Those things can work out really well, and those works can also work out that you don´t get much out of it at all. And I think in the end what determines how well it works, how well the academic and private partners their vision is aligned in the important things that have to be done. So it is kind of the same things with the smaller ones, but the more cooks you have, the more complex things get." • "My experience with [company name]: we put a lot of investment into academia, to develop new tools for us… We funded a number of academic translational projects. A few postdocs here, a few postdocs there. Clinical, methodological trial there and that was useful to us, and it helped us in the development of compounds like [product]. But when I look back at that, I realize that all of our competitors like [company name] and [company name] where funding similar methodological projects with all the academics. And it would have been much better, rather than... say if [company name] spend 1 million dollars on some technology development and [company name] was, and [company name] was, the IMI approach would have been much better. If 10 companies put in 1 million dollars and then IMI matches that with another... 10 million dollars, rather than having a 1 million dollar project you have a 20 million project which would really give you much more robust assays… And the big advantage for the drug companies in there is, that the drug companies are in the driving seat and they can say very strongly "we want you to develop a tool that looks like this because if you develop something like this, it would be very useful to us". And not just a tool, which makes a nice paper in Nature or something like that. The literature is full of tools that have been developed, published, and then the academics move on, and they never cross that translational gaps. So coming back to the Roadmap paper: the job of the drug companies in the IMI project is to kick that academic work across the translational gaps. That does make sense."
Category Radiopharma-ceutical Industry	***Statements concerning the topic "Benefits and Purpose of PPPs"***	• "For me the important thing of academic research or PPP, the important thing is that they are doing clinical trials in a manner that is recognised by regulatory bodies. If this means that they do their studies in a manner that is more likely to get data you can use for regulatory approval, then it would be a good thing." • "Hm, that is difficult. I felt that I don´t have enough experience to answer that, unfortunately. I haven´t been involved. My answer would be that they have not been particularly successful. But I wouldn´t high trust on that answer because I have not been close enough involved. But I don´t believe there weren´t any big successes." • "I think there is a very strong role for academia. I feel that there is, and there will always be a very strong load for academia. And because especially the RP companies rely very heavily on people in the university. They have the expertise, and I think that will continue without a doubt. Obviously, big pharma companies have a large in-house, and they have large organisations, but there will always be a mixture of a private company working with large academic in Europe." • "I am not that familiar with them. I am not aware they do it in the PET business. Maybe in therapy and drugs, but not in the PET business. The FDA is not involved. The last time the FDA got involved was with the Mayo clinic filed for an application for approval for Choline for biochemically

		recurrent prostate cancer and the FDA sort of helped them with their filling, but that was a unique situation that the Mayo Clinic gave up the right to make the Choline."
	Statements concerning the topic "Challenges in collaboration with academic institutions."	• "Er, I guess the probably needs to be a better understanding in the academic community of the difference between having a technology that shows interesting data from non-prospective studies (laughs). So when, for a lot of these agents that look interesting and therapies that look interesting, getting approval for it you need to get back to the drawing board to do a proper dosimetry study." • "I think either the academic community works in a more followed clinical trials process…or that it got an understanding that even you got interesting data in people, you will, actually for the regulators, still have to go through this proper regulatory process. So effectively those initial data what they have done is they de-risked the chance that the therapy works, but they haven´t decreased the total investment you have got to make the product into ah, something the regulator will approve." • "It [Academic institutions] is a fantastic resource for us, actually with the community. And we got loads of collaborations across the globe with different academic communities looking at technologies. So the ideas are fantastic (laughs), and the innovation and ideas are fantastic." • "I think the speed at which the academics work can be a problem. It can be at a slower pace, and also I think that most academic institutions are really in publishing and that can be a tension between the requirement to publish and the requirement to translate. And therefore both sides in a PPP have a different goal, which is not always resolved. If it is a proper risk sharing development of an innovative product that may be different, but I have not been involved in some of those." • "Well, I think fundamentally they have different goals, and you always have to deal with that. The academic institutions are not, in general speaking, not results driven, and not scheduled driven. They are knowledge driven. The businesses, of course, are somebody is giving them money, either they borrow it from themselves or somebody gave them a bunch of money, and they have a timescale, they need to go on the market, and so they are very sensitive to results. They are very focused. They want this result. The academics would be happy with almost any results, right? (Laughs) • "But there is this fundamental alignment issue, not that you cannot work… So once you understand that those have fundamentally different motivations, there can be issues about who owns the co-development. Like a product or a feature or something that is innovative and new which comes out of the working together. Obviously the business wants to have the right to do it and the institution, a lot of institutions especially in the US, have business offices that try to monetarize their research. And they want to get a piece of that deal. So that there is this IP relation, and funding, always funding."
Category Molecular Imaging Techn. Industry	***Statements concerning the topic "*Value and Concerns of PPP"**	**Value:** • "Well, on the one hand, of course, it's attractive because it's a consortium approach, you do not have to pay for everything. It's just a partnership." **Concerns:** • "Concerns are that it is sometimes difficult to get consensus among all partners. We are also involved in a few IMI projects, and you see that the academic side thinks academically, and the industrial partners come with the industrial mind-set into the project. The agreement is not so easy, in the sense that it works for everyone. • "In the IMI projects, we have seen that it is difficult to design the study design to be as rigorous as one would expect from commercial development of an imaging test." • "Closing the gap, yes in a sense, but you should not screw the expectations of the industrial side too high. Well, such an IMI project may be a good way to do some research, but it's not the panacea for developing imaging tests in a different way." • "Well, I can cite the Amypad Consortium as an example ... many academics are interested in researching things that are commercially negligible. Of course, from the point of view of the neuroscience community, they are academically valuable and would lead to good publications ... we're more

		interested in really showing utility, mainstream and influence reimbursement decisions." **Benefits:** • "I'm extremely open-minded ... I actually get a not inconsiderable share of research funds from the pharmaceutical industry." • "Earlier, in the last 5-10 years, we have had IITs, we continue to try, but now it is no longer possible without support from the pharmaceutical industry." • "Yes, if that helps, then that's good. But I always say that when the public sector joins the talk, it often gets complicated… I think the industry is able to see if there is a need or not, and there is an enormous need for prostate cancer in particular." • "Very little, one has heard little that it exists at all." • "I think that is an absolutely important part. And there's nothing wrong with that because, on the one hand, the industry has some interest in monetizing it, but we also have an interest in getting a biomarker, or a diagnostic tool, that supports us and is good… So we both have the same interest. " • "So that's just a normal course of things, the initial invention comes from any academic institution and then the industry is brought on board." • "On the other hand, as with urine markers, it is just as often that something is invented in the laboratories of the industry and they simply need a clinical sparring partner to help them with the clinical evaluation. So it's both ways, and that's absolutely normal." **Disadvantages:** • "The pharmaceutical industry has the legitimate interest to make a profit, but they slightly tried to dominate the study design and the rationale of the study. And I see that as a problem. The particular shortcoming that different companies are difficult to bring together and to work together. " • "It succeeds in many cases, but in some cases, it does not work, and that's a pity." • "…you have to be very critically. Because I have said it before, the sponsors determine what we do. And ... the (research) question you would like to have answered for yourself are actually not funded, but they tell us what we have to do… But you have to question it very critically; you have to say that very clearly." • "We've worked a lot with the pharmaceutical industry because it's actually the only ones that can fund larger studies. Say third-party funds. But more and more the industry tells us what we have to do. This has nothing to do with university research anymore..."
Category Medical Specialist	***Statements concerning the topic "*Benefits, Disadvantages of PPP"**	
Category Regulatory Specialist	***Statements concerning the topic "*Benefits, Disadvantages of PPP"**	• "Now in this sense you are going into subpopulations, small, rare cancers et cetera that is normally the area where collaborations between industry and academia are stronger because really industry then needs the academic, needs centres of references, networks and all of this stuff. And perhaps those could be right, right frameworks for some of these PPP. • "IMI is good at non-competitive stuff, so basic methodology, technology et cetera Now in this phase of the CD I wasn´t thinking immediately on something like IMI, because I thought the companies would be very interested in the certain type of biomarker, a certain type of drug. How can that be non-competitive? But I am thinking of this for the first time, so maybe the answer is a bit superficial." • "I have to pass on that one… But how these initiatives work, I have no idea, too little idea."

xiii. Statements regarding the topic "Research Focus Molecular Imaging" (Chapter 4.5, The Focus in Research and Development and the Future Role of Molecular Imaging, page 162)

Item	Manifestation	Example of literal expressions

Category Nuclear Medicine Physicians	***Statements concerning the topic "Research Focus Molecular Imaging"***	• "... we actually see ourselves as a companion diagnostic, which means we can assign patients to the right therapy based on their biological characterisation of the individual disease." • "So in clinical routine, the focus is still on standard procedures such as glucose metabolism rather than specific (targets) ... so FDG PET is also specific for Gluttransporter and Hexokinase, but ... of course less specific to specific tumours. In case of theranostic, we also have Companion Use with PSMA or DOTA compounds, Somatostatin Receptor Compounds." • "And of course, research is now increasingly moving in the direction of visualizing and quantifying very specific, drug-relevant targets. Including modern developments such as immune checkpoint inhibitors or things like PDL-1, PD-1. There are already compounds available for CXC4 or chemokine receptors. But this is the path taken in research, relatively little is translated into the clinic." • "It is quite possible that FDG PET will continue to be a very important pillar ... but the next area where PET prevails or will solve a lot is neurology, but it also the cardio area ... "" • "Alzheimer's will cost mankind a lot of money ... And I think you'll have to use a CD. And that's why the topic of neurological dementia ... is an important field of research." • "So for neuroendocrine tumours, there is still room for research and optimization right now, but I would say 90% of all initiatives are currently focused on prostate cancer. And the success of PSMA, both in imaging and therapy, that's just, you cannot choose any other word for it, as "fabulous" ... And there is of course still research on even better ligands, on combinations with different therapy nuclides be it Lutetium or Actinier ... I think that will be one of the priorities in the next five years. Henry Wagner ... the forefather of nuclear medicine once said: "FDG is the molecule of the century" and I would say "PSMA is the molecule of this decade", at least for nuclear medicine ... And in the forefront of the success of Theranostics and the therapy, of course, enormous efforts are now made to establish further target structures, which are suitable for the theranostic approach. For me, this currently covers three areas: breast cancer, ... lung cancer, third is colon carcinoma and fourth ... pancreatic adenocarcinoma." • "So there is a lot going on, of course, very difficult to say at this stage who will be ahead and what will be the next successful target structure. But there are already a few candidates who are really hot, yes." • There are several tendencies: ... for a while, there were doubters who thought the therapeutic application in the NUK has no future. Which cannot be said any more today... PSMA is a very promising therapy ... But there are also a lot of other companies ... that initiated controlled studies. The PSMA found its way out of academia, but there are some radioactively labelled antibodies, or some alpha-therapies, where small, but also large players in the pharmaceutical sector, invest a lot of money." • "The diagnosis is... (pause) Er, one hears very different opinions. I have recently heard the opinion of radiologists who thought that you no longer need FDG anyway and thus PET. Certainly, FDG has taken its place and it will be expanded here or there, and perhaps there are alternatives which will limit its use."
	Statements concerning the topic "Is the future in PET or SPECT?"	• "I see it in PET. Simply because you're more flexible with the labelling capabilities, and I think it's easier to attach a positron emitter to a biomolecule. SPECT emitters are just such big atoms that it's not that easy to (radio-) chemically attach the imaging signal so close to the target mechanism of treatment." • "And the problem with the PET radioisotopes, which are relatively short compared to the SPECT, I consider no problem. I believe that the availability of PET is not really a problem, at least in Germany. Not even in the US, I do not think that's a problem in any industrialized nation." • "If you had asked me 2 years ago, then I would have propagated SPECT even more, but my euphoria slowed down a little bit. Because ultimately it is crucial how sensitive the procedures are. Thinking about Companion Use and the preparation for radionuclide therapy, then I could imagine that it is sufficient to use SPECT to detect the target. But if you think about in-vivo tumour characterisation, the characterisation of the tumour biology or applied systems biology or something like that, then you do not get very far with SPECT." • "So the question is, how the technologies will evolve from the point of reimbursement ... that is difficult to predict because there is a political and supply component. But generally speaking of the technology and the

		upcoming development, I am also pretty sure that it will increasingly be PET-based." • "To the question of the availability, where possibly the PET, in comparison to the SPECT, has a disadvantage. I see a political and supply component.... Insofar SPECT is naturally also on the table since there are no reimbursement issues and also has advantages in availability. And that stands or falls with the industry commitment ... And, of course, some companies will probably focus more on SPECT, others more on PET when thinking about companion use. It will depend a bit on what technology will be implemented. Also, SPECT technology is improving, moving towards Cadmium–zinc–telluride digital detectors, maybe also ring detectors. Let's see what else is coming, but of course, PET is already much more accurate." • "Clearly in PET. SPECT, that's nonsense you have to be clear. Of course, it's easier and more accessible, but it's anachronistic! You have to move to PET, that's just the rethinking. You cannot work with a "Volksempfänger" if you could have a flat screen. That's of course nonsense. If you look at it short-sighted, to get it expanded quickly, you can think about SPECT. But if you want to go to a high level, you have to push PET and not SPECT." • "No, no, you can forget about SPECT. In this case, I'm brutal. But that's very striking." • "Interviewer: Interview partners from the pharmaceutical industry believe that PET is not interesting for them because it's simply globally not available. SPECT already! Interviewee: Yes, but the pharmaceutical industry does not understand imaging. If you would build me a SPECT scanner, which first is as quantitative as the PET, secondly has the same spatial resolution and thirdly produces tracers with equal good properties as the PET Tracer, then I am ok. But the worldwide availability of PET scanners is already on the rise. I understand that the argument of these pharmaceutical people is correct, but I do not see that practically." • SPECT will remain important for cardiac imaging and some other clinical indication. The future is PET!" • "If so, perhaps SPECT-CT will have a certain chance, again in the wake of substances that have already been successful in PET/CT. An example is, e.g. So-called technetium-labelled somatostatin analogous ... It is also called the PET/CT of the poor man, yes. (Laughing). The advantage is that these SPECT tracers can be billed in the outpatient area because there is an existing billing structure. The colleagues in the outpatient area can thus use the substances. The same is true for technetium PSMA... But I think a big success will continue to be PET/CT." • "Of course, when one looks beyond the borders of Germany, to the developing countries or to countries with less economic wealth, such as India or even China ... Of course, PET-CT will take a long time to get established, whereas SPECT or SPECT-CT is already routine in many nuclear medicine institutes. And thus, of course, there is a potential for technetium-labelled markers. But a real future, especially with regard to research and new development, I simply see PET/CT on top." • "SPECT will definitely play a role ... still purely because of capacity. If you look at it globally, SPECT has probably 10 times more capacity than PET ... Of course, PET has technological advantages, such as sensitivity and resolution for certain applications. For PSMA, PET has clear advantages, because the resolution creates a benefit. But there are applications where resolution is not what matters most."
Category **Pharmaceutical Industry**	***Statements concerning the topic "Is the future in PET or SPECT?"***	• " When the drug company is developing the drug it's developing it for a global market. So when [company name] is developing they're not just thinking of, certainly they think if you can sell it in the United States and EU, they are also thinking about China, Philippines, Brazil, Indonesia. These are important markets! If you going to have Diagnostic in your label you want to make sure it is available in every hospital in China, Philippines, Brazil otherwise you would not sell this drug. From that point of view you have PET agents... at least..., carbon is out of the question, fluorine can be challenging because of the half-life. Technetium is much more attractive. Gallium obviously with PET is more attractive, because you can use a generator and a nuclear medicine department can make it locally. And if I were looking developing a personalised healthcare compound, I would be very cautious about the fluorine agent." • "I will give you some figures, they may not be that accurate, and there is a general truth behind them. I heard it said, that for every PET scan that is performed in the world ten SPECT or scintigraphy scans are performed, and for every SPECT or scintigraphy paper there are ten PET papers. Those

		numbers may not be exactly right, but there is a truth behind it. That scintigraphy and SPECT are not sexy, whereas PET is incredibly sexy. PET is also expensive and so if you are an academic and you do have a PET facility you need to turn out a lot of papers. And if you are a young academics, like yourself, probably you think it's sexier to be in PET rather than SPECT."
Category Radiopharma-ceutical Industry	***Statements concerning the topic "Research Focus Molecular Imaging"***	• "...develop imaging agents for cancer. And so far we have been successful with one of those products. So we have been going through clinical trials to develop a product for prostate cancer, called [product name]. And we had that product approved in the US and Europe. And we think that agent has potential applications in other types of cancer too." • "Okay, so I would say that the mission of [company name] is to develop theranostic platforms so drugs which have both a diagnostic and therapeutic component, which is shared. Not necessarily identical compounds, but they are shared. So that the personalised medicine is essential, that patients who benefit from a therapeutic agent are identified by the diagnostic component."
	Statements concerning the topic "Is the future in PET or SPECT?"	• "Yes, that is a good question. Actually, because SPECT I think there will be research in SPECT and there is a whole lot of, you know there is a much wider uptake in SPECT than there is PET. If the real value of SPECT is going to be realized when SPECT/CT is available. I kind of think that SPECT/CT would be better than SPECT and most of the operators around SPECT and not SPECT/CT, because SPECT/CT explosion hasn´t happened yet, has it? If you factoring the costs of delivering the scan and the availability, SPECT/CT seems promising. But it suffers from access more than PET/CT, where SPECT there is no real access issue with SPECT, is there. But maybe that does not deliver the actual promise of SPECT as technology. And we only get the real promise of SPECT as a technology, but we have SPECT/CT everywhere." • "I think SPECT is definitely still an option. So the difference between SPECT and PET is based around the resolution, the spatial resolution of the imaging device. Not necessarily based on around basic physical properties. So if the SPECT cameras become more sophisticated as it appears they are, then I think SPECT and PET will have a role to play. And ultimately spatial resolution for a given price will determine how much SPECT and PET, not necessarily one or the other but rather how cheap the camera is for a given spatial resolution." • "Both are adequate, and given the cost circumstances both will remain, but PET will grow in the future. The opportunity to modify small molecules without significant influence on biodistribution is a clear advantage. With Fluorine the supply chain is already there."
Category Molecular Imaging Techn. Industry	***Statements concerning the topic "Research Focus Molecular Imaging"***	• "Well, I would say current mission and objective is the development of (pause) it is actually more (break) I would say the safety and efficacy is now self - evident, but the mission actually goes further in the utility of diagnostic tests. Because it is clear that safety and efficacy are not enough to bring diagnostic products on the market, get reimbursement and integrate them into the appropriate patient management. So currently the objective is to perform much more advanced phase III studies. We have to think about utility and of course health economics in the development of such products. " • "... since then, we have focused more on Life Cycle Management and push projects in the R&D pipeline, which are already more advanced in the development stage, so in Phase II or III. And in terms of personalised medicine, we initiated a study with an "old-fashioned" product ... to see if [product name] can predict that a patient needs a defibrillator (ICD) or not." • "Unlike as in CT and MRI, in MI when you want to expand the clinical indications it´s is generally tracer driven and probably requires a new specific tracer for that clinical area you want to go pursue... So and those new tracers might or might not drive something on the technology side… One example we had to do in the brain with the Alzheimer´s tracers …all the vendors came up with software to make that job easier, on linking the grey matter uptake of the amyloid tracers for Alzheimer disease relative to your reference region. So there was another case where the medical case, in this case, the software and to adapt to the tracer." • "Yeah, we do little investments… we do quite a bit of clinical trials for others, but we don´t charge them for the costs of things. It is sort of a small side business for us with the hope to get some more tracers on the market. And then we make investments in like; we gave support to the SNMs

		clinical trials network on getting the Gallium PSMA project moving. So we do funding of others we think are worth…"
	Statements concerning the topic "Is the future in PET or SPECT?"	• "So I would say that still ... we see the future in both areas... PET is a tough market but has a future because certain PET tracers will rather be produced than SPECT tracers. Purely from the technical view. On the other hand, PET is problematic ... because you either need your own infrastructure ... or you work with local partners ... There are also certain countries where SPECT has, aside from the big cities, advantageous logistics compared to PET. And because of the CZT solid-state detectors, the resolution in SPECT approaches the resolution of PET." • "And I think PET will continue to grow, but I think even SPECT… We traditionally still have more tracers in SPECT so, PET we just had one or two you know in the beginning and SPECT had ten or fifteen, depending on where you are. So that there was less need to expand the tracers for SPECT. But even in SPECT, there is a new prostate imaging agent coming, so SPECT will see some growth in prostate imaging. But most of the growth in our field will happen in PET in the future."
Category Medical Specialist	***Statements concerning the topic "Future innovative therapeutic management/ drugs."***	• "I think the next best step is risk stratification and I'm totally open for whatever tools we're going to use. Then the next step must be to treat biologically adaptive, big keyword: personalised therapy. That are the two big steps which have to come into our area [lymphoma] and will come because there are too many people working on it." • "So in prostate cancer, if imaging gets even better, focal treatment for prostate cancer may play a significant role. Such as brachytherapy, local photodynamic therapy, HIFU (High intensity focused ultrasound), or such treatments. I don´t see drugs in local therapy; there will always be physical energy applied, which irradiates the tumour locally.... Otherwise, at an advanced stage, the individualized target therapy will play a role." • "Ultimately, in 40-50 years, probably the entire treatment of cancer can only be handled with some supportive additional artificial intelligence. There will be so many markers, genetic markers, protein markers, the devil knows what will play a role, and from the whole hodgepodge of thousands of information and combination options, you have to find out the best therapy. And also the definition of what is the best therapy will not be feasible with clinical studies anymore ... maybe some kind of artificial intelligence has to do this task." • "I cannot say which way it is going. At the moment it looks like it's going into immunotherapy with the checkpoint inhibitors." • "What is also generally en vogue is the immunotherapy ... So the keyword is PDL-1 inhibitors, et cetera. This is a brand new drug class that is just very in vogue. But I think the big keyword of the future is the topic of liquid biopsy ... but also in general, to come back to the subject of nuclear medicine, the keyword theranostic is already big in the trend, high in the class." • "... for me, a 2-month gain in life is not the total breakthrough. For oncologists it is, and they are trying everything ... Probably the future will be in combination therapy. But I'm honest; we don´t know yet. And it's true that it's mostly triggered by industry. What annoys me... What keeps me so excited about these things is that ... We're investing millions and billions into metastatic patients, instead of putting a few million into prevention and early diagnosis and cure those patients with surgery or something else. Nothing happens here anymore. "
	Statements concerning the topic "Will Molecular Imaging have a role in new, future therapeutic strategies?"	• "Absolutely yes." • "My assessment is that functional imaging is evolving just as well ... but what I've seen so far is fascinating ... secondly, I think MI will continue to evolve as much as we do (IVCD). Many people are probably not yet aware that we even save costs. If we can use functional imaging, and / or other methods, to save patients from unnecessary therapies, or stop meaningless and start more meaningful therapies, that certainly also makes economic sense." • "So for prostate cancer, if imaging gets even better, focal treatment for prostate cancer may play a significant role." • "Yes, a very big one, the imaging is getting better and better and better and better ... That will go on, I'm sure." • "It depends on the topic of treatment and if you have a biomarker that is good enough that the concentration of the biomarker tells us" ok, does the patient have a response or not? ". … then you could do without the imaging diagnostics. If, however, the patient has any consequence because

	of the localisation of the tumour … imaging with corresponding sensitivity and specificity is still indispensable.”

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