Companion Diagnostics Development and Commercialization

A Case Study from the Diagnostics’ Perspective

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Abstract

The value proposition of Personalized Medicine is to deliver the “right drug, to the right patient, at the right time”. Companion diagnostics is the required tool for Personalized Medicine used to aid clinical decision making with the aim to identify patients who are most suitable for a given treatment approach and to avoid adverse effects. However, even 16 years after the first co-approval of a therapeutic drug and an associated diagnostic test (trastuzumab (Herceptin1) from Genentech and the HercepTest1 from Dako), the co-development and co-approval of drug-diagnostic pairs is a challenging task.

This study has the aim to identify major challenges for diagnostics companies when developing and commercializing companion diagnostics. This is achieved by (1) a literature research and (2) an empirical case study in form of interviews with diagnostics companies. The collected data is analyzed and discussed with focus on current regulatory and reimbursement frameworks in the USA and European Union. The co-development strategies and business models of companion diagnostics developers are identified.

The conclusion of this study is that the major hurdles for companion diagnostics development and commercialization are gaps in scientific evidence and lacking regulatory guidelines for co-development and clinical biomarker studies. Companion diagnostics commercialization is further challenged by poor reimbursement levels. The main strategy of diagnostics companies to address these challenges is the demonstration of a beneficial outcome for patients in form of clinical studies. Small companies with limited resources for clinical research receive funding from academic research grants, patient support groups, pharmaceutical industry, and governmental Innovation agencies.

Finally the formation of a new “pharma-diagnostics” sectoral innovation system as a result of the emerging paradigm of stratified medicine has been proposed.
**Key-words:** Companion diagnostics; in-vitro; EME; FDA; Stratified medicine; Biomarker, Clinical utility, Medical Devices

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<th>Abbreviation</th>
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<td>510(k)</td>
<td>pre-market notification</td>
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<td>ADR</td>
<td>adverse drug reactions</td>
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<td>AMCP</td>
<td>Academy of Managed Care Pharmacy</td>
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<td>CBER</td>
<td>Center for Biologics Evaluation and Research</td>
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<td>CDx</td>
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<td>CE</td>
<td>Conformite Europeenne</td>
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<td>CETSA</td>
<td>Cellular Temperature Shift Assay</td>
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<td>CLIA</td>
<td>Clinical Laboratory Improvement Amendments of 1988</td>
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<td>CMS</td>
<td>Center for Medicare Services</td>
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<td>CRO</td>
<td>Contract Research Organization</td>
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<td>diagnostic-related group</td>
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<td>Health Technology Assessment</td>
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<td>IMDRF</td>
<td>Medical Device Regulators Forum</td>
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<td>IPR</td>
<td>Intellectual property rights</td>
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<td>IVD</td>
<td>in-vitro diagnostics</td>
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<td>LDT</td>
<td>Laboratory Developed Tests</td>
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<td>MRI</td>
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<td>NGS</td>
<td>Next generation sequencing</td>
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<td>NICE</td>
<td>The National Institute for Health and Care Excellence</td>
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1 INTRODUCTION

1.1 The productivity crisis of pharmaceutical R&D

During the last decades there has been immense progress in science and technology, which should have a positive effect on the output of commercial drug research and development. Examples are the development of combinatorial chemistry (Hogan, 1997), the advances in DNA sequencing technologies (Meldrum et al., 2011) and high throughput screening (HTS) (Mayr and Fuerst, 2008). Other research fields with great importance which have developed are biotechnology, computational drug design and screening, and the increased accumulation of scientific knowledge including the elution of disease mechanisms and the discovery of new drug targets (Mittra and Milne, 2013). The management of the drug R&D process has also been refined in many disciplines (Joglekar and Paterson, 1986), including R&D portfolio management (Paul et al., 2010), costs reduction by outsourcing and management of the requirements of the regulatory authorities (Health et al., 2005).

Nevertheless it has become more and more difficult to discover, develop, and commercialize new products which can compete with existing products, (Mittra et al., 2011). This is due to problems in meeting regulatory requirements regarding safety, and that products have become too expensive to produce. Further on new developed therapeutics are not cost-efficient enough to meet the payer’s demands.

There is a productivity crisis. Increases in R&D investment have not resulted in an healthy output in form of product approvals (Mittra, 2008). The number of new drugs introduced to the market as compared to the increasing R&D expenses, has declined continuously (Scannell et al., 2012).

These problems have led to increased efforts of companies to increase productivity including mergers, acquisitions, spinouts, divestments, out-sourcing, more targeted pipelines, increased focus on translational medicine and organizational restructuring, and stratified medicine and biomarkers (Huckman and Strick, 2010, Ledford, 2011, Mittra, 2008). Pammolli et al claim that the pharmaceutical R&D productivity is suffering from R&D investments in highly risky disease areas, predominantly chronic diseases with the outlook of high reward (for example, Alzheimer’s disease, chronic obstructive pulmonary disease, diabetes, obesity, depression, multiple sclerosis and rheumatoid arthritis). These areas are risky because most chronic diseases are almost impossible to reverse or cure. But it is rational for investors to aim to achieve market exclusivity in difficult areas, with a higher expected return instead of in a low-risk but highly crowded market. (Pammolli et al., 2011). Many of these failures occur in the late phases of clinical development due to safety and efficacy issues.
1.2 Stratified medicine, a new business model

In the recent years there has been a growing interest from the scientific community and medical care professionals in personalized medicine. Stratified or personalized medicine has been valued to have a high potential with advantages over traditional medicine. Stratified medicine combines genomics and new diagnostic tools, which detect biomarkers. This is also termed personalized medicine but the term “Stratified medicine” is more correct by specifying that patient groups are targeted rather than the individual patients (Mitra and Tait, 2012).

Numerous studies show that there is a considerable variability response to drug treatments of individual patients. This can be explained by variation in disease heterogeneity, behavioral and environmental characteristics, and by variations resulting from individual genetic makeup (Pirmohamed and Park, 2003). Patients’ genomes have been shown to be accountable for 20–95 % of the variation in drug deposition. This is leading to significant variations in the clinical outcomes of individual patients treated with the same drug (Tang and Endrenyi, 1998). In addition, variations in drug deposition can lead to more severe adverse drug reactions (ADRs) in some patients due to differences in the bio-availability of the drug. ADRs accounts for drug-related morbidity and mortality in the US with costs estimated to exceed US$177 billion (Miller et al., 2011). In the US over two million patients are hospitalized every year as a consequence of drug-related serious adverse events (Lazarou et al., 1998).

However, the most common present treatment practice is largely based on an empirical or ‘trial and error’ approach. Drugs are prescribed for large patient populations, and the response of both the drug and overall patient population is predicted by the average probability of drug effectiveness. This approach is generating huge costs to the health providers, as a consequence of inefficient prescribing practices and a potential for serious adverse events in significant numbers of patients. In contrast, stratified medicine creates individualized models of drug use, in which drugs are prescribed for highly targeted populations based on pharmacogenomics and other medical or behavioral characteristics. Overall thirty to fifty percent of R&D drug projects are linked to biomarker with an expected rise in the future (Davis et al., 2009).

While stratified medicine offers the potential to revolutionize therapeutic interventions for physicians and patients, there are several challenges regarding the development and commercialization of stratified medicine. These obstacles include uncertainties regarding the relevant industry sectors involved, regulatory policy making and adaptation by the healthcare system (Hughes, 2009). Therefore engaging in stratified medicine is considered a risky business with no potential to fully replace conventional strategies (Ferrara, 2007).

1.3 Companion diagnostics

Companion diagnostics is used to identify patients who most likely respond to treatment. This can help to avoid adverse effects for patients who are unlikely to respond to treatment. Companion diagnostics can also aid to identify patients with a higher risk to develop side effects
towards a certain treatment. These diagnostic tests are becoming increasingly important as more new pharmaceuticals have indications that make the use of a diagnostic test necessary to determine the appropriate patient subgroup for treatment. Thus companion diagnostics is an essential part of stratified medicine because it can play an important role in drug development and for safe and effective personalized treatment. As pictured in Figure 1 the aim of companion diagnostics (CDx) is to identify the patient subgroup suitable for treatment with the corresponding pharmaceutical. This enables stratification of patients who are likely to respond to the corresponding treatment (A, orange box) and patients who are unlikely to respond to the treatment (B, red box) (Byron et al., 2014). Moreover, CDx-guided stratification helps to avoid adverse effects from the treatment in patients unlikely to benefit or with a higher risk of developing adverse effects.

The majority of companion diagnostics are in vitro diagnostic tests that detect the levels of protein or gene expression or identify specific genetic mutations. The test results will inform the clinician whether the stratified medicine is suitable for the patient (Byron et al., 2014) (See appendix for a list of the most common in vitro assays technologies which are commonly used as pharmacogenomics companion diagnostics in the field of oncology). The diagnostic test result is critical for the appropriate use of the therapeutic product since analytical inaccuracy could lead to misidentification of patients who will benefit from treatment. Vice versa patients could be treated without a resulting benefit risking toxicity of the drug. For certain drugs the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend biomarker testing before prescription (Abrahams et al., 2005).
1.4 Aim and Research Question

Diagnostics companies in the field of companion diagnostics (CDx) are dependent on a variety of stakeholders. These include pharmaceutical companies, regulatory agencies, payers, the clinical labs, physicians and the patients. All stakeholders have impact on CDx development in a variety of ways. This study is focusing on the regulatory, development, and business challenges which diagnostics companies face when developing and commercializing CDx. The principle research question which is guiding this study can be formulated as:

“What challenges do diagnostics companies face when developing and commercializing companion diagnostics?”

For clarity the research question can be subdivided into the following topics:

- How do current regulatory and reimbursement practices affect companion diagnostics development and commercialization?

- How is companion diagnostics development aligned to the drug development process in co-development partnerships with the pharmaceutical companies?

- What business models are used by the IVD companies to gain market access?

To guide the data collection an innovation theoretical framework, described in the next section, was used.

2 THEORETICAL BACKGROUND

This section discusses the concepts of innovation systems (IS) and co-evolution which are used as theoretical approaches in this study. The sectoral innovation system will guide this study as a theoretical framework with the aim to identify the key stakeholders which influence companion diagnostics development and commercialization and to characterize how relationships between diagnostics firms and other firm and non-firm organizations effect companion diagnostics development and commercialization. It will be interesting to examine to what extent current interactions, between regulatory agencies, the pharma and diagnostics industry, and the health care system, create opportunities or barriers for the development, diffusion and use of companion diagnostics in stratified medicine.
2.1 Innovation system approach

The theoretical framework that is used is the innovation system (IS) approach. The approach emphasizes the relationships between the elements of innovation processes and has a systemic view of these processes. Such approaches are understood as interactive with bi-directional learning feedback loops between market and R&D (Kline and Rosenberg, 1986, Dosi, 1988). By defining the boundaries scholars have been able to differentiate between systems with different focus. Besides the national innovation systems, which is defined geographically (Lundvall, 2010), the most important systems of innovation are the technological systems with focus on interactions in a shared techno-economic system (Carlsson and Jacobsson, 1997), the regional innovation systems (Cooke, 1992), and sectoral innovation systems with focus on industrial sectors as source for innovation (Breschi et al., 1997).

The chosen system of innovation for this study is the sectorial innovation systems approach. It is a useful theoretical framework, as it describes the interaction between different actors. In general a comprehensive description of innovation processes demands the consideration of different actors and how they interact. This is in particular valid for the sector of medical devices and pharmaceutic products since innovation processes in these industries involve a variety of firm-and non-firm organizations, policy agencies, institutions and research organizations.

Malerba (Malerba, 2002), defines a sectoral system as:

“a set of products and the set of agents carrying out market and non-market interactions for the creation, production and sale of those products. A sectoral system has a specific knowledge base, technologies, inputs and demand. Agents are individuals and organizations at various levels of aggregation. They interact through processes of communication, exchange, cooperation, competition and command, and these interactions are shaped by institutions. A sectoral system undergoes change and transformation through the co-evolution of its various elements” (p 250).

From this definition it is evident that the innovation and development process of medical devices and pharmaceuticals can be readily captured by a sectoral system approach. These sectoral systems consist of a wide variety of science and engineering fields which have a renewing effect on the research space. The different industrial actors are connected through networks and business relationship of various types. These networks include large firms and small firms, which are involved in different fields, like pharmaceutical, biotech, and medical devices. Innovation depends on a high number of organizations and institutions, including universities and public and private research organizations and investors. The demand and market authorization is controlled through the health system, regulatory agencies, and national legal systems.
The concept of the sectoral innovation system is based on a theoretical background, which includes change over time, and therefore is subjected to the laws of dynamics and transformation. This aspect of industrial dynamics and product life cycles has been described in detail in the literature (Utterback, 1996, Klepper, 1996) and goes back to the analyses of the long-term evolution of industries (Schumpeter, 1939, Kuznets, 1930).

A second important element for the definition of sectoral systems is the introduction of interdependencies and sectoral boundaries. The observation that sectors can develop links between related industries and therefore boundaries are not static but have the ability to change over time (Malerba, 2002) has importance for the study of interactions in stratified medicine. The concept of the innovation system as an interactive process is another important part of sectoral innovation systems and of high importance for this study. The message is that firms are not able to innovate in isolation. Innovation can be regarded as a collective process. The innovation process requires interaction between firms and other organizations such as universities, governmental agencies and other non-firm organizations (Malerba and Nelson, 2011, Lundvall and Johnson, 1994, Carlsson and Stankiewicz, 1991, Edquist and Johnson, 1997).

Firms are the main focus of the empiric part of this study and can be regarded as the key actors in a sectoral system (Malerba, 2002). They are the motor for innovation, production and commercialization of sectoral products, and play an important role in the generation, adoption and use of new technologies (Dosi et al., 2001, Nelson and Winter, 2009, Metcalfe, 1998). Furthermore heterogeneity of firms defines a sectoral system. The medical devices sector, including in vitro diagnostics companies which are the focus in this study, show a high level of heterogeneity with respect to firm size, maturity grade, and technology/product. This study will take into account different firm sizes by choosing established global acting companies and small companies in the start-up phase as study object.

As mentioned before, sectoral systems also include non-firm organizations. They have an effect on innovation, diffusion and production. These effects are different among different sectoral systems. This study will focus on the roles of the non-firm agents, mainly regulatory policy makers, in the theoretical part of the results in the format of a literature review. It is noteworthy and of importance for this study that the relationships between firms and non-firm organizations is of high relevance for innovation and change in the sectorial system (Nelson, 1993).

It is also important to mention the role of institutions in sectoral systems. Of major importance is the relationship between national institutions and sectoral systems. This includes the impact that national institutions have on specific sectoral systems (Levin et al., 1987). This is relevant for this study because changes in the regulatory and reimbursement policies on a national level with respect to stratified medicine could have different consequences for the pharmaceutical (therapeutic) sector and the diagnostics sector.
There are examples of cases in various advanced countries where national institutions put constraints on the innovation capacity in specific sectors. This can be due to mismatches between national and sectoral institutions and the elements of the sectoral system (Dosi and Malerba, 1996). It has been discussed in the literature that not only industrial actors may obstruct a functional innovation system, but also institutions and networks. An example is product development for the medical device or pharmaceutical market. Here marked entrance may be delayed by regulatory issues, leading to a lengthy diffusion process from the lab to the market (Carlsson et al., 2002).

3 METHODOLOGY

3.1 Study Design
As previously mentioned in the aim, this study will explore the challenges diagnostics companies face when developing and commercializing companion diagnostics. The study can be divided into two parts. The first part collects secondary data in form of an extensive literature review. The second part of this study is empirically gathering primary data from interviews with leaders in IVD companies who are familiar with or have an interest in companion diagnostics.

Since the literature review is limited to describe and collect existing information, this part of the study can be classified as descriptive research. Furthermore the study will also contain analytical research elements since it takes the firm perspective to understand and analyze the strategic choice of IVD companies.

The research process is based on the collection of qualitative data as found in the literature and from interviews. The collected data is then analyzed by interpretative methods (Collis and Hussey, 2013). The logical structure of this study is centered on a more general framework of factors which originate from triangulation of both findings from the literature and empirical data from interviews. It can therefore be classified as a combination of a deductive and an inductive approach (Carson and Coviello, 1996).

In order to develop specific interview questions innovation theory literature in general and innovation system theory specifically was consulted. Based on a reading of the innovation theory literature the innovation system theoretical framework was used as described in section 2.

3.2 Literature Research
Secondary data is collected in the literature review with the aim to provide an in-depth knowledge about the main regulatory and economic factors that affect the business of
companion diagnostics. The review includes articles from different journals, books and other published types of works. The literature landscape at Web of Science (Thomson Reuters), Science Direct (Elsevier), Scopus (Elsevier) and PubMed (NIH) was explored on a regular basis during the conduction of the study. The findings from the literature review were used to develop a framework in order to address the research questions. Furthermore the literature review also helped in the formulation of interview questions for the case study.

3.3 Interview
As this study will include data from actual companies and their strategies in developing and commercializing companion diagnostics, data will be presented as separated cases. The qualitative case study is a way to explore a phenomenon within its context using a variety of data sources (Baxter and Jack, 2008).

A case study is suitable when the study is designed to answer “how” and “why” questions; the researcher considers the contextual conditions as relevant to the phenomenon under study; or there are no clear boundaries between the phenomenon and context” (Yin, 2013).

In the second part of this study a qualitative case study method will be applied to collect in-depth information necessary to answer the research questions. A holistic approach to describe the business strategies of diagnostics companies with respect to companion diagnostics is deemed a valid research method since the external effects of industrial partnerships and the regulatory and economic environment are clearly beyond the influence of the researcher. The chosen selection criteria for companies had the aim to identify and include established global players in the in-vitro diagnostics (IVD) market with companion diagnostics products in the portfolio as a first target group. In order to get a wider perspective the second target group were small molecular diagnostics startup companies who strive to enter the companion diagnostics market, which could be identified in the Karolinska Institutet Science Park in Stockholm, Sweden.

The case study is conducted in form of interviews in a semi-structured format, which is a valid method for collecting primary data (Collis and Hussey, 2013).

3.4 Analysis of research results
The collection of secondary data in the literature research is used as an initial method of research. The information and findings from the literature review cover the perspectives of the various stakeholders and pictures the regulatory and commercial environment of stratified medicine. The information from the semi-structured interviews will give a picture on how IVD companies have adapted to the various uncertainties and issues facing the industry with regard to the development and commercialization of companion diagnostics. There will also be a focus on the size and maturity level of the companies included in the case study and how these
factors influence the choice of strategies for development, approval and market access. The analysis aims to identify and analyze information extracted from the literature and then triangulate those findings with the empirical findings of the specific real-word cases.

### 3.5 Ethical Considerations

The procedures for the interviews are clearly explained to interviewees before the interview proceed. The interviewees will be supplied with written interview guidelines that include the interview questions beforehand. The location of the interview has been chosen with agreement of the interviewees. Interviewees are not named without explicit permission. The interviewees have been given the opportunity to review the notes taken from the recorded contribution, which should be used in accordance with the wishes of the interviewees. The interviewees have been informed that the material is to be published or preserved as a public resource, and the permission has been given.

### 3.6 Limitations and Feasibility

The interviews will include global operating in-vitro diagnostics companies as well as small diagnostics developers geographically restricted to Sweden with main focus on the Stockholm area. Therefore this study will not catch regional differences regarding the interview outcomes. The interviews will give an insight on existing opinions, views, beliefs and reflections and hopefully current strategies and therefore valuable information on how the industry operates with respect to the research question. It is not possible to generalize results based on a qualitative study on a small number of respondents (Polit and Beck, 2010). A generalization of the findings to the whole industry and to all companies is therefore not suitable. The data collection depends on the willingness of disclosure information of professionals to be interviewed, which is a natural constraint on data that can be collected.

Finally the data collection is dependent upon the willingness of professionals to be interviewed, which is a natural constraint on data that can be collected.

### 4 RESULTS

As mentioned in the study design (section 3.1) this study can be divided into two parts. The first part collects secondary data in a literature review. The second part of this study is empirically gathering primary data from interviews with leaders in in-vitro diagnostics companies who are familiar with or have an interest in companion diagnostics.
4.1 Regulation of companion diagnostics
Since the approval of the first diagnostic pharmaceutical pair (trastuzumab HercepTestTM, Dako) in 1998, the US Food and Drug Administration (FDA) has taken the initiative in defining the standards for the companion diagnostics CDx regulatory pathway. The FDA’s efforts to define the regulatory landscape for CDx have also guided authorities and regulatory professionals worldwide. For that reason this section will focus on the FDA perspective of CDx regulation to illustrate the principal concepts and then point out the differences to the European regulatory framework set by the European Medicines Agency (EMA).

4.1.1 The regulatory policy in the United States of America
The different forms of approval required by the FDA before marketing of a medical device depend on risk classification. Medical devices are classified in risk classes I, II, or III. This also includes in-vitro diagnostic tests.

Premarket approval (PMA) is the process the FDA uses to evaluate the safety and effectiveness of Class III medical devices. Class III devices are needed to support or sustain human life, prevent impairment of human health, or have a potential, risk of illness or injury. (Food, 2013). PMA is the most stringent approval process required by FDA. The PMA process requires demonstration of safety and effectiveness through “adequate and well-controlled” clinical trials (Food and Administration, 2012). The majority of companion diagnostic tests have been categorized as high risk class III devices.

According to the FDA (Food and Administration, 2012) marketing of a Class I, II, and III device in the US with intend for human use, in the case that Premarket Approval (PMA) is not required, demands submission of a 510(k) to FDA unless the device is exempt from 510(k) requirements of the Federal Food, Drug, and Cosmetic Act. The 510(k) process applies to most Class II medical devices sold in the US and a small number of Class I and a small number of Class III devices. 510k premarket Notification requires that a new model of a device is compared for safety and effectiveness with another lawfully marketed model (that is not subject to PMA). A successful 510(k) submission results in FDA permission to market the new device (clearance). The Code of Federal Regulations Title 21 Subpart E describes requirements for a 510(k) submission (Food and Administration, 2011a).

To understand the challenges which are connected to the development of companion diagnostics it is useful to have a look at the FDA definition of companion diagnostics from 2011 draft guidance on in vitro companion diagnostic devices (Food and Administration, 2011b). The draft guidance stated that companion diagnostic devices are essential for the safe and effective use of the therapeutic product and that its use will be stipulated in the labeling of the therapeutic product.
An important consequence of this recommendation is that a therapeutic product might not be approved unless its companion diagnostic is cleared by approval, emphasizing the need for co-development and the need for formal FDA approval. Regulatory submissions such as Pre-Market Approval (PMA) are essential for successful global market access and distribution of the pharmaceutical/diagnostics product pair.

Further on determination of whether an assay provides "information that is essential for the safe and effective use of a corresponding therapeutic product" relates to the assay’s clinical utility. Clinical utility is the capability of an assay to improve patient outcomes in relation to the state of not using the assay (Rubin et al., 2014).

According to FDA rules CDx labeling must specify the intended use of the device and the name of the corresponding therapeutic (or therapeutic class, if applicable). Cleared or approved CDx will require a new pre-market approval (PMA) application to expand the labeling to include a new indication. Drug labeling should include a clear definition of the patient population in which the diagnostic test is safe and effective, if applicable (Food and Administration, 2011b).

The clinical development of a new assay makes it also important to determine if an Investigational Device Exemption IDE is required while the diagnostic test is under investigation. This is the case when important patient care decisions are being made based on an investigational test. An exception is phase I studies where the efficacy and safety of a new therapeutic is unknown and the FDA has allowed the use of an assay described for patient selection. The FDA might require an IDE filing when trial safety and effectiveness data is collected. This depends on the risk of use of the test, which is given when a premarketing approval (PMA) submission is supported. Use of an investigational device for clinical management often requires an approved IDE before start of the study, again depending on the risk of the device used to direct management, that is, whether or not an incorrect test result or a "bad test" could expose patients to serious harm or death (Food and Administration, 2009).

There is a second path for deployment of clinical assays that bypass the regulatory review process. Laboratory-developed tests (LDTs) are not cleared or approved by FDA. There are developed and commercially offered by laboratories that have been certified according to the Clinical Laboratory Improvement Act of 1988 (CLIA) through an accreditation process managed by the Center for Medicare Services (CMS) (Medicare and Services, 2012). Tests are setup and established at the site of a CLIA-certified laboratory and samples are sent to the laboratory for testing. There is no premarket evaluation and tests are regulated through checks of documentation during the course of a routine laboratory inspection.

It is of importance that CMS (CLIA) has no authority to mandate that either clinical validity or clinical utility be established for LDTs. These tests, in some cases include also companion diagnostics as well as other prognostic or diagnostic tests intended to help the clinician to choose between alternative treatment schemes. The availability of two paths to market, one
without a requirement for establishment of either clinical validity or utility, has remarkably expedited entry of new and cutting edge diagnostics into medical use. In 2010 the Tufts Evidence-based Practice Center found that 145 non–FDA-approved LDTs out of 212 tests for solid cancers, and 221 LDTs out of 388 tests for hematopathology were performed in laboratories for clinical use (Sun et al., 2010). The reason to have non-FDA approved tests was that some of these tests were defined as low risk diagnostics or they had been designed for rare diseases with no alternative tests (Food and Administration, 2010). But since 2011 the FDA has become increasingly concerned about the fact that LDTs aid in clinical decision-making. In the recent draft guidance “Framework for Regulatory Oversight of LDTs” the FDA intends to apply a risk-based framework to any in-vitro diagnostic (IVD) test that is offered as an LDT by a CLIA-certified laboratory similar to that used for IVDs in the FDA regulatory pathway (http://www.fda.gov/ucm/groups/fdagovpublic/@fdagovmeddevgen/documents/document/ucm416684.pdf, published online October 03, 2014). As an example High-risk (Class III) devices will need to undergo market review (i.e. premarket approval) including the requirement of adverse risk reporting.

4.1.2 The regulatory framework in the European Union

The current legal framework for medical devices in the EU, classifies companion diagnostics generally as in vitro diagnostic (IVD) medical devices (Directive, 1998). An IVD is defined in the IVD directive 98/79/EC as:

"reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information concerning a physiologic or pathologic state, or concerning a congenital abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures" (p. 12).

The IVD directive is based on a risk framework. In order to release a medical device on the EU market, the manufacturer must assign the device to a relevant risk category outlined in the directive. For example companion diagnostics designed to test for genomic biomarkers would be classified as general IVDs (low risk). In this case the presentation of clinical efficacy data or proof of clinical utility is not required. Low-risk IVDs are certified with the Conformite Europeenne (CE)–marking. This requires that the manufacturer “self-certifies” that the device meets the "essential requirements" for health and safety of patients and users and achieves the performance specified by the manufacturer. CE marked devices, have access to the European Economic Area which includes Iceland, Liechtenstein, Norway, and Switzerland and Turkey.

Certification of higher-risk IVDs, may involve a notified body. This depends on the risk classification of the devices and the conformity assessment route a manufacturer has chosen. A notified body acts under supervision of the national authority of a Member State. The notified
body is authorized to carry out appropriate conformity assessment procedures. This is also the case for IVDs which are put into service without market distribution. However, devices manufactured and used only within the same health institution are excluded from the IVD Directive according to the "in-house derogation" (Directive, 1998).

The European legislation on medical devices including companion diagnostics is under review. The Global Harmonization Task Force for medical devices (now replaced by the International Medical Device Regulators Forum (IMDRF), has proposed a new risk-based (class A, lowest risk; class D, highest risk) classification system (Force, 2007). Accordingly, companion diagnostics would be classified within class C. Class C devices bear a high individual risk, meaning a false result could lead to a life-threatening situation for the patient or impacting the health negatively in any way.

The conformity assessment procedure of companion diagnostics will be conducted by a notified body and therefore differs significantly from the simpler system of self-certification. Companion diagnostics will have to be in accordance to safety and performance requirements. This includes analytic performance and clinical performance. The clinical evidence has to be monitored throughout the life cycle of the device according to the manufacturer’s post market surveillance plan. After certification, notified Bodies will regularly asses the IVD in the post market phase (Commission, 2012b). During the assessment the notified body is required to consult the EMA or one of the medicinal product national competent authorities.

In October 2013, the European Parliament proposed amendments for companion diagnostics. This included the requirement for evidence of clinical utility of the device with respect to the patient’s health outcomes as result of the therapeutic intervention route as suggested by the test result. Another conformity assessment route, which can be seen as an equivalent to FDA’s premarket notification (510(k) procedure, suggests to involve reference laboratories to verify compliance with common technical specifications or with other solutions to ensure an equivalent level of safety and performance (Parliament, 2013). The discussion between European institutions to agree on a revised legislation is ongoing. The new rules could be gradually implemented from 2015 to 2019 (Commission, 2012a).

The EMA recommends co-development of the companion diagnostic and therapeutic product. This process should be designed to proof analytic validity of the diagnostic test at an early stage of drug development, clinical validity studies to ensure the capability of the assay to select patients, and ultimately clinical utility to establish that treatment with the drug after patient selection with the companion diagnostic is associated with improved benefit–risk balance compared with the absence of patient selection. However, the EMA is aware that this is an ideal scenario thus, the guidance also addresses situations in which biomarker discovery occurs during later stages of drug development before or after approval (European Medicines Agency, 2010). In contrast to the FDA regulatory legislation there is not yet a requirement that a companion diagnostic be approved by EMA before or after a corresponding drug is approved. In
addition there has been no requirement that only patients tested with a specific companion diagnostic will be treated with the respective targeted drug.

It can be concluded that while the fundamental guiding principles of the regulatory framework for CDx are similar between the U.S. and European Union, significant differences remain. One of the key differences is that European Medicines Agency (EMA) does not require co-development and approval of a CDx at the same time as the drug. However, a harmonization effort is underway to align the key differences between FDA and EMA guidance on development of CDx. One example is the proposed classification of CDx as high individual risk or moderate public health risk (category C), which would require EMA approval while FDA may determine if a CDx is subject to PMA or 510(k) review and approval on a risk-based analysis.

4.2 Health Technology assessment and reimbursement

The health care systems in EU and the US follow different Pricing & Reimbursement (P&R) policies for drugs and diagnostics. P&R of pharmaceuticals can be described as “value-based”. In contrast diagnostics is regarded as a commodity and priced in a cost-based way (Garrison and Austin, 2006). In vitro diagnostic have low reimbursement rates in many markets based only on the method. There is no consideration of the value the tests has for the patient.

The reimbursement system across European countries is organized in a “diagnostic-related group” (DRG) system (for example G-DRG codes in Germany or GHS codes in France). In this system related devices and procedures belong to one group with its own code. The code defines a set amount of money that will be reimbursed for each procedure (Goldfield, 2010). In the US, in vitro diagnostic is organized in the Current Procedural Terminology (CPT) code system. In general P&R for new diagnostic will be determined by the major payers and health authorities by comparing a new test with the existing reimbursement level of existing tests involving similar effort and cost.

An assessment of the clinical pipelines of 21 leading pharmaceutical and biotechnology companies has shown that between 12 and 50 percent of products in development involve stratified medicine (Fugel et al., 2012). This will cause additional cost for potentially high volumes of testing and for increased resources for testing services. Health Technology Assessment (HTA) has a key role in ensuring that resources are appropriately allocated.

There is no clear definition for value assessment of complex diagnostics in the EU or US. The challenges to determine the clinical and economic value of stand-alone or companion diagnostics can be explained by scientific barriers. There is often a lack of evidence regarding health outcomes and costs during development, only clinical validity (sensitivity and specificity of the test) has been established but the evidence for clinical utility is lacking (Deverka et al., 2010).
In the case where the test that will be used in clinical practice is identical to the test used in the pivotal clinical trials of the pharmaceutical, the health technology assessment can be considered as straightforward. The health outcomes from the treatment, informed by the companion diagnostic, are used as the basis for the evaluation of the clinical effectiveness. In contrast assessing a test that was not used in the clinical trials of the corresponding pharmaceutical, HTA organizations may have to conduct comparative diagnostic accuracy studies (Byron et al., 2014).

The UK HTA body, the National Institute for Health and Care Excellence (NICE), has developed policy for considering companion diagnostics using its Technology Appraisal and Diagnostics Assessment Programs (NICE, 2013).

It has been suggested by many observers that more flexible P&R systems are needed in order to support innovations and truly catch the value of diagnostic tests. This is regarded as critical to create stronger economic incentives for the development of stratified medicine approaches (Garrison and Austin, 2006, Seiguer, 2007). This opinion is also reflected by government commissioned reports which recommended changes in diagnostic coding and payment systems for diagnostic tests (PCAST, 2008, SACGHS, 2008).

4.3 Co-development of a diagnostic and a therapy
As described previously according to the FDA the challenges of proving clinical utility and reaching clearance or PMA approval can be addressed through a co-development strategy for both diagnostic test and therapeutic product. This co-development strategy is recommended by the FDA in the 2011 draft guidance on in-vitro companion diagnostic devices (Food and Administration, 2011b). Furthermore, the document outlined the co-development steps and its different possible routes. Due to the complexity of diagnostic therapy co-development the guidance document only functions as a general guidance. There are a number of potential scenarios for the co-development of a diagnostic test with the aim to identify responders to a certain drug:

The first scenario is co-development of a diagnostic and a therapy in the early beginning of the drug development process. This scenario will allow for an early development of a validated assay that will be clinically validated and ready for patient stratification in the pivotal clinical trials. Two recent co-approvals in the US have benefited from a diagnostic test by smaller trials and shorter approval times. Both Roche’s Zelboraf and Pfizer’s Xalkori drugs were approved in less than six months, ahead of their deadlines for the FDA to approval (Chabner, 2011, Shaw et al., 2011). However, this approach requires an early commitment from both the pharmaceutical and the diagnostic partners with coherent plans for risk and benefit sharing.

The second scenario describes co-development of a diagnostic and a therapy at a late stage of clinical development (typically beyond Phase 2 or 3). In this case the drug’s issues regarding
safety and efficiency in clinical development are addressed through the introduction of a
diagnostic test when a biomarker is available to identify patients relevant for treatment. The
drug developer may team up with a diagnostic firm, with convergence of two distinct business
models mid-way through drug development (Mittra and Tait, 2012).

A third scenario is the development of a diagnostic test for patient stratification during post-
marketing surveillance. Here safety or efficacy issues have been identified for a therapeutic
product already on the market and discovery and development of biomarker and diagnostic
test or the application of an existing diagnostic test is regarded as a way to overcome the issues
by stratifying the market (Mittra and Tait, 2012).

It is important to mention that there have been an increasing number of partnership
agreements between diagnostic developers and major players in the pharmaceutical industry.
Diagnostic companies of choice are those with a proven track record, such as Abbott (IL, USA),
Roche/Ventana (Basel, Switzerland), Dako (Glostrup, Denmark) and Qiagen (Venlo, The
Netherlands). For example in 2012 Roche/Ventana was partnering with Pfizer (NY, USA),
Æterna Zentaris (QC, Canada), Syndax (MA, USA), Bayer (Leverkusen, Germany), Millennium
(MA, USA) and Seattle Genetics (WA, USA). Other partnerships were formed in 2014 between
QIAGEN and Lilly with the aim of simultaneous analysis of DNA and RNA Biomarkers in common
Cancers. Lately there is also an increased number of partnerships with companies with highly
specialized companion offerings or new emerging technologies like Next Generation
Sequencing. In 2014 Illumina announced strategic Partnerships with AstraZeneca, Janssen and
Sanofi with the aim to exploit next generation sequencing (NGS) to redefine companion
diagnostics for oncology.

4.4 Interview results
For the case study three companies that develop and commercialize diagnostics products/
services were chosen as interview partner. Table 1 gives information about the size of the
companies, the role of the interview partner in the company, and a short description of the
products/services the companies offer. The company Roche is well known as a global player
with a rich portfolio of therapeutic and diagnostics products and an extensive R&D program.
Pelago AB and AdductAnalysis AB are start-up companies originating from research projects at
the Karolinska Institut in Stockholm, Sweden and at Stockholm University. Adduct Analysis AB is
close to launch a diagnostics service for clinical professionals in the field of oncology in Sweden.
Pelago Bioscience AB is a life Science Contract Research Organization that has not entered the
diagnostics sector yet, but has a desire to do so in the future.
Table 1: Information about the companies and interview partners

<table>
<thead>
<tr>
<th>Company</th>
<th>Size of company (number of employees)</th>
<th>Product /Service</th>
<th>Interview partner’s role</th>
<th>Date and place of interview</th>
<th>Indication in interview summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche AB</td>
<td>&gt;88000</td>
<td>The company develops and sells a wide range of pharmaceutical products and diagnostics</td>
<td>Global policy manager</td>
<td>2015-04-24 10.00am Roche AB 10075 Stockholm</td>
<td>Interview partner 1</td>
</tr>
<tr>
<td>Adduct Analysis AB</td>
<td>2</td>
<td>The company sells a service based on a patented TailorDose® method, suitable for determination of the active dose of cancer drugs with the aim to customize - the chemotherapy for each individual patient.</td>
<td>CFO</td>
<td>2015-05-11 14:00pm KI Science Park 171 65 Solna</td>
<td>Interview partner 2</td>
</tr>
<tr>
<td>Pelago Bioscience AB</td>
<td>5</td>
<td>The company is a Life Science Contract Research Organization established to accelerate the use and benefits of the patented Cellular Thermal Shift Assay “CETSA™” method in Drug Discovery and Development. The focus is to deliver physiologically relevant high quality Target Engagement data to customers</td>
<td>CEO</td>
<td>2015-05-12 10:30am Pelago Bioscience AB 171 65 Solna</td>
<td>Interview partner 3</td>
</tr>
</tbody>
</table>

Not all questions had the same relevance to all companies. Therefore some questions have not been answered by all interview partners. The following section shows the questions and then summarizes the answers of the interview partners.

4.4.1 Technologies, marketing and adaption by users

Question 1) What are the incentives of IVD companies to enter the field of companion diagnostics?

Summary: Interview partner 1: As a diagnostics company companion diagnostics allows you to choose an approach where you prove a clear medical need which is visible to the hospitals and patients. In this case the pricing and reimbursement structure should change to a more value-based approach, meaning diagnostics companies get paid for the whole system (including the value generated to the clinics and patients) instead of getting paid for separated parts of the system (technology platform, reagents etc). The aim is to create an ecosystem for value-based pricing. Example: if a new innovative diagnostic test (for example liquid biopsy) would reduce patients waiting time from diagnosis of disease to treatment radically, how would that reduce the health care cost? Value based payment for new innovative diagnostic test based on the cost benefit and patients outcome? What can the companion diagnostic company do? Prove the value!
Summary: Interview partner 2: There is a need for improvement in dose adjustment for known cancer drugs (to avoid underdosing = insufficient cytotoxic effect, and overdosing = too high (dangerous) toxicity to the patient. The product can also help to improve dose adjustment for drugs under clinical development (this could save money because fewer patients needed in the clinical studies, since dosing can be adjusted to be within the optimal therapeutic window. TailorDose® is a convenient tool for dose adjustment as only one blood sample is needed to obtain a measure of the accumulated blood dose of the active dose. This sample can be taken at a convenient time for the patient, up to weeks after the drug has cleared the system. This means that accurate dose data, and possibility to adjust the dosing, is accessible for patients within clinical trials at phase II and III. It will also be helpful for clinical development for rare cancer types where it takes time to recruit a sufficient number of patients, since the number of patients in the study can be reduced. This will save time and money.

Summary: Interview partner 3: The company was founded to commercialize the Cellular Thermal Shift Assay “CETSA” method which was invented by a professor at Karolinska Institutet and developed by the person who is now the CSO. Given the fact that this method is applicable to literally all biological samples, the company wants to make it useful to all patients, as soon as possible and as relevant as possible. Since the method is all new, the company has started with developing and offering preclinical drug discovery service work to establish the technology and brand it. The incentive to enter the diagnostics field is based on the fact that the method works in human tissue and therefore can put into good use for the patients. When looking at it from a commercial view the investments in clinical development are far higher than in pre-clinical development, therefore the potential savings for the customer are much higher and therefore there is as much bigger economic promise in in-vitro diagnostics rather than preclinical drug discovery.

Question 2: How can your IVD technology be applied as companion diagnostics?

Summary: Interview partner 2: The technology allows exact measurement of cytotoxic active components of the drug, this can be metabolites from pro-drugs (e.g., cyclophosphamide) or drugs designed to have inbuilt reactivity as such (e.g., ibrutinib). Measurement of the target drug can be combined with other drug measurements in multidrug therapies.

Summary: Interview partner 3: The method is covered by a method patent. Four steps are patented: Heating, cooling, separation and detection. The method works on all kinds of sample matrices and on most soluble proteins, the method is relevant for 50% of the drugable targets, the method can detect interaction between a small molecule (drug) and the protein, this way a target can be identified. The technology is only 2 years in the public domain. The technology has a variety of possible applications as a diagnostic tool which needs to be explored and validated.

Question 3: Who are your customers?

Summary: Interview partner 1: diagnostic laboratories and hospitals.
Summary: Interview partner 2: The hospitals and the pharma industry (for drug development).
Summary: Interview partner 3: Pharmaceutical companies who want to have support in target engagement in the preclinical development.

Question 4) How do you make sure that products/platforms have wide distribution and acceptance by the end user (clinical laboratories, medical doctors) that may offer the test in the market? (or how do you offer your product/service)?

Summary: Interview partner 1: Roche offers modular systems (pre-analytical sample preparation and analytical platforms with CE-certified test kits). There is a wide range of technologies including immunohistochemistry, molecular diagnostics, and clinical chemistry. The customers (diagnostic labs) can choose tailor made solutions according to their requirements and specialization (throughput, technology etc.)

Summary: Interview partner 2: Quote: “We are not selling a product which should be used without information; we are actually selling a diagnostic service.” Within this service the company offers a full solution regarding timing of blood samples, logistics to transport and measurement of the drug levels in the samples, data will be processed within the company, reported to the physician (oncologist) together with recommendation for future dosing of the drug. This means that the oncologist will receive an exact value(s) regarding the previous dose cycle, the level of the next dose cycle can only be decided by the oncologist himself. To bigger customers in the pharma industry it could be delivered as product (licensing-agreements). To the end user in the hospitals it could be delivered as a service. The company has collaborations with contractors who do the analysis according to the “Good Clinical Practice” (GCP) standard. The company is collecting ISO certificates for the defined steps in the working process within the company operations (equivalent to CE for products). When the service will be launched to the Swedish market there will be an “accreditation” of the analytical method (stability of assay, and confirmation for quality).

Summary: Interview partner 3: The company offers a service. The service is extremely customized and tailor-made. There is no product now but there is a desire to develop a product in form of kits/reagents. The interviewee also speculates about “point of care” instruments in the future, since the steps of the method (Heating, cooling, separation and detection) are simple. The company currently is a very standard contract research organization; the turnover is expected to grow linearly. To get a base turnover the company sells licenses on the method. The company also applies for funding for example from VINNOVA and takes part in innovation competitions to get funding for method development. For the preclinical work there is the desire to develop kits and buffers. This demands method development, for that the company has very limited funding. The development of specific CETSA instrumentation could be a goal in the future. There might be an issue that some parties use the CETSA method without fulfilling license agreements. Therefore products in form of a kit with adjusted and optimized components and reasonably priced could be a useful product. This could be in co-development with detection kit providers.
4.4.2 Companion diagnostics development strategy

Question 5) **What is the development strategy for companion diagnostics?**

**Summary: Interview partner 1:** The company has two parts, internally Roche has a co-development strategy between the pharma and the diagnostics part (unique for Roche, time saving since early cooperation). Other solution: a pharma company engages a diagnostic company at a certain point in the drug development process; this will lead to loss of time, depending on the point of cooperation. The company can develop the drug without companion diagnostics co-development and hope that someone will provide the diagnostics on the market or the right companion diagnostic could already exist on the market.

**Summary: Interview partner 2:** The company sells safety and increased efficacy, the company conducts clinical studies to show benefit to patients. The company uses analytical techniques which are highly accurate even though more costly. Quality of measurements is critical for patient’s safety, especially as the therapeutic window normally is narrow and the majority of the used drugs today are highly toxic. Permission to run clinical studies, where drugs are being actively dose adjusted, will be requested from the Swedish Medical Agency (läkemedelsverket).

**Summary: Interview partner 3:** Many projects supported by the technology are in the late stage of preclinical development on its way to clinical development. Therefore the assays could be ready for phase I and phase II clinical trials. The method is applicable for the whole preclinical value chain, and there might be a scenario that there will be a transition into clinical development together with the customer. The company could also develop the diagnostic itself, but currently no budget for R&D.

Question 6) **Does the company have an interest in developing new diagnostic tests for launched pharmaceuticals, for example as an alternative to the companion diagnostics used in the pivotal clinical trials of the pharmaceutical?**

**Summary: Interview partner 1:** Portfolio completeness of tests is a good differentiator in the market. Own tests are out-licensed to other companies. The company buys licenses to fill gaps. After buying licenses the test needs to be adapted to the platform; the result of the test can differ with platform type.

Question 7) **New IVD technologies with improved sensitivity over traditional methods or a wider range of applications are rapidly emerging. What are your strategies to compete with or adapt new promising technologies? (next generation sequencing (NGS) and mass spectrophotometry proteomics)?**

**Summary: Interview partner 1:** Example next generation sequencing (NGS): there is a high potential but NGS generates a high amount of data. Decision support is an important part of personal health care. The first step for decision support is gathering of information/data from a high number of individuals/patients. Common companion diagnostics from today is looking at 1-10 biomarkers (e.g. herg2 testing), NGS wants to look at 20 to 40 biomarkers or more,
medical professionals don’t want this due to problems to evaluate this amount of information. NGS is locally used for research purposes; it is difficult and risky to integrate research driven NGS into clinical diagnostics because of different standards in research and clinic. Estimated 5 to 10 years until the required data and computer technology is accessible and computer based decision making is established in standard health care. Besides of marketing the technological capabilities of a new technology like NGS, companies such as Illumina need to prove the medical value, this means collecting a lot of data and developing decision support platforms. The players in the market: Pharma- Diagnostics- IT companies: Health care is moving towards IT solutions! Diagnostic companies could become a sub-supplier to the IT companies who offer data handling and decision support to the medical professionals Strategy: Companies like Roche buy informatics companies to develop algorithm for treatment within disease areas like oncology, CNS etc. Conclusion: The technology can offer you extended data like the whole genome of a patient, but the medical care system is not yet ready for it. Roche’s general strategy to integrate new technologies which are not certified diagnostics yet: Companies with innovative technology solutions are bought and become part of the life science division where the new technologies are used in a research setting, if methods are good enough they can be moved into a clinical environment by CE-certifying them.

4.4.3 Regulatory environment and reimbursement

Question 8) How do current reimbursement policies support the development of high-value molecular test?

Summary: Interview partner 1: The company took the initiative to change payment from selling the components of the diagnostic test (hardware, reagents, chemicals) to selling the solution: When the diagnostic lab (customer) is delivering a result to the clinic the companion diagnostics provider gets paid. This is positive because it is a solution based situation. The suggestion is to prolong this solution based structure to include the patient, meaning if a patient shows progress (or there is a clinical proof that diagnostic test will lead to right medical intervention) the involved parties including diagnostics companies will be paid?

Summary: Interview partner 2: To apply for reimbursement there should be a written interest of the clinic and the value to the patients should be demonstrated (offentlig upphandling). The price needs to be balanced to the service. In order to enter markets in other countries it will be important to know the specific reimbursement systems and the requirements for the demonstration of value of the diagnostic test.

Question 9) How should regulatory agencies be engaged to enhance personalized medicine/companion diagnostics development?

Summary: Interview partner 1: Ask for value of diagnostics and medical technology, this will lower the total health care cost. There is need for the development of a good system for health technology assessment (HTA). Also the diagnostic lab has to ask for more value. Personalized
healthcare does not work without information for decision making, therefore from a regulatory perspective there should be a legal requirement for tools for decision making in what clinical situation a novel therapy is a the right choice. This would be an incentive for biomarker research and companion diagnostics development.

**Summary: Interview partner 2:** To show benefit, a large amount of data has to be collected. Therefore there is a demand that the analytical test is extensively used after clinical trials. If there is convincing data that the technology saves lives, the regulatory authorities should demand the use of diagnostic product/service on a regular basis.

### 5 ANALYSIS AND DISCUSSION

#### 5.1 Challenges of CDx development and commercialization

In this section the findings from the literature review and the company-interviews will be structured and discussed. The results from the literature research demonstrate that there are a number of challenges to be considered when developing diagnostics as a base for successful stratified medicine. This is partially due to the fact that the development processes of both therapeutic products and diagnostics are highly complex and fundamentally different. Historically, the development of both pharmaceutical products and diagnostics has been managed by very different types of organizations with different value chains and business models. Further on the co-development of drug and diagnostic requires considerable alignment and coordination between and among developers and regulators. The results from the company interviews give an indication on what strategies are used to address these challenges.

##### 5.1.1 Inconsistent regulatory standards

In the “theoretical background” section the important role of institutions in sectoral systems was discussed. When looked at it from a national level, the results of this study demonstrate that the regulatory frame works for the development of companion diagnostic tests differ in the United States and in Europe. In the United States, diagnostic and therapeutic approval applications are processed by the FDA. The Center for Devices and Radiological Health (CDRH), which is responsible for in-vitro diagnostics, cooperates with Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER). Both are situated in the FDA. In contrast, there is no overviewing European agency and therapeutic and diagnostic are often developed independently. The European in vitro diagnostic (IVD) Directive 98/79/EC from 2012 does not indicate any plans to create a pan-European body with the mission for a joint regulation of diagnostics and medicines in the future. The different regulatory requirements are
a clear hurdle for the development of therapeutics and companion diagnostics for the global market.

Both United States and Europe, have diverging requirements for the demonstration of clinical utility (Woodcock, 2010). In Europe, manufacturers only follow essential safety and performance requirements but do not have to demonstrate the impact of the diagnostic product on clinical outcomes. Additionally there is no need to show superior or equivalent effectiveness of a new diagnostic tool when compared to similar diagnostic that already exists (Fraser et al., 2011). In the United States, the requirement for premarketing approval by the FDA includes evaluation for analytical performance and clinical validity.

Furthermore, approved diagnostic products have to compete with laboratory developed tests (LDTs) performed by (CLIA)-accredited laboratories. CLIA has no requirement to determine either clinical validity or utility. FDA is aware of this situation and is planning to start regulating high risk LDTs. Regulation of LDTs and a more strict regulation of companion diagnostics in the EU are in favor of established, global acting diagnostic companies. An example is Roche Diagnostics, who provides specialized technology platforms for the use of CE/FDA approved diagnostic products in form of regents and test kits. The Roche representative in the interview has stated a desire that regulatory agencies should ask for value of diagnostics and medical technology, in order to lower the total health care cost, and that there is need for the development of a good system for health technology assessment (HTA).

Although the current situation creates room for exploratory development and rapid market access, there is a clear gap of evidence from performance and accuracy to actual health outcomes. This creates uncertainty for payers and health-care providers with respect to cost, risk and effectiveness (Cohen et al., 2013). Additionally it remains unclear whether patient interests are guaranteed, given the fact that the performance of many new LDT tests have not been well established and/or well documented (Byron et al., 2014).

5.1.2 Poor reimbursement levels for high-value diagnostics

As discussed previously, most diagnostics are priced on a cost- based model since the risks are regarded as lower and the development timelines shorter when compared to their therapeutic counterparts (Trusheim et al., 2013). There is a lack of rules for assessment of high-value diagnostics in the EU and the US. A possible way to facilitate market access for companion diagnostics could include pharmaceutical manufactures of the pharmaceutical product. Those may help with subsidizations of the respective diagnostic. It is obvious that stand-alone diagnostics which have not been co-developed in parallel to the therapeutic product will not be supported by a therapeutic developing partner and payers are skeptical and measure cost effectiveness according to their own evidence requirements.
The current U.S. and EU reimbursement systems do not reward the delivery of scientific evidence for clinical utility as required by HTA bodies and payers for cost-effectiveness evaluations because the commercialization will not cover its investment (Meadows et al., 2014). This situation leads to a lack of accurate and reliable biomarker tests. Payment for a diagnostic test should cover the R&D costs plus a reasonable profit margin if clinical utility has been demonstrated. This is the prerequisite for investors and researchers to invest in studies to demonstrate clinical utility. From the interview with Roche it became clear that the company takes initiative in transforming pricing for diagnostic products from cost- to value-based. They have negotiated a pricing with the customer laboratories for delivering a result to the clinic. This is a solution based pricing situation. The suggestion is to prolong this solution based structure to include the patient, meaning if a patient shows progress (or there is a clinical proof that diagnostic test will lead to right medical intervention) the involved parties including diagnostics companies will be paid accordingly, taking into consideration the value for the patient and cost savings for the health system.

5.1.3 Lack of guidelines for evaluating clinical utility
Diagnostic assays development in general includes the generation of data documenting the assay performance for analytical validation and for clinical validation. It is more challenging to demonstrate the association of the test result to clinical decision making and patient outcomes or to demonstrate an impact on costs. A way to collect this kind of evidence is through longer term clinical use and post-market commercial studies, which is regarded as expensive and time consuming by decision makers in charge of resources. A lack of clear uniform guidelines for assay developers on generating evidence of associations that are clinically useful makes these studies less critical to commercial success. However, earlier demonstration of utility as part of the assay development process would provide a greater chance of assay adoption. Insufficient evidence regarding treatment decisions and outcomes have been documented for a variety of commercially available diagnostic tests when reviewed for analytical and clinical validity (Meleth et al., 2013, Little et al., 2012). This might markedly change with new reimbursement conditions. A requirement of demonstration of clinical utility before payment by third-party payers will create significant incentives to develop new assays with patient outcomes in mind. A likely consequence is the introduction of fewer but better tests in the future.

The representatives of both Adduct Analysis and Pelago Bioscience have stated in the interview that clinical studies are performed to demonstrate that their diagnostic methods lead to a beneficial outcome for patients. To achieve this and cope with the high cost, both companies utilize their connection to academic research and funding. In addition they collect grants form patient foundations like the Breast Cancer Foundation and innovations agencies like VINNOVA in Sweden. This can be seen as a strategy of small companies to create R&D budgets, which they would otherwise lack.
5.1.4 Challenges in drug-diagnostic co-development

Diagnostic companies follow business strategies different from that of the pharmaceutical industry. They develop faster, with a higher percentage of success. From a diagnostic perspective, co-development with a therapeutic bears financial risks and uncertainty which has not been accounted for previously. The high failure rate of drugs in clinical studies can lead to the development of diagnostics for drugs that do not reach the market. Therefore diagnostics companies may wish for risk sharing strategies to reach a certain level of security. Royalties associated with the high win margin of the therapeutics could be an incentive to enter a co-development agreement. This could become a reality since the FDA requires the approval of a relevant CDx test before the accompanied therapeutic product can be released on the market, given the efficacy and safety of the product depend on the test. The introduction of an equivalent policy by the European Medicines Agency in the near future can be anticipated.

In the literature the Contract Diagnostics Organization (CDO) is discussed as a new business model, offering integrated services for parallel development of companion diagnostic tests as part of the drug development to pharmaceutical companies (Cotter et al., 2012). The CDO is up-to-date with the changing developmental, regulatory and reimbursement landscapes for diagnostics. This development is evident given the fact that numerous partnerships and alliances have been formed between pharmaceutical companies and diagnostics developers.

The company Roche has a unique position since the Roche group is housing both a therapeutically and diagnostics branch with R&D departments. According to the Roche representative in the interview, this can be seen as an advantage since it allows early co-development collaborations and efficient risk management. However, “Roche Diagnostics” has also formed alliances with external pharmaceutical companies for integrated companion diagnostics development.

Another possible route into a clinical co-development scenario has been described by the CEO of Pelago Biosciences: The patented CETSA method is applicable for the whole preclinical value chain, and there might be a scenario that there will be a transition into clinical development together with the customer from the pharmaceutical sector. So this could be an appropriate track for a small contract research organization with focus on life science and preclinical development, to enter the diagnostics sector.

5.2 Inside CDx Business Strategies

The interview partners gave an interesting view into business strategies regarding companion diagnostics. The different strategies will be compared in this section. It will be useful to investigate whether differences in business models can be aligned to the size and maturity level of the three investigated companies. Both start-up companies (Adduct Analysis and Pelago Bioscience) own patented methods that are offered as services to the customer. Their value
proposition is a complete solution to a customer problem. They offer an integrated solution, with contractors for analytic measurements in the value chain.

In case of the contract research organization Pelago Bioscience, the service can be very exploratory. The CETSA method can be applied to answer very specific questions regarding target engagement; therefore every project is different and requires a tailor-made solution. Pelago Bioscience’s customers are global and local players in the pharmaceutical industry. Pelago Bioscience has recently partnered with a distributor, who will offer CETSA to the Japanese market. The versatility of the CETSA method makes it a promising tool for companion diagnostic testing in the future. However, more experience and knowledge has to be accumulated to identify by what means the method can be applied as diagnostics. Depending on the character of the product idea, diagnostic tests could be developed by the company alone or in partnership and alliance with a variety of potential partners, including pharmaceutical companies, life science and biotech companies with specialization in protein detection technologies, diagnostics companies and academia.

Adduct Analysis, has developed a method which is ready to be applied as a diagnostic test. Target customers for this service are the oncology departments of the hospitals. Another target group is the pharmaceutical industry, where the service can support clinical drug development projects. The service will be released on the market exclusively in Sweden in the beginning. There is also the consideration to sell licenses to pharmaceutical companies, who have in-house capabilities to conduct the testing independently. To fulfill future demand outside of Sweden it is considered to form partnerships with local distributors. The service can also be made available to new markets by out-licensing to local diagnostic providers.

Roche, who can be seen as a representative for established global acting players in diagnostics sector offers integrated diagnostics platforms to their customers which are automatized and allow high volume testing. The customer (clinical labs) exploits these platforms to provide a service to the clinic. The technology platform is modular and allows conducting a large variety of diagnostics tests. It is important to mention that Roche provides the technology base as well as the reagents and components in the test kits for free. According to the Roche representative in the interview, the idea is to sell a diagnostic test as a solution to the medical professionals and patients. Revenue will flow down to the diagnostics provider once a test has been used in the clinic. This is a strategy to promote value-based pricing for in-vitro diagnostic tests with the aim that eventually the impact of the diagnostic tool on the patient’s health outcome will be considered to determine the real value of the diagnostic test and reimbursement adjusted accordingly.

It can be concluded that all three diagnostics companies have a main strategy in common to influence customers and policy makers. That is the demonstration of a beneficial outcome for patients in form of clinical studies. Small companies like Pelago Bioscience and Adduct Analysis
with limited resources for clinical research receive funding from academic research grants, patient support groups, pharmaceutical industry, and governmental Innovation agencies.

Roche is mainly competing with other diagnostics providers who offer similar technology platforms. One factor to stay attractive to the customer is completeness. Therefore new diagnostic tests have to be added to the platform, those could have been either developed in-house or acquired by licensing agreements. In contrast Pelago Bioscience and Adduct Analysis generate value by the ownership of superior methods which currently outperform the competing technologies. Thus small companies in the development phase like Pelago Bioscience and Adduct Analysis face a fundamental threat from novel innovative technologies by competing developers.

The Roche representative gave an interesting view on how Roche is dealing with new, emerging technologies, with the potential to disrupt the market for companion diagnostics. A technology like “Next Generation Sequencing” will lead to more complex diagnostic testing and physicians will be overcharged with information. According to the opinion of the Roche representative it will take an estimated 5 to 10 years until the required data and computer technology is accessible and computer based decision making is established in standard health care. Besides marketing the technological capabilities of a new technology like NGS, companies such as Illumina need to prove the medical value, this means collecting a lot of data and developing decision support platforms. Thus, it can be speculated that the player who is gaining immense importance in the market besides pharma and diagnostics companies is from the IT sector. In General health care is moving towards IT solutions and diagnostic companies could become a sub-supplier to the IT companies who offer data handling and decision support to the medical professionals. As a strategy companies like Roche buy informatics companies to develop algorithm for treatment within various disease areas.

5.3 The pharma–diagnostics sectoral innovation system

The most important development coupled to the emerging new paradigm of stratified medicine, can be captured by the newly evolving “pharma–diagnostics” sectoral innovation system. There are two industrial sectors which have been coexisting with different development processes and commercialization strategies. In the pharma industry, institutions have had a significant impact on the innovation process. In contrast for traditional IVD developers, as a part of the medical devices industry, institutions would not influence the innovation process to the same extent, since regulatory demands are far less stringent. However, as mentioned before between 12 and 50% of current clinical projects are based on Stratified Medicine and the investment in biomarker research is expected to increase by 53% between 2010 and 2015 (Development, 2010). In stratified medicine the diagnostics are linked much closer to the therapeutic product. A growing knowledge base from extensive biomarker research makes diagnostic testing an essential tool for clinical drug development, and even
more important, inevitable for the safe and efficient application of the therapeutic product in health care. The regulatory agencies, with the US FDA in the lead, have started to react with new guidelines for therapeutic-diagnostics co-development and more stringent risk classifications for companion diagnostics. In particular, there will be a demand for co-approval of a drug-diagnostics pair in order for the therapeutic product to gain market access. This is leading to the cross-sectorial formation of new partnerships and networks. Alliances have been formed between diagnostic firms with no experience in clinical testing and pharmaceutical companies that adopted patient stratification for clinical testing. Mergers and acquisitions are carried out to acquire complementary competencies for the development of stratified medical products. Thus, both industries undergo change and transformation through the process of co-evolution, leading to a transformed sectorial innovation system that fits the demands for the new products in the area of personalized medicine. The motor for this development is the rapid progress in knowledge and technology.

The results of this study have clearly demonstrated inconsistencies in the regulatory landscape which frames the development and commercialization process of companion diagnostics. Differences in the regulatory policies between the US and Europe as well as within the EU are accountable for hurdles faced by globally acting diagnostics and pharmaceutical companies. As discussed in the theoretical framework section, innovation systems need limitation by the definition of clear boundaries. The boundaries of sectorial systems which include globally acting firms and a globally acting research community often exceed national frontiers. For sectorial systems with a high demand of regulation due to the requirement to guarantee safety for the population, as it is the case for medical devices and pharmaceuticals, a misbalance with the regulatory institutions has a major impact (Carlsson et al., 2002).

It has become clear in this study that a lack of adaptation of formal norms and regulations inside the national institutions puts constrains on the development of innovation in the pharma–diagnostics sectoral innovation system. Nevertheless it can be anticipated that extensive knowledge accumulation and an increasing demand for personalized medical products through physicians and the health system will be beneficial for the development of innovative products. The high demand and therefore high potential for commercialization will help the industrial elements (pharma and diagnostics) to overlap in a way that innovation can be facilitated with the aim to create a rewarding market for personalized medicine. Further on, to preserve the interests of patients the innovation process requires interaction between firms and other organizations such as governmental agencies, non-firm organizations and universities. This is in accordance to the findings in the literature which describes the innovation system as a collective interactive process (Malerba and Nelson, 2011, Lundvall and Johnson, 1994, Carlsson and Stankiewicz, 1991, Edquist and Johnson, 1997).
6 CONCLUSION

Personalized medicine offers the potential to revolutionize therapeutic interventions for physicians and patients. However, the stratified medicine business model is challenged by gaps in scientific evidence and lacking regulatory guidelines.

Companion diagnostics are critical to personalized medicine for effective and safe development and application of a personalized drug. The FDA and the EMA recommend that biomarker testing is to be performed before prescription of certain drugs. Nevertheless there are only 21 diagnostics tests on the market, which have received FDA approval as companion diagnostics. This number is low, given the fact that to date 137 FDA- approved therapeutic products contain recommended molecular diagnostics information on the label.

To understand the challenges IVD companies face when developing and commercializing companion diagnostics this study has mainly focused on the regulatory landscape. From the literature research it has become clear that both the regulatory policies in the EU as well as in the US are based on risk evaluation. However, the US Food and Drug Administration (FDA) has benchmarked the companion diagnostics regulatory pathway. PMA approval for CDx requires demonstration of safety and effectiveness through “adequate and well-controlled” clinical trials. The demonstration of clinical utility is coupled to risks and investment levels which are unknown to the diagnostics industry. Furthermore the current pricing and reimbursement of IVD diagnostics is not value-based. This makes it difficult to cover for increased R&D investments needed for clinical investigations during companion diagnostics development. In the European Union as for now companion diagnostic is classified “low risk” and does not require proof of clinical utility, but the European legislation on medical devices including CDx is under review and it can be expected that CDx will be classified as higher-risk IVDs. This may involve reviews by notified bodies and the requirement to demonstrate clinical utility.

The inconsistent regulatory standards in the EU and the US as well as on an international level within the EU bear challenges for the global commercialization of companion diagnostics. The market competition with unregulated, laboratory-bound “laboratory developed test” (SDTs) puts another layer of complexity to the commercialization issue. Additional challenges for the diagnostics industry identified in this study are the poor reimbursement levels for high-value diagnostics and the lack of guidelines for evaluating clinical utility. A way out of this vicious cycle is a drug-diagnostics co-development strategy. According to the FDA a therapeutic product might not be approved unless its companion diagnostic is cleared by approval. Therefore the pharmaceutical industry has incentives for early alliances with diagnostics developers. This includes risk sharing and even payment of royalties to the diagnostics partner once the drug-diagnostics pair has reached the market.
An interesting finding in this study is that the three companies interviewed, had matching business models. Adduct Analysis and Pelago Bioscience offer services with the goal to provide a complete solution to the customer. Roche is offering a product platform to their customers, but with a result based payment strategy. The three business models will allow the collection of evidence that the diagnostic services/products will generate value to the health system, with the aim to create demand to the customer (health professionals, patients) and awareness of regulatory agencies regarding the value of the diagnostics.

In this study it has been postulated that the appearance of the stratified medicine business model has transformed the diagnostics and the pharmaceutical sector. A new sectoral “pharma-diagnostics” innovation system is currently under formation. So far a lack of adaptation of formal norms and regulatory polices puts constrains on the development of innovations in the pharma–diagnostics sectoral system. It can be anticipated that extensive knowledge accumulation and an increasing demand for personalized medical products by the health system will help the institutional and industrial elements to reshape in a way that innovation becomes a collective process in order to deliver value to the society.

7 OUTLOOK

New technologies, like “Next Generation Sequencing” will lead to more advanced but also more complex diagnostic testing. Professionals in the industry have estimated that it will take 5 to 10 years until computer technology can keep up with the data overload and IT based decision making is established in standard health care. Thus, a new player who is gaining immense importance in the market besides pharma and diagnostics companies are IT companies. In general health care is moving towards IT solutions and diagnostic companies could become a sub-supplier to the IT companies who offer data handling and decision support to the medical professionals and take responsibility for medical decisions which impact the patient’s life.

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### 9 REFERENCES


MELETH, S., WHITEHEAD, N., EVANS, T. & LUX, L. 2013. Technology assessment on genetic testing or molecular pathology testing of cancers with unknown primary site to determine origin.


<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Platform or technology</th>
<th>Diagnostic test value type</th>
<th>Drug and diagnostic examples</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation or mutations</td>
<td>Sequencing</td>
<td>Generally binary</td>
<td>No current examples</td>
<td>Test results depend on the percentage of cells with mutations (that is, there is a lower detection limit); may measure non-specific exons</td>
</tr>
<tr>
<td></td>
<td>Quantitative PCR</td>
<td>Generally binary</td>
<td>Cobas 4800 BRAF V600 Mutation Test; TheraScreen K-RAS Mutation Kit</td>
<td>Test results depend on the percentage of mutant sequences, adequate specimen integrity and sufficient DNA to be detected</td>
</tr>
<tr>
<td>Protein expression</td>
<td>Immuno-histochemistry staining</td>
<td>Generally continuous based on the intensity and proportion of cells with the given intensity; ordinal intensity scoring of currently approved tests</td>
<td>Dako HercepTest (detects HER2 protein expression)</td>
<td>Generally semi-quantitative and non-automated evaluation; test results can depend on pre-analytical tissue processing factors</td>
</tr>
<tr>
<td>Gene expression</td>
<td>Quantitative real-time PCR</td>
<td>Generally continuous</td>
<td>No current examples</td>
<td>Manual macrodissection may be necessary for samples with low tumour cell density</td>
</tr>
<tr>
<td>DNA copy number</td>
<td>FISH or chromogenic in situ hybridization</td>
<td>Generally continuous; could be treated as binary if the diagnostic is a complete loss of copy number or high-level amplification</td>
<td>HER2 FISH pharmDx Kit; PathVysion HER-2 DNA Probe Kit; Her2 Dual FISH DNA Probe Kit</td>
<td>Relatively complex assay technology and interpretation</td>
</tr>
<tr>
<td>Fusion protein product</td>
<td>FISH</td>
<td>Threshold is set at specific percentage of cells; essentially a bimodal distribution</td>
<td>Vyssin ALK Break Apart FISH Probe Kit</td>
<td>Relatively complex assay technology and interpretation</td>
</tr>
<tr>
<td>Gene signature</td>
<td>Next-generation sequencing</td>
<td>Could be treated as binary based on gene signature</td>
<td>No current examples</td>
<td>Complex assay technology and interpretation</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2 (also known as ERBB2). *This table shows the types of diagnostic assays used in oncology for each type of biomarker and their potential challenges in determining what constitutes a “biomarker-positive” or “biomarker-negative” readout. The H-score is a semi-quantitative intensity scale used to describe immunohistochemistry staining, and is calculated by the weighted combination of staining intensities of the cells and the proportion of cells stained at a given intensity. |

**Table 1: Diagnostic assays used in oncology. Nature Reviews Drug Discovery 12, 743–755 (2013)**
doi:10.1038/nrd4101

### Glossary

**510(k)**
A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed that is not subject to PMA.

**Antibody**
A blood protein produced in response to and counteracting a specific antigen. Antibodies combine chemically with substances which the body recognizes as alien, such as bacteria, viruses, and foreign substances in the blood.

**Bio-availability**
The proportion of a drug or other substance which enters the circulation when introduced into the body and so is able to have an active effect. Consumer health technology
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Biomarker</td>
<td>A naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified.</td>
</tr>
<tr>
<td>Companion diagnostics</td>
<td>Tests that provide information about a patient’s genetic and genomic characteristics, and are in turn used to guide decisions about treatment with specific drugs.</td>
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<tr>
<td>in vitro</td>
<td>Process performed or taking place in a test tube, culture dish, or elsewhere outside a living organism.</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>The branch of genetics concerned with determining the likely response of an individual to therapeutic drugs.</td>
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<tr>
<td>Phase I clinical trail</td>
<td>Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.</td>
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<tr>
<td>Phase II clinical trail</td>
<td>The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.</td>
</tr>
<tr>
<td>Phase III clinical trail</td>
<td>At least two (and often more than two treatment options) are compared. Phase III studies are usually randomized, meaning that patients receive either the investigational treatment or the standard treatment in a non-ordered way.</td>
</tr>
<tr>
<td>PMA</td>
<td>A process of regulatory review to evaluate the safety and effectiveness of certain medical devices. It is the most stringent type of device marketing application required by the Food and Drug Administration.</td>
</tr>
<tr>
<td>Stratified medicine</td>
<td>Approach which subdivides patients into groups based on their risk of developing specific diseases or their response to particular therapies.</td>
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