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MASTER'S THESIS – THE MASTER INNOVATION SCIENCES

The introduction of regulation 2017/746 on In-Vitro Diagnostics in the European Union. The end of the era of Companion Diagnostics?

An overview of the CDx development process and its relevant factors and relations.

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Abstract.

Companion Diagnostics (CDx) are mandatory biomarker based assays used to stratify patients for the safe and effective use of a specific corresponding medicinal product. In the last twenty years the number of medicinal products developed with a CDx increased and so has their role in targeted healthcare. In May 2022 new regulations on the market approval of CDx in the European Union become fully applicable. Important change with the current regulatory situation is that CDx are no longer considered as low-risk assay and can enter the market by self-certification of the manufacturer, but are classified as high risk assays and require conformity assessment by a notified body. Consequently, manufacturers must provide evidence of clinical by conducting clinical studies and set-up a comprehensive quality management system and post-marketing surveillance programme. In this thesis, the potential consequences of these new regulations on CDx development has been reviewed by interviewing manufacturers involved in CDx development and reviewing opinion articles from interest organizations. Additionally, by analysing the influence of other factors, such as patents, market size and competition, presence of a scientific base, resource availability, potential partnerships, reimbursement and adoption by healthcare professionals, an overview was provided on the influence of these factors on CDx development and its innovation activities with the aim to manage CDx development and to contribute to targeted healthcare.

It is expected that with the introduction of these new regulations the innovation activities in small diagnostic companies and health institutions will be hampered. However, CDx development will remain interesting for large diagnostic companies and pharmaceutical companies. The major drivers in this respect lie within the possibility for the diagnostic companies to acquire a potential monopoly position and the pharmaceutical company having the ability to compete in markets with many competing products present. Future CDx development and its expansion to other disease areas greatly depends on research conducted on disease pathology and involved biomarkers. Nevertheless, the concept CDx rely on, i.e. measuring a limited amount of biomarkers for the prescription of a specific medicinal product, is not considered to be future proof. Healthcare institutions are expected to perceive increasing difficulties in organizing healthcare when more CDx enter the market and patients need to be tested multiple times before prescribing an effective medicinal product. Future prospects, therefore, lie within the assembly of relevant biomarkers in one single assay comparing potential medicinal products.

Keywords: Companion Diagnostics, targeted healthcare, in-vitro diagnostic regulation, drug-diagnostic codevelopment process

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Glossary

Analytical performance: the ability of a device to correctly detect or measure a particular analyte.
Clinical performance: the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user.
Companion Diagnostic (CDx assay): a medical device which provides information that is essential for the safe and effective use of a corresponding [adjunct] drug or biological product.
Complementary Diagnostic: medical device that is associated more broadly, usually not with a specific drug but with a class of drugs, and not confined to specific uses by labelling, with consequent ramifications for economic, regulatory and strategic considerations.
European Medicines Agency (EMA): is a decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.
European Union (EU): group of 28 countries that operates as a cohesive economic and political block.
Food and Drug Administration (FDA): is a federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments. The FDA is responsible for protecting and promoting public health through the control and supervision of, among other things, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, and medical devices.
Health Institution: means an organisation the primary purpose of which is the care or treatment of patients or the promotion of public health.
In-Vitro Diagnostic (IVD): any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software 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.

- **Commercial developed IVDs:** those IVDs that are performed using commercially manufactured kits and equipment by private organizations and used within health institutions in clinical decision making and management.
- **In-house developed IVDs or lab developed tests (LDTs)**: IVDs that have been developed (or modified) inside a health institution (non-commercial IVDs) and used within this health institution in clinical decision making and management.

In-vitro Diagnostic Regulation (IVDR): Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.
Medical Device Regulation (MDR): Regulation (EU) 2017/745 of the European Parliament and of the council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.
Medicinal Product (Drug): Any substance or combination of substances presented as having properties for treating or preventing disease in human beings
Notified Body (NB): an [external] organization accredited by a EU member state to assess the manufacturer's conformity to the essential requirements of the directive/regulation that is in place.
Post-marketing Surveillance System: all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the

market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive action.

Quality Management System: system that covers all parts and elements of a manufacturer's organisation dealing with the quality of processes, procedures and devices. It shall govern the structure, responsibilities, procedures, processes and management resources required to implement the principles and actions necessary to achieve compliance with the provisions of the IVDR.

Self-certification or Self-declaration of conformity: a special document, which the manufacturer signs to say that the product meets all of the requirements of the applicable directives. It must be issued by the manufacturer, or by the person placing the product on the EU market if the manufacturer is not based in Europe.

Scientific Validity: the association of an analyte with a clinical condition or a physiological state.

1. Introduction.

Companion Diagnostics (CDx), introduced to the market in the 1980s (Agarwal, 2012), are diagnostic assays used to pre-screen a patient for the safe and effective use of a corresponding medicinal product (Olsen & Jørgensen, 2014). By measuring specific biomarkers the assay is able to identify those patients likely to benefit from a specific treatment (Agarwal et al., 2015) and those for which the treatment will be ineffective and/or are at increased risk of adverse reactions (European Parliament, 2017). In other words, a CDx assay can predict the likelihood of whether a medicinal product will be effective before the product is prescribed. Consequently, patients likely to benefit from the treatment with the medicinal product can be selected before therapy is started. Additionally, for patients that have been tested negatively, an ineffective treatment is prevented and the search for another therapy with a better 'fit' can be started at an early stage in the treatment process. The predictive and selective characteristics of CDx show great functionality in enabling tailor-made therapies (Olsen & Jørgensen, 2014), by replacing the 'one-size fits all' (Kalia, 2013) and the 'trial-and-error' paradigm (Jørgensen, 2015) with more targeted healthcare based on a patient's unique characteristics (Ginsburg & McCarthy, 2001). For patients, this means that unnecessary and serious side-effects, which can lead to additional and expensive healthcare, can be minimized or prevented (Davis et al., 2009) and therapeutic value can be maximized (Gaultney et al., 2011). In this way, CDx become a 'gatekeeper' for clinicians in therapy decision making (Jørgensen, 2013).

In the last twenty years the number of medicinal products developed with a CDx assay has grown rapidly and it is expected that this number will continue to expand (Agarwal et al., 2015), resulting in more targeted healthcare. With the rise of the number of CDx that determine the future use of medicinal products, and *'could cause serious risk of injury or death if they [CDx, red] do not function properly'* (Fridlyand et al., 2013, p. 2), regulatory authorities felt the responsibility to set standards regarding the development and market approval of CDx. In 2005, the United States (U.S.) Food & Drug Administration (FDA) was the first regulatory body that initiated a concept paper on several issues related to CDx development (Jørgensen, 2013), leading to the introduction of regulatory oversight on market approval for CDx in 2011 (Fridlyand et al., 2013). Until now, however, CDx assays have not been subject to any regulatory requirements in the European Union (EU) and could enter the market under self-certification carried out by the manufacturer itself (i.e. self-declaration of conformity). However, as of May 27th 2022, new regulations (REGULATION (EU) 2017/ 746) (as of now referred as new regulations or IVDR) that regulate, among other diagnostic assays, the market approval of CDx will become fully applicable in the EU (European Parliament, 2017).

Introducing regulations can have a major impact on the innovation activities of organizations and industries (Blind, 2012) and should, ideally, be designed in such a way that they protect the interest of society on the one hand and preserve the incentive of organizations to invest in innovation activities at the other hand (Crafts, 2006). However, as the (indirect) impact of new regulation is not always known beforehand, there is a risk that new regulations reduce innovation activities unintendedly. Especially, the introduction of new regulations in the healthcare sector is a challenge for regulators: there is the need for the rapid access to new and potential life-saving products and the need to ensure safety by demanding comprehensive data on the effectiveness and risks at the same time (Eichler et al., 2008).

In the new regulations, CDx are for the first time specifically addressed and considered to be high risk devices, whereas under the old directive CDx were undefined and therefore considered to be low risk devices (Enzmann et al., 2016). Consequently, the new regulations require the CDx assay manufacturer to provide (clinical) evidence on the performance of the assay, including its scientific validity, analytical and clinical performance. Furthermore, manufacturers need to implement a comprehensive quality management system and a post-marketing surveillance program (Ansari, 2013; European Parliament,

2017; Pignatti et al., 2014). Different authors (e.g. Enzmann et al., 2016; Olsen & Jørgensen, 2014) raise their concerns that these new regulations increase the development time and expenses of CDx, resulting in more expensive CDx assays that take longer before they are available on the market. Evidence from the heavily regulated pharmaceutical industry in which similar regulations are in place shows that stricter regulation, among other factors, may inhibit the development of new medicinal products (e.g. Abraham et al., 2003; Moors et al., 2014). This could imply that the development of new CDx assays and thereby its aim to contribute to the evolvement of targeted healthcare will be hampered by the introduction of new regulation.

A stagnation of CDx development due to this new regulation can be considered undesirable as they are believed (e.g. Trusheim & Berndt, 2015) to be of added value for society and patients. Therefore, this thesis aims to investigate the potential impacts of the new regulation on the development process of CDx and identifies options to design interventions to manage CDx development. To design adequate interventions it is important to know the development process of an innovation in detail (Nooteboom & Stam, 2008). Based on the concept paper on drug-diagnostic codevelopment issued by the FDA in 2005 (see Hinman et al., 2006), Jørgensen and colleagues (2012; 2013; 2018) drafted a model on the CDx development process. This linear model represents the steps that need to be conducted by the manufacturer of the CDx assay, in conjunction with the development steps of the corresponding medicinal product, to get a validated CDx on the market. As such, this development model does not provide an overview of other actors involved and potential other factors affecting this development process. Insights from innovation studies (e.g. Carlsson & Stankiewicz, 1991; Cooke et al., 1997; Edquist 1997; 2001; 2004; Freeman, 1987; Nelson, 1993), however, learn that the development, production and use of innovations is shaped by other actors than the manufacturer and can be considered as socio-technical in nature. In other words, the development of innovations is not only dependent on organizational or internal factors, but also influenced by environmental or external factors that can be out of range or cannot be affected by the organization that develops the innovation. Organizations do not operate and innovate in isolation (Edquist, 2001), but are part of a larger system: the Innovation System (IS). Alonso (2017) provides an overview of factors affecting the development process of diagnostic products in general. Medical assays and diagnostics alone are extremely heterogenous and include wide-ranging technologies (Stern, 2017), making it difficult to suggest that these factors all have the same effect and relation on the development process of individual products or technologies. By providing a detailed overview of the development process of CDx, including the internal and environmental factors that affect the development process, this thesis intents to link the suggested linear CDx innovation process on organization level with an innovation system approach by identifying both internal and external factors and actors relevant to CDx development to identify potential bottlenecks and new targets for innovation policy. By interviewing manufacturers, this thesis focus on the level where CDx development is actually initiated and conducted. As a result, this thesis is guided by the following research question:

What are the factors, actors and their relations relevant to the development process of CDx from a manufacturers perspective in the European Union? And what intervention options do they envision to maintain or increase CDx development to contribute to targeted healthcare?

This thesis continues with a more detailed description of CDx and the opposed regulatory changes for the approval of both commercial and non-commercial developed CDx in the EU in section 2. In section 3, the IS approach will be further elaborated upon and the factors proposed by Alonso (2017) will be explained according their relation to innovation and development activities. Section 4 describes the used methods of this research, followed by the results in section 5 after which conclusion are drawn and reflected upon in section 6.

2. Contextual background.

2.1. What are Companion Diagnostics?

Medical tests play an important role in healthcare decision making and clinical management as they are used by healthcare professionals to gain information about (1) the presence or absence of a disease, (2) to develop a treatment plan, and (3) to monitor the results of the treatment and the progression of the disease (Fineberg, 1978; Derksen et al., 2011). In the process of clinical decision making the test result invites for a clinical response from the healthcare professional, such as to start, stop, or modify the treatment or to do nothing at all (Derksen et al., 2011). For diagnostic assays, biomarkers are particularly measured to gather the information needed (Milne et al., 2015). A biomarker can be defined as a *''characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention''* (Puntmann, 2009, p. 538). Biomarkers are especially measured to identify specific characteristics of patients with the aim to define subpopulations for which particular treatments will be beneficial. The development of targeted healthcare and medicinal products for specific patient populations is the result of research that indicates that diseases are heterogenous and consist of different subtypes, each requiring a specific medicinal product. (disease x, figure 1).

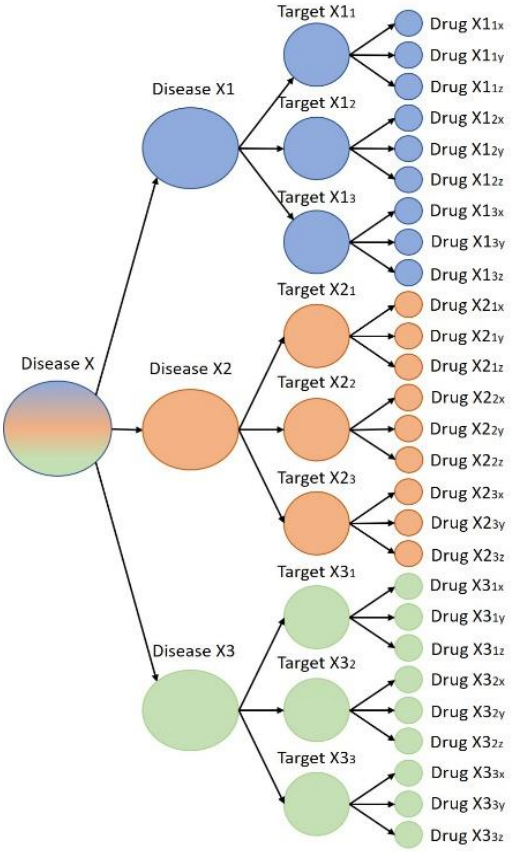

Figure 1: Overview of a heterogenous disease, including its biological subgroup, targets linked to this subgroup and medicinal products developed for these targets. Adapted from Jørgensen, 2011.

Two main groups of diagnostic assays that measure specific biomarkers to select patients for medicinal products in the approach of targeted healthcare can be distinguished: CDx and complementary diagnostics (Milne et al., 2015). Key difference between these groups is determined by the obligation of using the assay before prescribing the medicinal product. While CDx are linked to a specific medicinal product within its approved label and are considered to be mandatory before prescription, complementary diagnostics are associated more broadly with a class of medicinal products, meaning that its use is not restricted by the label of a specific medicinal product (Milne et al., 2015). The following definition of CDx is used in this research: *'a CDx assay is a medical device which provides information that is essential for the safe and effective use of a corresponding [adjunct] drug or biological product' (*FDA, 2018a; EMA, 2019). As such, CDx (1) identify patients who are most likely to benefit, (2) or at increased risk for serious side effects from a treatment with a particular medicinal product (figure 2) and (3) monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness (FDA, 2018a; EMA, 2019).

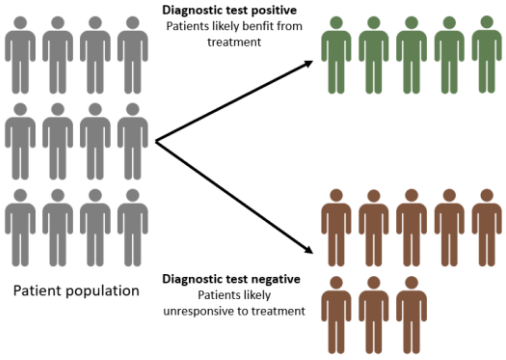

Figure 2: Defining patient (sub)populations on test outcomes performed by a CDx assay before prescribing the corresponding medicinal product. Authors own compilation.

2.2. Changes in the regulatory approval of CDx with the introduction of Regulation (EU) 2017/746 on In-Vitro diagnostics.

In the European Union, market authorization of medical devices, such as diagnostics tools, is regulated separately from medicinal products (Fridlyand et al., 2013). Diagnostic tests that measure biomarkers on bodily samples, like blood and tissue, are considered to be in-vitro diagnostics (IVDs) (Fridlyand et al., 2013; Pignatti et al., 2014)[1]. IVDs are currently approved in the European Union under the IVD directive (IVDD) prescriptive list-based classification system (98/79/EC), but will only be approved under the IVDR as of the 27th of May 2022, after a 5-year transition period in which products can be on the marker under the directive or regulation (figure 3).

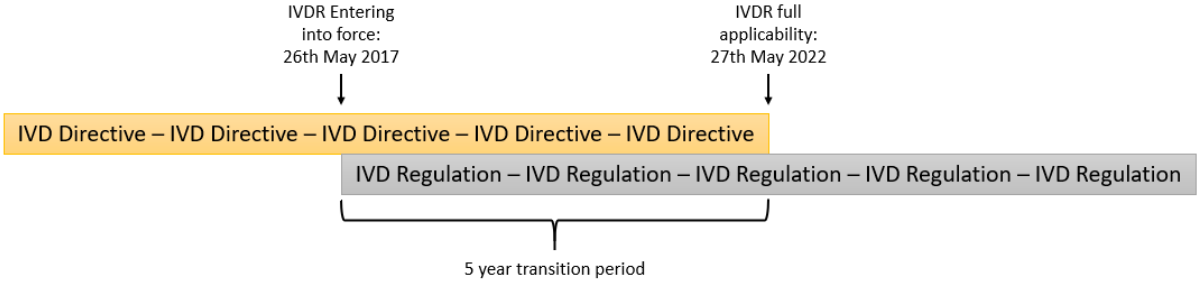

Figure 3: IVD directive – IVD regulation timing overview. After the IVDR entered into force on 26th of May 2017, IVDs can be on the market under both approval systems during the 5-year transition period. After 27th of May 2022, IVDs can only be on the market when approved under the IVDR. Authors own compilation.

The new regulation has the main aim to protect and ensure the safety of customers while stimulating innovation activities: *''This regulation aims to ensure the smooth functioning of the internal market as regards in vitro diagnostic medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small and medium-sized enterprises that are active in this sector. At the same time, this Regulation sets high standards of quality and safety for in vitro diagnostic medical devices in order to meet common safety concerns as regards such products''* (European parliament, 2017, p. 1).

2.2.1. The approval of commercial developed CDx under the IVDR.

Under the new IVDR, commercial developed IVDs are approved under a rule-based risk classification system (Annex VIII in IVDR) (table 1), conformity assessment procedures and clinical evidence (European Parliament, 2017). The risk classification system determines (1) who is responsible for the assessment and approval of the IVD and (2) what the manufacturer should establish and what data should be provided and assessed, both pre- and post-market, to get the assay approved and certified in the EU. Other than risk category A for which the manufacturer is able to get the IVD assay on the market by self-certification, risk categories B, C and D involve notified bodies who assess and certify the IVD (table 1). A notified body (NB) is '*an [third party] organization accredited by a EU member state to assess the manufacturer's conformity to the essential requirements of the directive*' (Olson & Jørgensen, 2014, p. 5). When approved and verified confirm the specific requirements of that risk category the NB assigns a CE mark for that specific assay, enabling the IVD to enter the market in the EU.

[1] Text in Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic: ''*It should be made clear that all tests that provide information on the predisposition to a medical condition or a disease, such as genetic tests, and tests that provide information to predict treatment response or reactions, such as companion diagnostics, are in vitro diagnostic medical devices*''.

Table 1: Risk classification categories for IVDs under the IVDR. Adapted from Pignatti et al., 2012.

Class	Risk Level	Examples of devices	Approval by
A	Low individual risk and low public health risk	Buffer solutions, washing solutions, clinical chemistry analyser, general culture media	Manufacturer of the product (self-certification)
B	Moderate individual risk and/or low public health risk	Pregnancy self-testing, vitamin B12, urine test strips, cholesterol testing, fertility testing	Notified body
C	High individual risk and/or moderate public health risk	Companion Diagnostics, blood-glucose self-testing, genetic tests, sexually transmitted agent testing	Notified body
D	High individual risk and high public health risk	HIV blood diagnostic, HIV blood donor screening	Notified body

In the new IVDR, CDx are specifically addressed and defined and are as such considered to be class C products (see Annex VIII, rule 3 in IVDR) (table 1). Therefore, commercial CDx assays, both new assays and assays already on market (re-approval is needed) are subject to regulations involving: (1) a performance evaluation report in which the scientific validity, analytical and clinical performance of the device must be demonstrated, (2) establishment of a comprehensive post-marketing surveillance plan and (3) the implementation of a quality management system (Ansari, 2013; European Parliament, 2017; Pignatti et al., 2014) (figure 4) (see for more details appendix I). One of the most important changes for commercial manufacturers is the need to conduct clinical performance studies to prove the clinical utility of the assay: ''*Clinical performance studies shall be carried out unless it is duly justified to rely on other sources of clinical performance data*'' (European Parliament, 2017, p. 148). This means that any manufacturer of a CDx assay should perform clinical performance studies, unless the CDx assay is a so called ''*me-too*'', follow-on or generic device: an assay that is similar to already known assay, i.e. original prototype, in terms of technologies used, biomarkers measured etc and is not subject to any changes that distinct the me-too assay from its prototype.

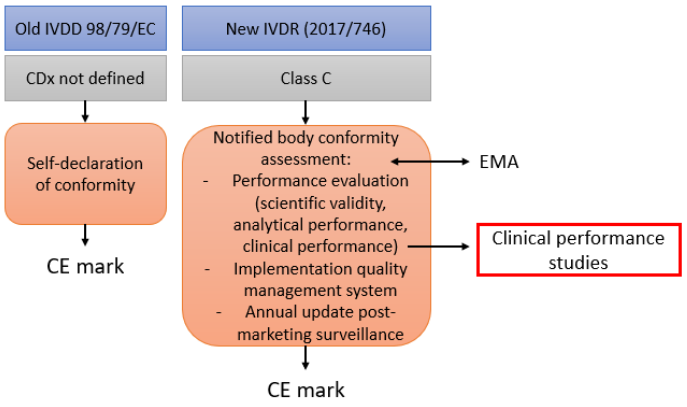

Figure 4: Pathway to CE marking of a commercial developed CDx under the old IVD directive and the new IVD regulations. Partly adapted from Pignatti et al., 2014.

Other than other IVDs in risk category C, the EMA, which main task is to approve medicinal products for the European market, also needs to assesses in collaboration with the NB the performance of the CDx assay for its use in combination with the medicinal product (European Parliament, 2017).

2.2.2. The approval of in-house developed CDx under the IVDR.

The new IVDR also applies to in-house developed IVDs, in the IVDR refered to as lab developed tests (LDTs). These assays have been developed in health institutions and are used within its laboratory to test samples with the intention to use the test results in clinical decision making (De Bruijn & Roszek, 2015). Under the IVDR in-house developed IVDs have exemption from the estensive regulatory demands that apply to commercial IVDs: ''*with the exception of the relevant general safety and performance requirements set out in Annex I, the requirements of this Regulation shall not apply to*

devices manufactured and used only within health institutions established in the Union'' (European Parliament, 2017, p. 19).

Although, in-house developed IVDs do not need to pass an extensive pre-market approval process, specific requirements are set with the use and development of in-house developed IVDs (see article 5, ltd 5a-5i in IVDR, p. 19) to ensure patient safety and supervise the fit of the assay with its intended purpose. The most important requirement is that health institutions are only allowed to develop and use in-house developed IVDs if no IVD is commercially availble that is able to fulfill patients needs: *''the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market''* (European Parliament, 2017, p. 19). This means that hospitals and other health institutions need to use the commercially developed CDx over in-house developed CDx, if availble, and must provide justification of their manufacturing, modification and use of in-house CDx.

3. Theory

3.1. Innovation development: a non-linear process.

Innovation development includes *''all the decisions, activities and impacts that occur from recognition of a need or a problem, through research, development and commercialization of an innovation, through diffusion and adoption of the innovation by its users to its consequences''* (Rogers, 2003, p. 137). In the traditional linear model (e.g. Cooper & Kleinschmidt, 2011; Rogers, 2003; Tidd & Bessant, 2001) innovation development is presented as a pipeline of consecutive stages, starting at scientific research, followed by product development at ending with the adoption and use of the innovation by the end-user. In this approach innovation activities are understood as a process of the organization itself. Based on this model Jørgensen and colleagues (2012; 2013; 2018) explain the different stages important in CDx development, referred to as the Drug-Diagnostic codevelopment model (figure 5). In this model the CDx assay is developed in conjunction with the medicinal product and both products are approved and introduced on the market at the same time.

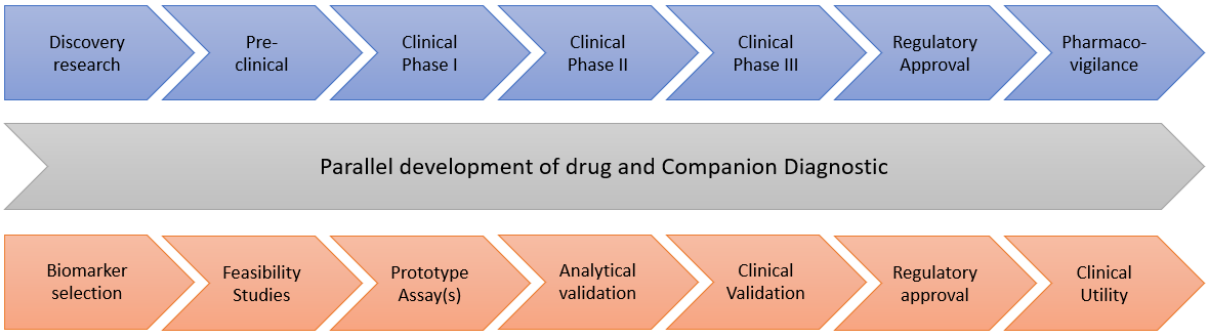

Figure 5: The drug-diagnostic codevelopment model. The upper (blue) pipeline illustrates the development process of the medicinal product and the lower (red) pipeline illustrates the development process of the CDx assay. Adapted from Jørgensen, 2012.

In the drug-diagnostic codevelopment model the individual development stages of the CDx assay (lower red pipeline, figure 5) and the corresponding medicinal product (upper blue pipeline, figure 5) are distinguished. The codevelopment of a CDx assay and a corresponding medicinal product starts with biomarker discovery and selection on the diagnostic side and compound identification on the pharmaceutical side. After establishing the feasibility of potential biomarkers, the development of an assay is started in conjugation with the pre-clinical and first-in-man phase I studies. After markers are analytical validated, the assay is incorporated in the clinical phase III studies of the medicinal product to provide evidence on the relationship between the predictive and selective characteristics of the CDx

assay and the effectiveness of the medicinal product for regulatory approval. A detailed description of this development process and its stages is provided in Appendix II. In this model, a pharmaceutical company typically partners with a diagnostic company and both are considered as the primary developers in this model (Milne et al., 2015), sometimes also partnering with other organizations, such as research institutes and consultants (Moore et al., 2012). Only six percent of the medicinal product-CDx combinations are developed within the same manufacturer. However, little is known where and under what circumstances in the development process these partnerships are being established.

Literature suggesting that innovation development is the result of social and economic processes (e.g. Kuhn, 1962; Nelson and Winter, 1977; Bijker et al., 1989) contributed to the acknowledgement of innovation not being a linear process. In other words, organizations are understood to be embedded in a wider system (Edquist, 1997; 2001; 2004) in which their innovation activities are also influenced by external factors, which cannot be affected by the organization developing the innovation. As a result, the CDx codevelopment model as described above is not perceived as solely a process of its manufacturer(s), but is also influenced by external factors. This conception of the innovation process being a non-linear process involving a range of factors can be explained by the innovation systems approach (Freeman, 1987; Edquist, 1997; 2001; 2004; Lundvall, 1992). An innovation system (IS) can be defined as: *"all important economic, social, political, organizational, and other factors that influence the development, diffusion, and use of innovations"* (Edquist, 1997, p. 14). From this theoretical perspective a better understanding of the empirical realities of complex innovation processes can be acquired by mapping and explaining the influence of its system features on the development process of the innovation under subject. Those system features include actors, the relations among them and the institutions present that shape these relations (table 2).

Table 2: System features of an innovation system. Adapted from Wieczorek & Hekkert, 2012.

Innovation System Feature	Subcategory	Examples
Actors or players	Civil society	-
	Companies	Start-ups, large firms, multinational firms
	Knowledge institutes	Universities, research centers, technological institutes
	Governmental bodies	Regulatory authorities, (inter-)national governments and ministries, patent offices
	NGO's	Charity organizations
	Other parties	Financial organizations, consultants, intermediaries
Interactions	At level of networks	University-industry (public-private) cooperation
	At level of individual contacts	Contact between individuals of different organizations or actor groups
Institutions	Hard institutions	Rules, laws, regulations, instructions
	Soft institutions	Customs, common habits, routines, established practices, traditions, ways of conduct, norms, expectations

The different actors present within a system, such as companies, knowledge institutes, consumers, and governmental bodies, are defined as *''formal structures with an explicit purpose and they are consciously created''* (Edquist & Johnson, 1997, p. 47). The IS approach does, however, not imply a collective and coordinated action in favor of the development, diffusion and utilization of the

innovation as actors have a unique role and objective in the system (Wieczorek & Hekkert, 2012). Different perspectives of actor roles are described in the literature, including the perspective of the role they play in the innovation system, such as users, producers, intermediary and supportive organizations (Smits and Kuhlman, 2004) or based on their economic activity, such as companies and consumers (Woolthuis et al., 2005). These differences in roles and objectives can result in that the interaction or relation between actors may be unplanned, unintentional and can even result in conflicts or tensions (Bergek et al., 2008). The actions of actors and the relations among them are however strongly influenced by institutions: *''a set of common habits, norms, routines, rules or laws that regulate the relations and interactions between individuals, groups and organizations''* (Edquist & Johnson, 1997, p. 46). Whereas hard institutions, such as the legal system, force actors to adhere to these institutions if otherwise certain 'punishments', such as fines or the removal of products from the market can be initiated, soft institutions represent ''unwritten'' rules, such as norms, habits and routines specific for organizations or geographical areas (Wieczorek & Hekkert, 2012).

In the literature a variety of specific innovation system perspectives have been developed to study the non-linear process of innovation activities on a national level (National Innovation Systems e.g. Freeman, 1987; Nelson, 1993; Lundvall, 1992; 2007), regional level (Regional Innovation Systems e.g. Brackzyk et al., 1998; Cooke et al., 1997), sectoral level (Sectoral Innovation Systems (e.g. Malerba, 2002; 2004) and technological level (Technological Innovation Systems e.g. Carlsson & Stankiewicz, 1991; Hekkert et al., 2007; Bergek et al., 2008). The main difference between these various innovation system perspectives is their boundaries. Whereas the systems on a national and regional level focus on innovation processes in a specific geographical area, sectoral innovation systems focus on innovation processes regarding a specific set of products having the same knowledge and technological base and technological innovation systems on a specific technology only. Whether a IS should be spatially, sectorally or technologically delimited, depends on the purpose or the object of study. However, the different perspectives can complement each other rather than excluding each other, meaning that a combination of perspectives can be used to explain what determinants are important in a specific innovation process. However, just mapping the system features and the boundaries of a specific IS does not explicitly addresses what 'happens' in the system (Edquist, 2001). Therefore, it is key to focus on factors that result from the presence and role of different organizations and institutions in the IS under investigation that influence the development, diffusion and use of innovations (Edquist, 2001). However, what factors are important in the innovation process varies among different innovations. Additionally, Edquist (2001) emphasizes that that some factors might have a greater influence on the innovation development process than others, but cannot be seen as independent of each other as they can support and reinforce each other.

3.2. Factors important in the development of diagnostics.

Following the IS approach, the codevelopment model from Jørgensen and colleagues (2012; 2013; 2018) can be complemented by internal and external factors influencing this development process. Departing from the work of Alonso (2017), six factors are identified (intellectual property landscape, market (size), regulation, resources, adoption by users, and reimbursement) influencing the diagnostic product development process and should be taken into account when designing a commercialization strategy (figure 6 on the following page). For each of these factors their influence on the innovation development process has been explained, and where possible complemented with literature from the healthcare sector.

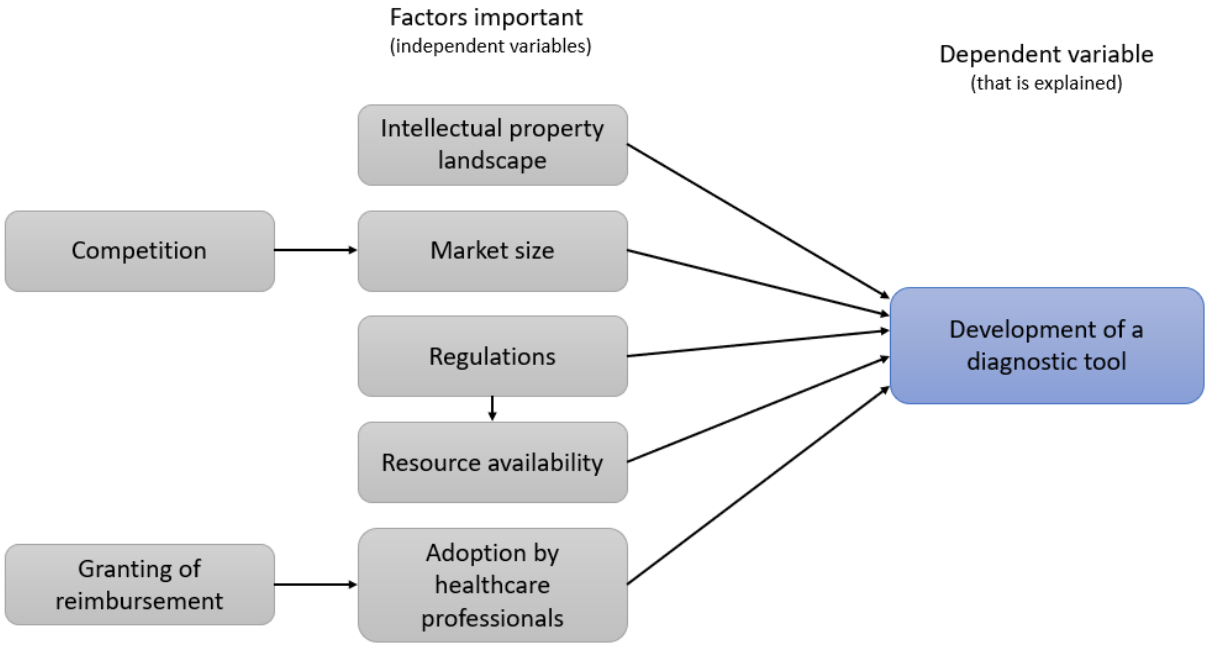

Figure 6: Overview of factors proposed in the literature affecting the development of a diagnostic assay. Authors own compilation.

Starting with the intellectual property landscape, a patent provides its owner with market exclusivity increasing the value of the invention for a limited period by legally obstructing any other organization from using the technology, tool or compound described in that patent (Gilbert, 2006; Moors et al., 2014). Research on whether patents inhibit innovation activities is divided and ambiguous (e.g. Gold et al., 2010) as patents both tend to stimulate and hamper innovation activities. Today, the medical device industry and the pharmaceutical industry are one of the main users of the patent system (Allan et al., 2018; Grabowski, 2002; Moors et al., 2014) with the main aim to generate revenues from sales and to get a financial return on the investments made (Gold et al., 2010; Moors et al., 2014). Especially in industries like the pharmaceutical industry were the development of new medicinal products is very expensive (latest estimates predict that medicinal product development costs $2870 million (DiMasi et al., 2016)) and imitation costs cover only a small fraction of the originator's costs (Grabowski, 2002), investing in innovation activities and new product development is perceived as not attractive without having protection. This is supported by the work of Mansfield (1986) who indicated that sixty percent of commercial introduced inventions in the pharmaceutical industry would not have been developed at all without patent protection, whereas these numbers were found much lower for other industries, like machinery (17%), petroleum (25%), textiles and motor vehicles (both zero percent). However, patent protection does not guarantee total prevention from competition as other organizations can invent around the patent and can develop substitute products (Gilbert, 2006). Yet, studies suggest that organizations tend to avoid research projects holding many patents by other organizations (OECD, 2003), others argue that existing patents stimulate innovation activities by finding new ways to 'invent around' existing patents (e.g. Walsch et al., 2003). Another way patents can stimulate innovation activities is through knowledge spillovers as patents are publicly published, providing other organizations with new knowledge for future developments (Gilbert, 2006; Moors et al., 2014). However, patents can also solely be used as a strategy tool to hamper innovation activities from other organizations without new products being developed by the owner (Moors et al., 2014; Palomeras, 2003). Furthermore, research indicates (e.g. Gold et al., 2010; Lanjouw, 2005; Moors et al., 2014) that patents reward low risk incremental innovation over high risk radical innovations as no distinction is made between these two for the duration of the patent, questioning whether patents actually result

in the introduction of innovative products. Additionally, there is the concern that patents are used in the healthcare sector to create a strong market position to increase the price of products, resulting in expensive products providing limited benefits for patients. In this way and by blocking other organizations from developing potential life-saving innovations, patents have the potential to inhibit patients access to medical care (Gold et al., 2010).

When looking at market size, a specific unmet need of customers is needed in the first place to create a necessity for new products and services being developed (Tidd & Bessant, 2005). However, the size of the market is especially important for profit-oriented organizations as it directly influences the revenues of an organization and thus the profitability of the investments made (Pindyck & Rubinfeld, 2013). In 1966, Schmookler already documented a causal relationship between potential sales and innovation. In other words, markets having many customers and low development costs will likely receive the greatest and earliest attention, where other markets that are considered to be less profitable due to high development costs and/or a smaller number of customers will be ignored (Porter, 1990). This is confirmed by research in the pharmaceutical industry (e.g. Acemoglu & Linn, 2004; Dubois et al., 2015) which documented that the development of medicinal products and related innovation activities was driven by market size and the potential profits provided by those markets. In absence of statistical research on casual relationships between market size and innovation activities in the diagnostic industry, Gelijns & Halm (1991) did report that in the medical device industry some innovations, such as the cardiac pacemaker and the pH maker, were not developed and produced by large organizations as the market of those products was at first considered to be very small and not considered profitable enough to invest in. Those markets were eventually served by small companies (Gelijns & Halm, 1991).
However, organizational level profitability does not only involve the amount of customers in a certain market, but is also dependent on the presence of competing products as described in the early work of Schumpeter (1934, 1950). Markets having limited competing products provide organizations with large marker shares and relative high profits. However, high profits attract other manufacturers to invest in product development with the aim to introduce imitated or substitute products. In this way, competition increases, decreasing market share and profitability of the original product(s) as the time passes (Porter 1990; Roberts, 1999). If new entrants introduce improved products successfully, these new product(s) can replace original products and possibly result in incumbents leaving the market. This process is also described in the literature as creative destruction (e.g. Christensen, 2013; Schumpeter 1934). In this way, rivalry among competitors tends to stimulate innovation activities as organizations should innovate to improve or develop new products in order to keep or create market share to ensure organizational survival (Porter, 1990). This is confirmed by research in the pharmaceutical industry indicating that innovative propensity positively effects sustaining profitability in the long run by still being able to compete with rivals (Roberts, 1999)

Another relevant factor is the presence of regulations: ‘’*the implementation of rules by public authorities and governmental bodies to influence marker activity and the behavior of private actors in the economy*’’ (Blind, 2012, p. 5). The impact of regulations on innovation activities is determined by (1) the extent of the compliance costs and the (2) incentive effect to invest (Blind, 2012). Compliance costs can be defined as ‘’*what it costs regulatees to meet the requirements of those who regulate them*’’ (Hood et al., 1998, p. 63-64), whereas the incentive effect is related to the degree organizations are encouraged to perform innovation activities. In the most ideal situation, regulations have been designed in such a way that the compliance costs and limitations on freedom of action do not exceed an organizations incentive to invest in innovation, while at the same time protecting the interests of society. However, the ability to cope with compliance costs to adapt to regulatory change is

organization specific and depends on the internal and external competences individual organizations have (Cook et al., 1983). Organizations that are able to build or shift their resources and activities radically, as described in the dynamic capabilities approach, have the possibility to transform and to comply to regulatory change (e.g. Teece et al., 1997; Teece and Pisano, 1994). Organizations that are less able to profitably build and renew resources and assets, are threatened in their existence, while others can adapt and continue to grow (Cook et al., 1983). Research (e.g. Grabowski et al., 1978; Thomas, 1990; Wiggins, 1983) on the effect of regulations in the pharmaceutical industry found a significant effect on development costs of new medicinal products resulting in declining innovation activities in general, but especially in smaller firms. Smaller organizations were not able to build the (financial) resources needed to meet the compliance costs of pharmaceutical regulation and needed to leave the market. In contrast, large companies benefitted from the leave of smaller companies as this resulted in less competition and increased sales (Thomas, 1990).

Another factor important in the development, design and manufacturing of products is the availability of resources: *''tangible and intangible assets firms use to conceive of and implement their strategies''* (Wernerfelt, 1984, p. 138), which can be distinguished in financial resources (e.g. equity capital, debt capital, retained earnings etc), physical resources (e.g. technologies, facilities, materials, equipment, buildings etc) and human resources (e.g. the training, experience, judgment, intelligence, and insights of individual workers) (Barney & Arikan, 2001; Wernerfelt, 1984)). The resources needed vary among products and industries, but in general do only product development projects that get adequate and the specific resources needed have a chance to succeed (Chirstensen, 2013). Following the resource-based view, developed by Wenerfelt (1984) and Barney (1986), the resources an organization develops or acquires determines its innovativeness and its ability to develop new products. One of the main assumptions in this view is that the presence and amount of certain resources is heterogenic among organizations, resulting in a difference in innovativeness between organizations and ability to adapt to changing environmental conditions as described above (regulations).

In order to be able to compete with existing products and to get adopted, new products must be superior and deliver unique benefits to its user, i.e. it is about 'being better' than the competition. In their research, Cooper & Kleinsmidt (2011) show that products having unique and superior benefits are adopted more often than products only offering limited benefits, resulting a greater competitive advantage and market shares. The drive of being superior over other products on the market, stimulates innovation activities to improve and develop new products. This, however, arises the question what makes certain innovations superior over others. Rogers (2003) developed a theoretical model in which five attributes of innovation (table 3) are being distinguished that influence the rate of adoption. This framework has been applied in the clinical context by e.g. Cain & Mittman (2002) and Sanson-Fisher (2004), see for examples table 3. However, as users will not adopt products having no or limited benefits over existing products, the introduction of new and improved products increase the complexity of developing future products that need to be even more superior (Scannell et al., 2012). Except for innovation related characteristics, different actors or change agents can also influence the rate of adoption or even have the power to determine the adoption decision of users (i.e. type of innovation decision) (Rogers, 2003). Adoption rates can also dependent on the activities of other actors than the manufacturer as shown in the research of Gagliardi et al (2018) on the diffusion of the medicinal product Abacavir and its CDx assay in Italy. In this specific case, incorporating the use of the CDx assay as a necessary component in the clinical guidelines by the ministry of health contributed significantly to its adoption by healthcare professionals.
One specific aspect mentioned in the literature influencing the adoption of healthcare products by healthcare professionals is the granting of reimbursement by national authorities. Reimbursement

plays an important role in using or prescribing healthcare products when healthcare professionals take the expenses for the patient into account. Without reimbursement patients can be unwilling or unable to pay for the use of medical assays (Huttin & Andral, 2000; Schreyögg et al., 2009). In other words, the granting of reimbursement affects the accessibility of products and therapies (Schreyögg et al., 2009), influencing the number of potential customers and the turnover of the healthcare product (Stark & Jaeger, 2011). Consequently, manufacturers would have little incentive to develop new products if not covered by reimbursement. This is especially visible for indications present in low and middle income countries were the lack of a social reimbursement system and poverty is an impeding factor for medicinal product development, even though the presence of a large market (Kremer, 2002). This is confirmed by the research of Clemens (2013) showing that the assignment of reimbursement drives medical innovation. However, the decision on whether reimbursement is granted also relies on 'being better' in terms of cost-effectiveness than therapies and products already reimbursed (Schreyögg et al., 2009). Authorities will not grant reimbursement to expensive new therapies or products if no or limited clinical benefits for patient are documented.

Table 3: Perceived attributes of innovation that influence the rate of adoption by users.

Perceived attributes of innovations	Definition (see page 265 and 266 in Rogers, 2003).	Examples when applied to the clinical setting	Relation with rate of adoption
Relative advantage	Degree to which an innovation is perceived as being better than the idea it supersedes	Cost-effectiveness, clinical benefits for patients	Positive relation
Compatibility	Degree to which an innovation is perceived as consistent with the existing values, past experiences, and needs of potential adopters	Early detection of life-threatening diseases, presence of infrastructure to run tests.	Positive relation
Complexity	Degree to which an innovation is perceived as relatively difficult to understand and use	Difficulty in administering medicinal products (pills vs injection), difficulty of using tests and interpreting results (need of education/training).	Negative relation
Triability	Degree to which an innovation may be experimented with on a limited basis	Demonstration at conferences (knowledge about existence)	Positive relation
Observability	Degree to which results of an innovation are visible to others	Documented effectiveness and clinical utility of medicinal products and diagnostics	Positive relation.

4. Methodology.

4.1. Research design.

To identify and gain insight in (1) motives to develop a CDx assay or the corresponding medicinal product, (2) partnerships and (3) actors and factors relevant to the CDx development process, including expected consequences of the new regulation and (4) potential interventions to manage CDx development, interviews were held with manufacturers, which included diagnostic companies, pharmaceutical companies and health institutions. The aim of these interviews was to obtain an in-

dept understanding of the CDx development process. The data from the interviews was complemented with information from opinion articles from interest organizations. Thereby, to validate the information provided in section 2.2 and appendix I on the regulatory changes and to identify the consequences of the IVDR on CDx development interviews with regulatory experts were held and a symposium with two speakers on the IVDR was attended. Identified actors and the relationships among them have been mapped to provide a structural analysis of the CDx innovation system. Opinion articles from interest organizations were also checked upon intervention proposals.

4.2. Data collection.

4.2.1. Semi-structured interviews.

Recruitment of respondents & selection criteria.

To identify diagnostic companies involved in CDx developments a FDA list of approved CDx assays, which included information on its manufacturer[2] was used. To identify those companies engaged in CDx development without already having a CDx on the market, tables 3 and 4 from the article of Naylor & Cole (2010, p. 7-10) were consulted. Companies of both lists were checked upon (1) its existence (companies can be acquired by other companies or can be closed), (2) presence in the EU and (3) involvement in CDx development (company offers a CDx or is involved in CDx development). In total 28 companies were identified that meet these criteria and were approached for an interview (see for an complete overview of companies appendix III) from which five responded positively.

A desktop research was conducted to look for academic hospitals that are engaged in the development of CDx assays for in-house use. The keywords ''institute'', ''public organization'', ''university'', and ''hospital'', in combination with ''manufacturing'', ''development/developing'', and/or ''agreement'', and in combination with ''biomarker'', ''companion diagnostics'' or ''CDx'' were used to find (academic) health institutions involved in biomarker based assay and CDx development. Ten (academic) hospitals or health institutions were found to be engaged in CDx development in the EU and were approached for an interview (see appendix IV) of which five respondents from four different institutes responded positively.

For the identification of pharmaceutical companies engaged in the development of CDx for their medicinal products, three different recruitment methods were used. First of all, the same FDA list was used to identify manufacturers of the corresponding medicinal product for the approved CDx assay by checking the NDA (New Drug Application) number of the medicinal product (see Appendix V). This list was complemented by table 4 from the article of Naylor & Cole (2010, p. 10) that provided an overview of pharmaceutical companies that entered a CDx development deal with a diagnostic company in the period 2000-2010. Finally, for all diagnostic companies found in appendix III, an additional web search was conducted to identify possible partnerships with pharmaceutical companies later than 2010. The keywords *''[name diagnostic company]''* in combination with *''agreement'', ''cooperation'', ''contract''* or *''partnership''* and *''pharmaceutical company''* in combination with *''Companion Diagnostic''* or *''CDx development''* were used to identify pharmaceutical companies in the development of a CDx assay for the medicinal product (see column 3 appendix III). Pharmaceutical companies found were also checked upon its existence (companies can be acquired by other companies or can be closed) and presence in the EU. In total, 23 pharmaceutical companies were found to fit these criteria and were approached for an interview. Four of them responded positively and interviews were held.

Finally, snowball sampling was used to increase the number of respondents having expertise in the field of CDx development and/or the IVDR. In total, six respondents, including all regulatory experts, were recruited by snowball sampling.

[2] List of cleared or approved Companion Diagnostic devices: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

Respondents.

In total, 20 respondents were interviewed in the period October 2018 – February 2019 (see table 4, section 5 for an overview). Interviews were held in Dutch or English at the workplace of the respondent in the majority of the interviews (x=13). Those interviews with respondents located in different EU member states, such as Italy, Belgium, Denmark, Sweden, Ireland, UK[3], and Switzerland[4], Skype, Webex or phone was used to conduct the interview.

Interview guide and templates.

During the interviews questions were asked to identify (1) motives to develop CDx or the corresponding medicinal product, (2) potential partnerships in the development process, (3) potential factors that could affect the CDx development process, (4) consequences of the introduction of the IVDR, and (5) preferred interventions or policy measures to stimulate CDx development. Interview templates were adapted on the role of the manufacturer (developing CDx assay or corresponding medicinal product) and the imposed the regulatory changes for specific manufacturers as described in section 2.2.1. and 2.2.2. (commercial vs non-commercial). These adapted templates can be found in appendix VI and VII. For the regulatory experts the interview templates described in appendix VIII and IX were used.

During the interviews respondents were encouraged to be profound in their answers and explanations, to avoid misunderstanding. Each interview was recorded (with permission of the respondent), transcribed, and a report of the interview was send to the respondent for confirmation[5]. If an interviewee had the wish to change or to provide additional information on their points of view, an addendum was added before the final data analysis.

4.2.2. Opinion articles from interest organizations.

Opinion articles were used in this research as an additional data source to identify specific views of actor groups on potential factors, consequences of the IVDR and interventions concerning CDx development. In the absence of articles providing an overview of interest groups representing actors in the IVD and/or CDx industry, the website from the medical device industry[6] was used to identify interest organizations representing actors involved in CDx development. As 'medical device' is a broad term used for any device that is used for medical purposes, any association was checked upon whether the actor it represented had also a role in CDx development, such as (1) in-vitro diagnostic companies, (2) (bio-)pharmaceutical companies, (3) healthcare professionals (physicians and laboratory personnel), (4) patients, (5) relevant regulatory authorities, such as Notified Bodies. As many national interest groups are member of an interest group operating on EU level, national and EU interest groups were crosschecked on potential members not listed by the website. In total, 61 interest groups were identified (appendix X). Many of the interest groups (x = 35), however, did not had a website in a language, Dutch or English, known by the researcher and were therefore not searched for opinion articles to avoid misinterpretation. Any opinion article or position paper found was scanned on its content in advance and included for analysis when it covered views on (1) the need of personalized medicine and targeted healthcare in general and/or CDx specifically, (2) any factors important in developing IVDs or CDx, (3) the new IVDR, and (4) interventions to stimulate IVD or CDx development.

[3] At the time of interviewing the UK was still part of the EU. Furthermore, both UK respondents were part of international operating organizations present in other EU countries than the UK.

[4] Switzerland is not a EU member state, but the EU IVDR was adopted by the Swiss Federal Council on 25 October 2017 and covers all points arising from the new EU regulations that apply as of 26 November 2017.

[5] Recordings and interview reports can be requested.

[6] http://www.medicaldeviceindustry.com/deviceassociation.html

In total 42 opinion articles from 11 interest organizations published in the period November 2012 – December 2018 were included in this research (see appendix X) and further analysed.

4.2.3. Symposium speakers.

To verify the regulatory changes as stated in section 2.2. and appendix I and to identify consequences of the new IVDR on CDx development a mini symposium involving two speakers from a (1) service company specialized in IVDR consulting and (2) a Notified Body was attended. This symposium took place on 14th of November 2014 at the MEDICA conference in Düsseldorf, Germany and was organized by the diagnostic company Future Diagnostics (Wijchen, The Netherlands). The talks were recorded, transcribed and summarized in a report.

4.3. Data analysis.

The identities of the respondents were anonymized by replacing their name with unique codes. The interview reports (including addenda), opinion articles and symposium reports were all analyzed and coded by using the program Nvivo (QSR International Pty Ltd). In the first round of coding, parts of the interview reports and opinion articles were categorized in broad categories that considered: (1) motives to start development process, (2) partnerships, (3) all individual factors that affect the CDx development process: (3a) regulation (IVDR and possible consequences), (3b) adoption by healthcare professionals, (3c) competition and market size, (3d) patents (intellectual property landscape), (3e) reimbursement, (3f) resources, (3g) and scientific base (new factor found) and (4) possible interventions. In the second round of coding, open coding was applied and all text within one of the broad categories was segmented in substantial codes, which described underlying mechanisms or issues, involved actors, different aspects, intentions, strategies, time, intensity etcetera. Finally, these substantial codes were linked to each other based on their contexts, consequences, i.e. causal relationships, and patterns of interaction on the development of CDx[7]. All interview reports were also coded according to its actor group (column 2, table 4 section 5) to identify and compare the similarities and differences in interests, views and roles between the actors groups.

4.4. Structural analysis CDx innovation system.

The term CDx innovation system is in this research referred to as the set of distinct actors, relations and institutions which contribute to the development and diffusion of CDx in the EU. The CDx system is operationalized as a combination of a sectoral, regional and national IS. The IS was sectoral delimited by referring to CDx as a specific group of diagnostic assays that measure biomarkers for the safe and effective use of medicinal products. CDx development is subject to European regulation and policy regimes, such as the IVDR, and therefor regional delimited. Individual EU member states have their own healthcare system (see Health System reviews from the European Observatory on Health Systems and Policies). Consequently, national boundaries are present in the innovation system under investigation as well. However, these geographical boundaries are not completely closed as CDx and their corresponding medicinal products can be sold in different countries in EU and the technologies used can originate from different companies, institutions and universities located in different nations and geographical areas in- and outside the EU. The article of Naylor & Cole (2010 a) was used to identify the actor groups present in CDx development: CDx manufacturer, pharmaceutical company, patient, physician, payer, testing laboratory, and regulatory authorities. Information from this articles was complemented with information from Health System reviews from the European Observatory on Health Systems and Policies and the IVDR (see European Parliament, 2017) to identify the roles and interactions between the actors involved.

[7] Coding schemes can be requested.

5. Results.

The results are structured according to the four steps of this research: (1) the motives of manufacturers to develop a CDx assay or corresponding medicinal product, (2) the formation of partnerships between manufacturers and other organizations, (3) the different factors found influencing CDx development and (4) potential interventions to stimulate CDx development. In total, 20 interviews (table x) were conducted and the recordings of 2 symposium speakers (SYM 1 & SYM 2), as well as 42 opinion articles (OA) were analysed. An overview of the respondents interviewed, including a short description of the organization is provided in table 4.

The majority of the respondents (x=17) were aware of, or agreed to, the definition to CDx used in this research (see section 2.1). When their definition did not match the definition used in this research properly, the researcher provided the respondent with the definition used to ensure that the respondent and the researcher were discussing the exact same matter.

Table 4: Overview of respondents interviewed according to their stakeholder group (commercial IVD or CDx manufacturer, medicinal product manufacturer, academic health institution and regulatory experts).

Stakeholder group	Respondent	Description organization & function respondent
Commercial IVD or CDx manufacturer (diagnostic company)	DC 1	Global diagnostic company having CDx on the market and running CDx development programs. Interviewee is customer solution manager.
	DC 2	Dutch based diagnostic company developing IVDs (no CDx on the market). Interviewee initiates personalized medicine initiatives.
	DC 3	Global diagnostic company having biomarker based IVDs on the market for oncology (no CDx on the market). Interviewee is responsible for market access and reimbursement trajectory.
	DC 4	Global diagnostic company having CDx on the market. Interviewee is medical affairs specialist and diagnostics project manager.
	DC 5	Global diagnostic company running CDx development programs (no CDx on the market). Interviewee is medical affairs specialist in CDx development.
	DC 6	Global diagnostic company specialized in designing biomarker driven clinical trials & CDx development (no CDx on the market). Interviewee is CDx development manager.
	IO 1	Dutch interest organization representing (IVD and CDx) diagnostic companies. Interviewee is an advisor with regard to regulation, reimbursement and policy.
	SC 1	Service company committed to bringing different manufacturers and other organizations together and providing advice with regard to CDx development. Interviewee is founder of the organization.
Medicinal product manufacturer (pharmaceutical companies)	PC 1	Global pharmaceutical company having CDx for some medicinal products on the market and is involved in different partnerships with diagnostic companies to develop CDx for new medicinal products. Interviewee is scientific biomarker advisor.
	PC 2	Global pharmaceutical company having CDx for some medicinal products on the market and is involved in different partnerships with diagnostic companies to develop CDx for

		new medicinal products. Interviewee is regulatory affairs manager.
	PC 3	Global pharmaceutical company having CDx for some medicinal products on the market and is involved in different partnerships with diagnostic companies to develop CDx for new medicinal products. Interviewee is manager precision medicine.
	PC 4	Global pharmaceutical company involved in different partnerships with diagnostic companies to develop CDx for new medicinal products. Interviewee is regulatory affairs specialist diagnostics.
Academic Health institution that develops in-house IVDs and CDx	AHI 1	Dutch academic hospital that develops IVDs and CDx for in-house use. Interviewee is head of pathology department.
	AHI 2	Swiss academic hospital that develops IVDs and CDx for in-house use and has partnership with a diagnostic company for CDx development. Interviewee is head of R&D unit in medical genetics and pathology.
	AHI 3	Dutch academic hospital that develops IVDs and CDx for in-house use. Interviewee is medical practitioner in oncology.
	AHI 4	Dutch academic hospital that develops IVDs and CDx for in-house use. Interviewee is medical practitioner in oncology.
	AHI 5	Dutch academic hospital that develops IVDs and CDx for in-house use. Interviewee is scientist in molecular pathology and head of laboratory molecular diagnostics.
Regulatory experts	RE 1	Dutch based law firm. Interviewee is specialized in EU regulations relating to medical devices and IVDs.
	RE 2	EU regulatory services/consulting company for IVDs. Interviewee is co-owner and regulatory affairs expert.
	RE 3	Regulatory authority that regulates the market entrance of medicinal products. Interviewee is regulatory affairs specialist related to CDx.

5.1. Motives to develop a CDx assay or corresponding medicinal product.

Before discussing the motives of manufacturers to develop a CDx assay, respondents consider these assays to be beneficial for patients as it results in the prescription of medicinal products that are effective (DC 3, DC 4, DC 6, IO 1, SC 1, PC 1, PC 2, AHI 2, RE 3, OA = 10). Consequently, CDx can be used for a more effective deployment of much needed (financial) resources (DC 4, IO 1, SC 1, PC1, AHI 1, AHI 2, OA = 7). The latter is, however, contested by two respondents from healthcare institutions (AHI 4, AHI 5) as targeted diagnostics also demand for the development of new and most likely expensive medicinal products.

5.1.1. Motives of diagnostic companies to develop a CDx assay.

As most diagnostic companies are private and profit oriented companies, the main 'driver' is to gain profit (DC 4, DC 5, DC 6). Developing CDx is considered interesting in this respect as it is included in the label of the medicinal product as one of the compulsory tests required before describing the medicinal product (DC 1, DC 2, IO 1, PC 1, PC 2, RE 2). In other words, the diagnostic company can hold a monopoly position for a particular medicinal product, especially when no other CDx are (yet) validated. As one of the commercial developers explained:

> *''Companion Diagnostics are the key to the medicine cabinet. Physicians can only prescribe a medicinal product when the Companion Diagnostic is used and provided a positive test result'' (DC 2)*

Formulated reasons to not develop a CDx assay relate first of all to the risk to end up with an assay, connected to a medicinal product that does not result in more effective clinical outcomes for a specific patient population (DC 2, DC 6). This means that using a CDx assay to define patient populations does not result in added value in clinical decision making. Another articulated reason is the additional procedures that need to be conducted as a result of the direct relationship with the medicinal product. This includes the additional development steps and data gathering, the additional authority for medicinal product evaluation, such as the EMA, that assesses the assay and related (time and financial) resources that are needed (DC 2, DC 5, IO 1, PC 3, RE 2, RE 3). These additional procedures are believed to negatively affect the motivation to develop a CDx over other complementary assays that measure biomarkers and only need approval by one authority. Furthermore, respondents point to the difficulty to access clinical samples to validate a CDx and high risk IVDs by themselves (DC 2, DC 6, AHI 2) (see for overview table 5).

5.1.2. Motives of pharmaceutical companies to develop a medicinal product that requires a CDx assay.

Pharmaceutical companies are, just like diagnostic companies, private and profit-oriented companies, aiming to generate financial gain with selling medicinal products. However, dividing a patient population in subpopulations by using a CDx assay would , in the opinion of one consulted commercial developer, result in a smaller market for the pharmaceutical company to get revenues from. This would negatively affect the decision to develop a medicinal product in combination with a CDx assay (DC 2). This is contested by other respondents emphasizing that a CDx assay is key to position the medicinal product in the market in which already many other products are present (DC 3, DC 4, IO 1, SC 1, PC 1, PC 2, PC 4, RE 1, RE 2). CDx are able to show higher effectiveness rates of the medicinal product, increasing the possibility to compete with the products on the market and accelerate market approval, saving resources and development time (DC 3, SC 1, PC 1, PC 2, OA = 2). Furthermore, these higher effectiveness rates and the limited amount of patients that will be treated with the medicinal product by using CDx can also accelerate and increase the possibility to get reimbursement (DC 2, DC 3, PC 2, PC 3) (table 5). In this way, CDx increase the success rates of new medicinal products:

> *''In projects were the right patients were identified, there was a greater chance that the medicinal product became a success. Therefore, precision medicine has become a central approach in medicinal product development. 90% of our portfolio is now following the precision medicine approach, in which diagnostics have become very important'' (PC 3)*

For pharmaceutical companies, there is, however, also the risk that no relation between the effectiveness of the medicinal product and the population divided by the CDx assay has been found (DC 2, PC 1, PC 3), resulting in losing the investments in the initial CDx assay and increasing development time when looking and validating a new assay. (PC 1, PC 3) (table 5).

5.1.3. Motives of health institutions to develop a CDx assay for in-house use.

All respondents from health institutions emphasize that their institutions frequently develop assays or adapt commercial assays to use in clinical decision making instead of purchasing a complete commercial assay. This so-called in-house development is first of all stimulated by the lack of commercial assays available to diagnose, mostly extraordinary, patients (AHI 2, AHI 5). Other motives to develop or adapt assays for in-house use include (1) reducing purchasing or operation costs (DC 6, PC 1, PC 2, AHI 1, AHI 3, AHI 4), (2) increasing the overall quality of an assay, such as adapting cut-off points or reducing the time-to-result (AHI 1), (3) to increase the fit or compatibility of the assay within the existing processes in the health institution (AHI 1, AHI 4) or (4) to reduce the development time to ensure early accessibility (AHI 3) (table 5). Except for developing assays for clinical decision making,

health institutions also adapt or develop assays research purposes (AHI 5). For example, specific biomarkers can be added to assays to identify a possible relation of that biomarker and treatment outcomes with a medicinal product (AHI 5).

Table 5: Overview of articulated motives to invest in the development of a CDx assay or the corresponding medicinal product.

Diagnostic company	Pharmaceutical company	Health institution
Motivation to invest in the development of an CDx assay		
Including the use of a specific CDx assay in label of corresponding medicinal product provides manufacturer monopoly position	CDx can position the medicinal product, especially in disease areas with already a lot of existing products: - potential to accelerate the market approval process - Potential to accelerate reimbursement approval process	Lack of commercial available assays that meet needs to diagnose extraordinary patients.
		Reduction of costs
		Increase quality of the assay
		Increase the compatibility of the assay
		Reduce development time
		Assay is developed for research purposes.
Motivation not to invest in the development of an CDx assay		
Risk medicinal product is not effective for the subpopulation	Treatable population becomes smaller, resulting in less revenues	Commercial CDx assay fully the meets needs and expectations of the health institution.
Difficult access to clinical samples to validate assay	Risk CDx assay does not separate responders and non-responders perfectly	

5.2. Formation of possible partnerships in the CDx development process.

When the CDx assay is developed simultaneously with the medicinal product, and not afterwards, a partnership between the diagnostic company and the pharmaceutical company is typically established (DC 4, DC 5, DC 6, IO 1, SC 1, PC 1, PC 2, PC 3, PC 4). In these partnerships, the pharmaceutical company has a leading role by initiating and (financially) supporting CDx development (DC 4, DC 5, DC 6, IO 1, SC 1, PC 1, PC 3, PC 4, RE 1). Pharmaceutical companies prefer those CDx assays that are able to stratify the responders and non-responders perfectly developed by diagnostic companies that operate globally to enable the possibility to offer the medicinal products in as many regions as possible (DC 4, PC 4). During the interviews three possible moments in the medicinal product development process in which this partnership can be established were identified: at an early stage, before phase 3 clinical trials, and after phase 3 clinical trials (table 6 & figure 7, 8 and 9).

The formation of a partnership at an early stage in medical product development is feasible when similarities in biomarkers in patients not benefitting from existing therapies are found and knowledge on disease pathology is present (PC 3). In this partnership the assay is initially developed as CDx assay during the pre-clinical stages and allows for a greater support of the pharmaceutical company (DC 6). In the second and third model, the CDx assay and the medicinal product are in the first place developed separately by the manufacturers and searches the pharmaceutical company in a later stage of the medicinal product development process for a suitable diagnostic partner (DC 4, DC 5, DC 6, PC 1, PC 4). In the second model this is mainly caused by a lack of knowledge on the pathology and involved biomarkers (PC 4), which is gradually gathered during the first four phases of medicinal product development (DC 4, DC 6, PC 2). However, in the third model the medicinal product was initially developed as an all-comer product, but failed to demonstrate high enough effectiveness rates during

phase III studies to enter the market as such. By identifying patients responding to the medicinal product that have specific biomarkers, a CDx assay can be used in a retrospective cohort study to ''rescue'' the medicinal product from failure and investment losses (DC 2, PC 2). In both the second and third model, the pharmaceutical company prefers a partnership with a diagnostic company already developed and analytical validated an IVD assay (for complementary purposes) measuring the biomarkers needed to save time and resources on the development of a new assay (DC 4, IO 1, PC 1, PC 2, PC 4). Important in all three models is that both the CDx assay and the corresponding medicinal product are approved at the same time to ensure that the unavailability of one of the products does not lead to restricted use of the other (PC 2, PC 3).

Table 6: Differences in partnerships in the codevelopment model between the manufacturer of the medicinal products and the CDx assay when established at an early stage, before phase III clinical studies or after phase III clinical studies.

Partnership at an early stage	Partnership before phase III clinical studies	Partnership after phase III clinical studies
Development medicinal product and CDx is rather parallel	Development medicinal product and CDx separated until phase III clinical studies	Development medicinal product and CDx separated after phase III clinical studies
Pathology and biomarkers are known before medicinal product development	Pathology and biomarkers are (partly) unknown before medicinal product development	Pathology and biomarkers can be known or unknown > development of medicinal product is initially as all-comer
Pharmaceutical company can fully support development of CDx assay	Pharmaceutical company can only support clinical validation of the CDx assay	Pharmaceutical company can only support clinical validation of the CDx assay
CDx assay initially developed by the diagnostic company as a CDx assay	CDx assay initially developed by the diagnostic company as a complementary diagnostic assay	CDx assay initially developed by the diagnostic company as a complementary diagnostic assay
Clinical evidence based on a prospective cohort study	Clinical evidence based on a prospective cohort study	Clinical evidence based on a retrospective cohort study

In the case, a CDx assay is developed for a medicinal product already on the market a diagnostic company can form a partnership with a health institutions to access clinical samples for the analytical and clinical validation of the assay (SC 1, AHI 2). This specific form of partnership has the advantage of obtaining input from actual users of the assay, such as the physicians and the laboratory personnel, to optimize the assay and meet the specific needs of these users (DC 5, AHI 1, AHI 2, AHI 5). For the health institution a partnership with a diagnostic company enables early access to assays to optimize clinical decision making (PC 2, AHI 2).
Diagnostic companies can also form a partnership with companies or institutions specialized in specific aspects in CDx development offering specific services, such as research activities, mediator activities to align the pharmaceutical and IVD industry, and help with regulatory aspects (SC 1, RE 1).

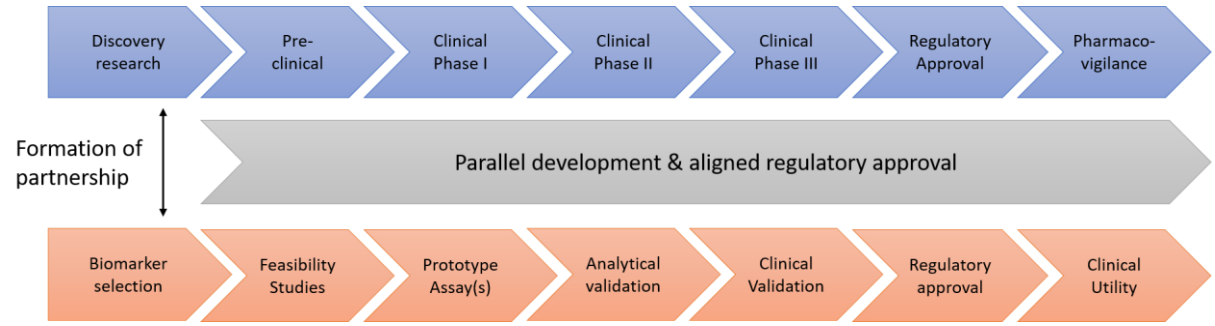

Figure 7: Formation of a partnership at an early stage in the codevelopment model. Authors own compilation.

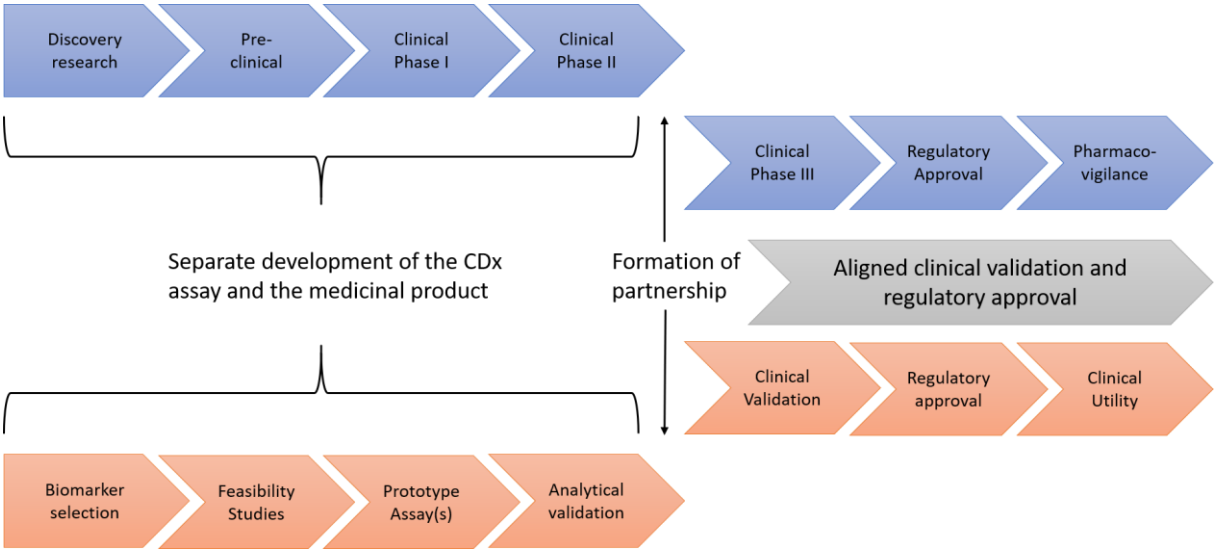

Figure 8: Formation of a partnership before phase III clinical trials. Authors own compilation.

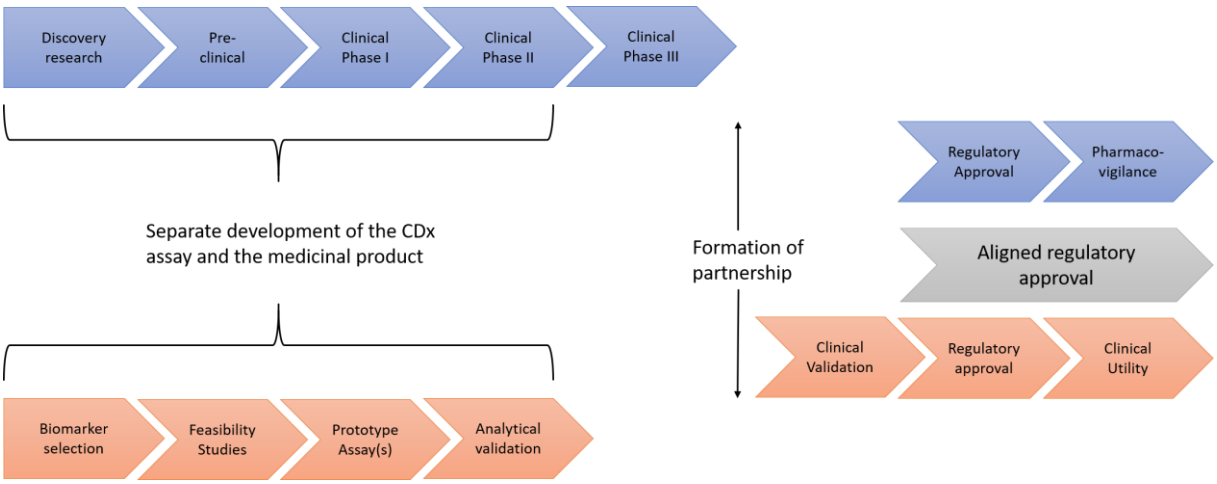

Figure 9: Formation of a partnership after phase III clinical trials, rescue option. Authors own compilation.

5.3. Factors important in the CDx development process.

In total, seven factors, apart from the need to find a suitable partner(s), were identified as important in the CDx development process: the intellectual property landscape, market size and competition, scientific base, availability of resources, regulation, reimbursement and adoption by healthcare professionals. All factors proposed by Alonso (2017) were identified as being important in CDx development, but was complemented with an specific articulated factor by respondents: the presence of a scientific base. Whereas some of these factors have a more prominent role in the early stage of CDx development and can affect the incentive of manufacturers to start the development process (e.g. presence of competition, market size, presence of a scientific base, and the presence of patents), others have an effect throughout the development process (e.g. finding the right partner & presence of resources), and some are more present at the final stage in the process (e.g. regulation, granting of reimbursement and the adoption by users)(see figure 10, page 34).

5.3.1. The intellectual property landscape: presence of patents on measuring technologies and platforms.

Starting with the intellectual property landscape, patents can be used by manufacturers in CDx development to patent technologies and measuring platforms. It is, however, not possible to patent biomarkers, such as proteins or genes (SC 1, PC 4, OA = 1). Patents both tend to stimulate as inhibit CDx development. Patents stimulate by rewarding individual innovation activities by increasing the possibility to earn back investments made (PC 1). However, patents are also used as a strategy tool to block other manufacturers and to decrease competition in CDx development (DC 1, RE 1). For CDx specifically, competing organizations can still measure the identified biomarker that is considered suitable for stratifying patients, but need to develop new technologies or platforms to avoid interference with the existing patents (RE 1). In cases where it is not possible or considered as difficult to develop new technologies, organizations have the possibility to license patented technologies (DC 5) or taking over the organization owning the patent (DC 1).

5.3.2. The availability of a scientific base: existence of knowledge on disease pathology and biomarkers.

Knowledge on disease pathology, including its cause, mechanisms of development and expression, and involved biomarkers, is considered key in CDx development (DC 4, DC 5, IO 1, PC 2, PC 3, PC 4, AHI 1, AHI 2). In-depth knowledge on disease mechanisms and the discovery of biomarkers to stratify patients, enable manufacturers to develop CDx assays for new indications and to improve assays already on the market. The degree of knowledge that is present today on disease pathology and involved biomarkers differs among (sub)diseases, resulting in inequalities in CDx development among indications. Oncology is an example in which already many research has been conducted, resulting in the presence of a scientific base to develop CDx (DC 4, DC 5, PC 2, PC 3). Consequently, the majority of the CDx present today have been developed in this area, spurring competition as over the years multiple CDx have been developed and approved for the same medicinal product (SC 1, DC 6). Respondents expect that when more research is conducted in other disease areas than oncology, CDx development also becomes feasible for other indications (DC 4, IO 1, PC 2, PC 3, PC 4, AHI 1, AHI 2):

> *''The development of CDx depends on the knowledge on the biological mechanism of a particular disease in order to know what biomarkers play a role within this mechanism and can possibly included in a CDx assay'' (DC 4).*
>
> *''In CDx development a good hypothesis is needed. In disease areas other than oncology a lot of research on molecular pathways still needs to be done in order to make CDx possible'' (PC 3).*

5.3.3. Market size and competition: number of patients for which the medicinal product is being considered.

In general, the market must be large enough for both the diagnostic and pharmaceutical company to earn back investments made, and to make some profit to ensure company survival (SC 1, IO 1, DC 4, DC 6, AHI 5). Therefore, markets having many patients with a certain (sub)condition are considered to be most interesting for commercial manufacturers to develop CDx assays for. However, market size is not always a decisive factor in the decision to develop a product. Larger companies, who have access to more capital and resources, also develop from ethical considerations products for smaller markets if these investments can be compensated with the sales of other products (DC 4, PC 4). Furthermore, in the absence of commercial assays, non-profit driven health institutions develop assays for specific and small patient populations (AHI 3, AHI 5). Even though, the market size of a CDx assay is larger than the market size for the corresponding medicinal product as only a proportion of the patients for which the medicinal product is being considered is tested positively (PC 2), this was not articulated as a inhibiting factor for pharmaceutical companies not to invest in CDx development. As pharmaceutical companies use CDx to better position the medicinal product in the market (see section 5.1.2), the higher effectiveness rates in these smaller populations can be used to ask a higher price for the medicinal product, compensating for the smaller marker (SC 1, PC 1, PC 2, PC 4). Depending on the similarities in pathology and biomarker involvement, diagnostic and pharmaceutical companies will try to expand their market and revenues by also trying to get market approval for other indications than the initial indication for which the product has been approved for (DC 3, SC 1, PC 4).

The market share of a product depends on the presence of other competing IVDs or CDx. The degree of competition is, however, based on the description of diagnostic testing in the label of the medicinal product (IO 1, PC 2). Although no agreements have been set yet on referring the use of diagnostics in the label in the EU (IO 1, RE 3), two different possibilities were identified during the interviews: (1) need to test for specific biomarkers or (2) need to test for specific biomarkers using a specific approved assay (IO 1, RE 3). The latter is preferred by diagnostic companies as healthcare professionals are restricted to use those assays mentioned in the label. In this way, a CDx assay does not compete with other (in-house developed) assays and complementary IVDs measuring the same biomarker, increasing the possibility to get a monopoly position if no other assays are mentioned in the label yet (DC 1, DC 2, DC 6, PC 1, PC 2, RE 2). In other words, by referring specific assays in the label of the medicinal product, competition is minimized and potential market share and revenues are increased. This was also articulated as one of the main motives of diagnostic companies to develop a CDx assay (section 5.1.1.).

5.3.4. Regulation: consequences of the IVDR on CDx development.

Articulated consequences of the new regulations can be divided in two categories: those directly related to the regulatory demands itself and those related to the system parts that needs to be established in order the IVDR to function properly. These so called system constraints are in this case the result of parts of that system that are not in place yet rather than a misfunctioning of these parts.

Consequences related to the regulatory demands.

Different respondents and writers of opinion articles welcome the new regulatory demands with the goal to improve the overall quality of IVDs, to harmonize the quality among assays, and to enhance patient safety (DC 3, DC 4, DC 5, DC 6, SC 1, PC 3, PC 4, OA = 11), but there are also doubts whether the new regulations actually stimulate CDx development from both commercial and non-commercial developers.

When looking at commercial assays the new regulations are perceived by respondents as more strict and complex (DC 5, IO 1, RE 2, RE 3, SYM 1, OA = 8). The majority of the respondents expects that for the (re-)approval of IVDs and CDx under the new regulations large amounts of financial resources and

specific regulatory expertise is needed (x = 12, SYM 1, SYM 2, OA = 8), often not available within small companies. Consequently, small companies are expected not able to complete a full CDx development trajectory, forcing them to pursue other strategies, such as to shift their focus to products in lower risk categories or to concentrate on specific stages of CDx development like biomarker discovery, or to leave the CDx market (x = 12, SYM 1, OA = 5). As respondents highlight that many innovation activities come from small companies, there is the concern that with the leave of those companies the development of innovative and potential life-saving technologies and CDx will come into play (AHI 4, RE 1, OA = 4), as articulated by the writer of this opinion article:

> *''More than 95% of the IVD companies are SMEs* [small and medium enterprises, red]. *A significant part of them will not survive if we let this go. Jobs, growth and innovation will be impacted by such an unnecessary increase in EU bureaucracy. We need to be aware of such existing risk and try to minimize it'' (Opinion article MedTech Europe).*

Furthermore, respondents articulate the possibility that diagnostic companies will discontinue products if those products need large investments for reapproval and generate only small revenues (DC 2, DC 4, IO 1, PC 1, PC 2, AHI 1, AHI 2, AHI 5, RE 1, RE 2, OA = 5). The amount of investments needed depends on what information is already in-house for those products, i.e. the data ''gaps'' between the IVDD and IVDR that need to be filled (DC 4, PC 2, PC 4, OA = 2). Especially, large global operating companies have an advantage in this respect as it is likely that they already have data in-house for the approval of their products in countries having similar regulations in place, such as the U.S (DC 3, DC 4, DC 5, DC 6 IO 1, PC 3, AHI 2). In this way, the data in-house needs to be translated to fulfil IVDR requirements, rather than conducting clinical trials to gather new data. In the absence of data, companies having a limited amount of resources in-house can decide to discontinue products, leading to the possibility that health institutions can choose among less products or even face unavailability of products for rare indications (AHI 2, AHI 4, RE 2). Product discontinuation can, however, reward those companies willing to invest in the reapproval of their products as the removal of certain products increases the market position of those left (PC 1, AHI 1) and possibly stimulate CDx development in the short-run.

Furthermore, it is also expected that with the impediment of using in-house assays over commercial developed assays, the need from health institutions to perform innovation activities will be decreased if healthcare professionals are restricted to the use commercial developed assays (DC 4, AHI 5). Healthcare professionals must increasingly show the additional value for patients of using an in-house developed assays over commercial assays (DC 4, AHI 1 RE 2), even though all respondents emphasize that in-house developed assays are not necessarily of less quality than commercial developed assays:

> *''I am not aware of any literature saying that in-house developed assays are of worse quality than commercial developed assays. This is, however, assumed by the new regulation'' (AHI 3).*
>
> *''If the hospital can demonstrate that the in-house developed assay meets a certain norm, there is no need to force the use of a commercial developed assay'' (AHI 4).*

The easiness of showing the additional value of an in-house developed assay depends on the diagnostic information available commercial assays can provide in relation to the information needed for that particular patient. As the development of in-house assays is often stimulated by the lack of commercial assays for patients having rare indications (AHI 2, AHI 5), the ability to show the additional value of in-house assay is easier for those institutions treating extraordinary patients having specific needs:

''The main raison for developing assays in-house is the lack of commercial assays available for specific patients. As in this hospital often patients are being treated that have specific and rare indications, there is in many cases no commercial assay available for these patients. Companies usually develop assays for a large patient population that do not meet the specific patient's needs of our patients. At this moment, 70-80% of the assays used in this hospital is developed in-house''

Another, undesirable, consequence respondents warn for when impeding use of in-house developed assays over commercial assays, is that the stronger market position of commercial developers can result in an increase in the price of commercial assays, leading to higher healthcare expenditures and possibly an increasing pressure on reimbursement premiums for patients and citizens (DC 4, IO 1, PC 1, AHI 1-5, RE 2). However, there is also the possibility that with the discontinuation of commercial products (see above) the new regulations can have a countereffect and actually stimulate in-house development when for specific indications no commercial assays are not on the market anymore (AHI 1, AHI 5).

In the new regulations no specific requirements are defined for the corresponding medicinal product and the approval of the medicinal product remains separated and thus approved by another authority: the EMA (RE 3). All respondents from pharmaceutical companies therefore do not expect major consequences in their daily practices and emphasize that they already have data from clinical studies in-house to re-approve the CDx on the market for their medicinal products.

In sum, the new regulatory demands are expected to decrease the innovation activities from smaller companies and health institutions and are envisioned to be in favour of larger companies, as the new IVDR has the ability to create a strong market position. In this way, respondents articulate that for those larger companies it remains interesting to invest in CDx development (PC 1, PC 2, PC 3, RE 1, RE 2).

Consequences related to possible system constraints.

Four parts of the system needed for CDx manufacturers to comply with the new regulatory demands are still outstanding: translation of the IVDR demands to standards and guidelines, division of roles NBs and EMA, availability of reference labs and the availability of NBs (SYMS 1, SYMS 2, OA = 5).

Standards and guidelines are needed for manufacturers to know exactly what data should be delivered and how clinical studies should be designed to obtain this data for market approval (DC 4, PC 2, OA = 9). In the case that standards and guidelines are not available at the end of the transition period, manufacturers are not able to (re-)approve the assays under the IVDR and face delays in market entrance or temporarily market removal. For CDx specifically, the role and responsibility of the EMA and NBs in the evaluation of a CDx assay in relation to a given medicinal product is still unclear (RE 3, OA = 2). For both CDx manufacturer as the medicinal product manufacturer, this may lead to an unpredictable market approval pathway and potential delays when there is a duplication of work or conflicting assessments and approval decisions.

Furthermore, reference labs are needed to assess assays in high risk categories, such as CDx, but are expected to be ready at the end of 2020 (SYM 1). As a result, assays in high risk categories can be assessed and (re)approved under the IVDR, leading to market delays and potential temporarily market removals (OA = 2).

Additionally, and articulated by many respondents as an important part of the system not in place yet, is the lack of NB capacity (DC 4, DC 5, DC 6, IO 1, PC 2, PC 3, PC 4, AHI 5, RE 2, SYM 1, SYM 2, OA = 8). This lack of NB capacity has several causes. First of all, only a proportion of the NBs operating under the IVDD also applied to certify under the IVDR, of which none of them has been designated yet (OA =2), a significant decrease of available NBs is expected (DC 4, IO 1, PC 2, PC 3, PC 4, AHI 5, RE 2, SYM 1, SYM 2, OA =8):

'' There has been no 'big bang' in applications by current notified bodies to be (re-)designated under the new regulations'' (Opinion Article Irish Medtech (September 2018)).

Secondly, as under the IVDR, NBs will be involved in the (re-)approval of 90% of all IVDs, which was only 10-20% under the IVDD, a significant increase in workload is expected for those NBs applied (IO 1, PC 4, RE 1, RE 2 OA =7). Thereby, a proportion of these NBs also applied to certify under the new medical device regulation (MDR) becoming already fully applicable in 2020, resulting not only in even more work for those NBs, but rise the concern these NBs are not preparing for the IVDR yet as the IVDR becomes later applicable than the MDR (PC 4, RE 1, OA = 3). As many of the IVDs, including CDx, need NB oversight for the first time, respondents and industry associations also question the competence and expertise present to certify these assays (PC 2, PC 3, RE 1, OA = 10). Some NBs that are aware that special knowledge and expertise is needed try to employ new personnel, but face difficulty to find qualified personnel having the expertise needed (OA =3). Taking everything together, there is the worry that there is not enough NB capacity to certify all current and new IVDs in time, putting the availability of those assays at risk and obstructing patient's access to these assays (DC 4, IO 1 PC 2, PC 3, AHI 5, OA =6):

> *''Industry is growing more nervous every day, as it seems increasingly likely that we will have too few Notified Bodies, available too late, covering too few product categories, and (above all) with far too little capacity'' (Opinion article MedTech Europe (25-05-2018)).*
>
> *'' To make a success of the regulations, the medtech industry needs Notified Bodies to be available and up-and-running as early as possible, for both IVDs and medical devices and for all applicable fields of technologies. Without this, the system faces a serious risk of "bottlenecking," i.e., too many medtech products under review simultaneously, with Notified Bodies having too little time and too little bandwidth'' (Opinion article MedTech Europe (27-11-2017))*

In conclusion, with the system parts not in place yet, the capacity to bring new innovative products on the market is limited, potentially resulting in restricted innovation activities concerning CDx development.

5.3.5. Specific resources needed in CDx development.

To develop a CDx assay, specific resources are needed, such as clinical samples to validate the assay (DC 2, AHI 2, AHI 5) and specialized employees like molecular specialists, bio-informaticians, bio-statisticians, quality management people, and soft-ware builders (DC 6). The need of resources to develop future CDx has a strong link with the introduction of the IVDR. Respondents expect that additional resources are needed to fund innovation activities and to validate a CDx assay, including clinical samples, regulatory expertise and financial resources. Firstly, as clinical studies need to be conducted to approve a CDx assay under the new regulations, the difficult to access clinical samples can inhibit the development of CDx for medicinal products already on the market as diagnostic companies rely on partnerships with health institutions to validate the assay (AHI 2). However, less problems with accessing clinical samples are perceived when the CDx assay is developed simultaneously with a medicinal product. In this way, the CDx assay is validated during the clinical studies of the medicinal product and does the pharmaceutical company provide access to the clinical samples (PC 1, DC 5). Furthermore, respondents expect that special regulatory expertise is needed to design the clinical studies in such a way that the right information is obtained for CDx market approval is particularly difficult for those companies having no experience with regulations in other countries (DC 2, RE 2). Additionally, respondents expect that the costs to finance CDx development increase vastly (PC 1, AHI 2, AHI 4, RE 1, RE 2, OA =5). Mainly smaller companies are perceived to be unable to step-up in resources level change strategies or leave the CDx market, inhibiting innovation activities from these companies (see section 5.3.4.).

5.3.6. Adoption by healthcare professionals: physicians and laboratory personnel.

Respondents identified two user groups important in the adoption of a CDx assay: laboratory personnel that conducts the assay and the physician who interprets and uses the test results in the prescription of a medicinal product. Several variables were articulated during the interviews as being important in the adoption of a CDx assay. Some of these variables applied more to the characteristics of the assay (attributes of innovation), whereas others were more related to how the assay was communicated to these users and to whom decided to use the CDx assay (table 7).

Table 7: Variables important in the adoption process of CDx by physicians, laboratory personnel or both. (+) represents a positive relationship with CDx adoption and (-) a negative relationship.

	Physician	Laboratory personnel	Both
Attributes of innovation	Clinical utility: - increase in effectiveness medicinal product when using CDx assay (+) - time-to-result (+)	Compatibility: - compatibility with existing technologies and need of materials (+) - measuring limited amount of biomarkers (-)	Services provided by the manufacturer: - education and training (+) - maintenance services (+) - financial support (+)
	Granting of reimbursement (+)	Costs of purchasing and using CDx assay (-)	
		Complexity: operation difficulty and need of specific materials (-)	
Communication channels	Presence in medical guidelines (+)	-	Previous experience in clinical trials or during education (+)
Type of innovation decision	-	-	Authorities: part of label medicinal product (++)

For the adoption of CDx specifically, it is of importance that the use of the assay contributes to better clinical outcomes for the patient when compared to other assays on the market, which can be used for stratifying patients in the prescription of the corresponding medicinal product. In this respect, it is important that all biomarkers relevant in determining clinical effectiveness are being measured, but also that the test outcome is reliable, robust and available short after testing (DC 1, DC 3, DC 5, AHI 1-5). However, the freedom of adopting a CDx assay and the possible influence of other variables in table 7 greatly depends on the decision from authorities to include the CDx in the label. Although no decisions have been made yet on how the use of as CDx assay will be referred in the label (IO 1, RE 3), all above described variables will be nullified if the use of a specific CDx assay is included in the label. This means that a patient must be tested with the CDx mentioned in the label anyway before describing the medicinal product (AHI 1). In this respect, two respondents from health institutions particularly mentioned that the concept of mandatory measuring a limited amount of biomarkers creates difficulties for laboratories in the long run. They explain that in the case the amount of CDx medicinal product combinations for a particular indication that enter the market increases, laboratories need to conduct multiple assays for each patient to identify the most suitable medicinal product, requiring more time, people, materials and money to do so. In other words, using different CDx assays to determine the most effective medicinal product becomes inefficient and a time and resource consuming procedure. It would therefore be beneficial to merge all CDx assays for an indication into one major assay to measure all important biomarkers at once, immediately providing an outcome on what medicinal product is best (AHI 4, AHI 5). As one of the two healthcare professionals articulated:

''It is a good first step that manufacturers think about what specific patients respond to the medicinal product. However, Companion Diagnostics do not provide a complete picture on what available products will be effective for a patient, but only provide a result about the possible use of a specific drug from a specific manufacturer. If the development of Companion Diagnostics continuous and the use of such assays are referred to in the labels, this can pose a problem for the organisation of healthcare if several tests have to be performed for each patient before knowing what medicinal product may be suitable. Therefore it would be good to develop one large panel that provides information for the prescription of various products'' (AHI 4).

Taking this together, the development of future CDx can be put at risk if health institutions are forced by the labels of medicinal products to use specific and multiple assays before the most effective treatment option has been found. This time and resource consuming procedure is not favoured by health institutions and is expected to create resistance to CDx in the future (AHI 4).

5.3.7. Granting of reimbursement: patient access to CDx assays.

Respondents articulated the importance of reimbursement in the adoption of CDx assays and the corresponding medicinal product to enable patient access to those products (DC 1, DC 3, PC 2, PC 3, PC 4, OA = 1) (table 7). However, in contrast to market authorization, reimbursement is assessed and assigned by national authorities, all having their own criteria and assessment procedures (DC 3, DC 4, PC 2, PC 3, AHI 2, OA = 1). Differences in data requirements and assessment procedures pose problems for individual manufacturers as there is the likelihood that the data for gathered for market approval does not match the data needed to get national reimbursement. Consequently, this can result in a inequalities of access across the EU (OA = 1) as manufacturers probably need to gather additional data for specific authorities in some cases, increasing development time and costs (DC 3, PC 2, PC 3). Thereby, for CDx it is not only important that the assay itself, but also the corresponding medicinal product is reimbursed, enabling access to the 'whole package' (PC 4, OA = 1).

5.3.8. Putting everything together: a complete overview of factors, actors and relations important in the CDx development process.

In figure 10 an overview is provided on all factors identified in this research as being important in CDx development. These factors not only affect CDx development directly, but also each other.

In summary, patents stimulate CDx development by providing manufacturers market exclusivity for their technologies or measuring platforms to recoup their investments. However, they are also used as a strategy tool to minimize competition to increase market share. Key in the ability to develop a CDx assay in the first place is the availability of a scientific base on pathology and potentially involved biomarkers. This availability also determines where in the codevelopment model the pharmaceutical company can start the search for suitable diagnostic partner who can develop a CDx assay measuring the biomarkers needed to stratify patients: an early stage or before phase III clinical trials. Although the actual regulatory approval is conducted in the second last stage of the development process, the regulation in place determines how the validation stages of the CDx assay and the (pre-)clinical studies of the medicinal products should be designed to gather the data needed for market approval. Extensive regulations, like the IVDR, increase the need of resources, such as capital and expertise, during the CDx development process. In this way, the IVDR is expected to create a high entry barrier for new manufacturers and forces organizations that are unable to step up in resources to leave the market, creating stronger market positions for those manufacturers still operating. Finally, the adoption of CDx greatly relies on the decision of authorities to include its use in the label of the medicinal product. In this way, other variables that are perceived as important in the adoption process, such as reimbursement, costs and compatibility are nullified.

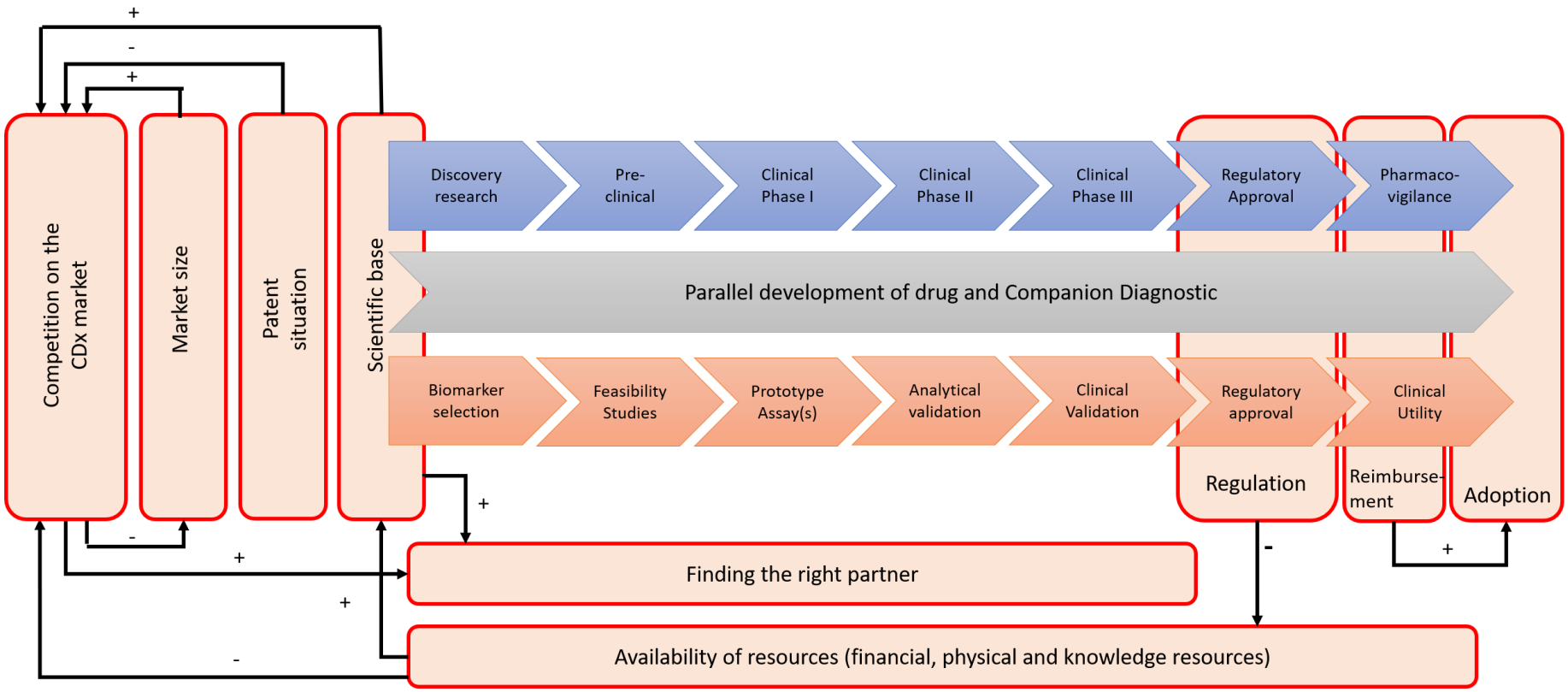

Figure 10: Overview of all identified factors relevant to the CDx development process, including their main place of interaction

The CDx innovation system: a structural analysis of actors and the relations among them.

As can be seen in figure x, diagnostic and pharmaceutical companies are just two of a number of actors present in the CDx innovation system (figure 11). The role and operation activities of other actors present affect directly or indirectly CDx development. Overview of these roles of actors can be found in Appendix XI.

As explained in section 5.2, a diagnostic company typically forms a partnership with a pharmaceutical company (interaction 3) in the development of a CDx assay, but can form partnerships with health institutions (interaction 15), service organizations and (public) knowledge institutes (interaction 10), who might receive funding from the government (interaction 11). Patent applications from pharmaceutical and diagnostic companies are reviewed and granted by national (interaction 9) or European patent offices (interaction 1). The market approval of the medicinal product (interaction 2) is in principle regulated and approved separately by a different authorities. The EMA reviews and approve the market application of medicinal products (interaction 2), whereas a notified body, funded by national governments (interaction 18), is responsible for the approval of the CDx assay (interaction 8). However, due to the introduction of the new regulations, initially proposed and introduced by the European Commission (interaction 4 and 7) after approval of the European Parliament (interaction 5), the notified body reviewing the CDx application needs to consult the EMA (interaction 6). After market approval a manufacturer can sell its product to health institutions (interaction 12). If the prescription of a specific medicinal products is being considered by a physician, a CDx assay will be conducted by laboratory personnel to determine the effectiveness of the medicinal product (interaction 16). In turn, the test result is used by the physician in the prescription of the medicinal product to the patient (interaction 19). Health institutions can be inspected and supervised on the quality and accessibility by public organization or authority (interaction 13).

After market approval, national authorities, review the manufacturers application for reimbursement. If reimbursement is granted (interaction 14), health reimbursement companies compensate health institutions for the care provided according individual arrangements set between the health reimbursement company and the health institution (interaction 17). In this way, health institutions can offer the care to patients (interaction 19) without taking their expenses into account if this specific patient has a contract with the healthcare reimbursement company (interaction 20).

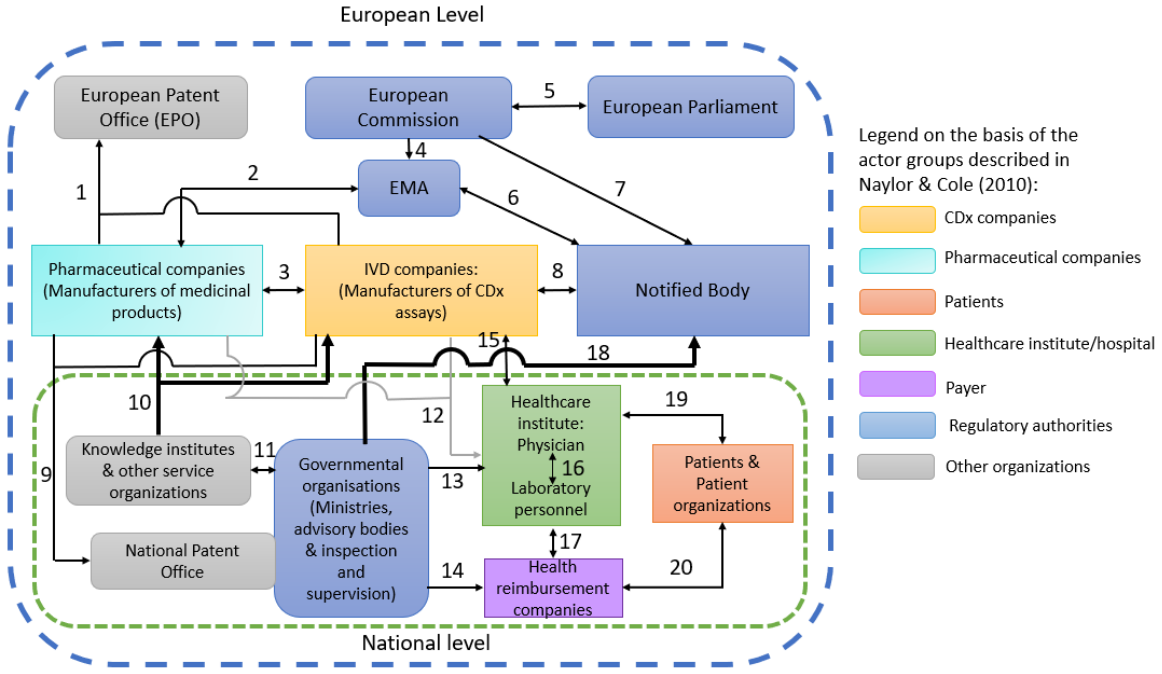

Figure 11: Structural analysis of the CDx innovation system in the EU. Authors own compilation.

5.4. Possible interventions to stimulate CDx development.

In order to come towards an effective design and development of interventions respondents emphasize that authorities should involve different actors. Different respondents articulated the feeling that with the design of the IVDR not all actor groups were equally represented (AHI 1, AHI 3) or did not match with the purpose of diagnostics in relation to targeted therapies, i.e. providing information useful information in clinical decision making for individual patients (DC 2, DC 3 IO 1, PC 4).

Although, the majority of respondents (x = 12) articulated the possibility of reduced innovation activities from small companies and/or health institutions, the need of stimulating CDx development by introducing interventions or policy measures was not explicitly mentioned as something required. This can be explained by the idea that a potential monopoly position is worth the effort for large diagnostic companies to step up in resource level to develop CDx (DC 4, PC 1, AHI 3, AHI 5, RE 1, RE 2). Furthermore, pharmaceutical companies are expected to continue their investments in CDx development to position future medicinal products in the market (PC 1-4).

Respondents articulated three possible interventions to stimulate CDx development: (1) funding for R&D projects to understand pathology mechanisms and to discover biomarkers to enlarge the scientific base, (2) streamlining market approval and granting of reimbursement, and (3) the requirement to look for biomarkers to stratify patients for medicinal products. With the funding of research projects, respondents emphasize the discovery of pathology mechanisms and biomarkers increases the possibility to introduce CDx in other disease than oncology or existing assays can be complemented with new biomarkers for an even more specific diagnosis and the prescription of targeted therapies. Secondly, not only would it be preferable to streamline the data requirements to get market approval and reimbursement of one specific product across all EU member states as explained by the following quote, but in the case of CDx and its corresponding medicinal product also the approval and granting of reimbursement for both products simultaneously. In other words, both products need to receive market approval and granting of reimbursement at the same time, avoiding the possibility that one of the two product cannot be used, putting both products on the side line.

> *''It would be good for the CDx development process if reimbursement processes would be harmonized. At this moment this is not the case and companies need to spent a lot of effort to satisfy the different regulatory requirements. However, essentially all regulators want the same: safe and effective drugs and diagnostics, but it is a different way to get approval'' (PC 3)*

Finally, the requirement from medicinal authorities to include biomarkers in medicinal product development whenever it is possible in order to get approval was articulated to increasingly require pharmaceutical companies to look at subpopulations for their medicinal products. In this way, pharmaceutical companies are more forced to develop medicinal products for subpopulations that might require a CDx assay over all-comer products.

6. Conclusion & discussion.

This research identified different motives, partnerships and factors, including the potential consequence of the new regulations, from a manufacturers perspective related to CDx development and their potential suggestions for interventions in order to contribute to targeted healthcare.

CDx are perceived as valuable innovations optimizing patient's health as effective medicinal products are being prescribed and ineffective products are avoided. However, there was no consensus among respondents whether using CDx could lead to savings in healthcare expenditures. Although, the majority of the respondents articulated that CDx can establish changes in clinical decision making, saving expenditures of ineffective treatments, CDx enable a growing category of new and expensive therapies at the other hand. The development of CDx is indeed for pharmaceutical companies considered by respondents to be beneficial as CDx facilitate in the demonstration of higher effectiveness rates and thus medical value for new medicinal products, enabling the possibility of new products to move to first-in line treatment. CDx development allows for competitive advantage, financial gains and company survival by opening markets for new therapies, making the targeted health care approach an attractive strategy. Several studies (e.g. Jørgensen, 2008a, 2008b; 2015; Jørgensen & Hersom, 2016; Milne et al., 2015) highlighted that already a proportion of the pharmaceutical companies are increasing their investments in biomarker and CDx development, expecting the number of medicinal products having a CDx to grow. These predictions and the articulated benefits of developing CDx in this research seem to indicate that pharmaceutical companies are increasingly moving towards the development of more individualized medicinal products. Are we approaching the post-all comer/blockbuster era?

Although the investments in CDx development from pharmaceutical companies seem to grow in the future, this is less evident for the actual developer of the CDx assay, the diagnostic company. Articulated motivation for a diagnostic company to develop a CDx assay lies within the inclusion of the assay in the label of the medicinal product, resulting in a strong market or even monopoly position by the 'mandatory use' of the assay. However, as no decisions are made yet by EU authorities on including a CDx assay in the label, the development of CDx over complementary assays for the European market seem uncertain.

Articulated financial benefits that can reduce healthcare expenditures lie within the possibility that CDx can accelerate the market approval process of the corresponding medicinal product. By using CDx, the effectiveness of a medicinal product can be demonstrated at an early stage or in smaller studies, saving the pharmaceutical company time and resources. In this way, the pharmaceutical company needs to invest less and has more patent time left to earn back the investments made, leading to potential price reduction of new and effective medicinal products. However, both in the EU and US medicinal products with a CDx are still mainly approved by traditional procedures. Only a few cases of medicinal products are present in the literature, such as crizotinib (Xalkori) (Chabner, 2011) that were approved on the basis of less data, but showed extraordinary clinical effecicency. To reduce healthcare expenditures related to the medicinal products, medicinal product regulatory authorities should think about additional guidance or special designed clinical trials for medicinal product CDx combinations to achieve this reduction, but still ensuring patient safety.

In the codevelopment model, the development of a CDx assay and corresponding medicinal product is proposed as a coherent process. However, this thesis identified that the development of the CDx assay and the corresponding can be conducted separately from each other. Whether partnerships are established at a later stage in de development process depends on the presence of knowledge on disease pathology and potential biomarkers and the intention of the pharmaceutical company to develop a medicinal product for a specific patient population. In the absence of this knowledge it is

difficult to predict what kind of CDx assay can be combined or should be developed to match the medicinal product. Furthermore, when looking at partnerships established after phase III clinical trials, there was no initial intention from the pharmaceutical company to develop the medicinal product for a subpopulation and is the CDx assay used as a rescue option for the medicinal product that is unlikely to be approved as all-comer due to lower expected effectiveness rates. Multiple cases of medicinal products, such as AstraZeneca's Iressa, being 'rescued' by a CDx assay are present in the literature (see Agarwal, 2012). With the identification of multiple different partnerships in this thesis, the assumption that CDx assays are developed in conjunction with the medicinal product does not apply to all CDx development projects. The possibility of developing a CDx assay in conjunction with a medicinal product highly depends on the availability of a scientific base and the intention of the pharmaceutical company, which are out of reach of the diagnostic company.
Additionally, respondents articulated that one of the preferences of the pharmaceutical companies in later stage partnerships is that the CDx is already developed by the diagnostic company and only needs to be clinically validated. In this way, separate CDx development can be experienced as a risky business if diagnostic companies develop assays before knowing that those assays will be used by the pharmaceutical company in the first place. However, as literature suggests (e.g. Agarwal et al., 2015) that the diagnostic industry is less wealthy than the pharmaceutical industry, there are stronger budget constraints within diagnostic firms to take such risks. This risk can probably only be taken by the few wealthy diagnostic companies present.

The development process of CDx is perceived as complex with the identification of different factors in this thesis that not only affect the CDx development directly, but also reinforce each other. One of the reasons to investigate the influence of (external) factors on the CDx development process in this thesis was the introduction of new regulations on IVDs and CDx in the EU. The intention of the new regulations to support innovation from small and medium enterprises (SMEs) is not envisioned by respondents as these stricter and complex regulations demand for large amount of (financial) resources and expertise often not available within these smaller firms. In this way, respondents expect that smaller companies, often responsible for innovation activities, are not able to complete a CDx development process and need to change strategy or leave the market, leading to less CDx related innovation activities. Thereby, respondents expressed their concern for the possibility that assays will disappear from the market if the investments needed to get re-approval exceed the potential revenues, putting patient access and the prescription of the most effective therapy at risk. With the potential leave of smaller companies and their products and the impediment of use in-house developed assays over commercial developed assays, respondents raise the concern that those companies still operating will use this market position to increase the prices of their products, increasing the healthcare expenditures and eventually reimbursement premiums of citizens. This event of large companies benefitting from the leave of smaller companies has also been described in the literature in relation of the introduction of new regulation in the pharmaceutical industry (e.g. Moors et al., 2014; Thomas, 1990), leading to the dominance of 'big pharma'. Although, rising prices of much needed and potential life-saving products is not perceived as a decent act , the real impact of such price risings would still be limited. Only 0.7% of the total healthcare expenditures in Europe is spent on the use of IVDs (MedTech Europe, 2018), of which even a smaller percentage on the use of CDx. Furthermore, Cook-Deegan et al., (2009) documented that monopoly positions in the diagnostic industry did not result in consistently higher prices than assays without a monopoly.
Potential price raisings due to strong market positions that are the result of the leave of companies or restricted use by labelling can be controlled by easing the regulatory burdens to expand labels for already approved assays as proposed in the latest draft guidance by the FDA (2018b). According to this guidance, diagnostic manufacturers already having a CDx approved on the market by a pre-market

approval process, might get market approval for another indication relying on the same biomarkers on the basis of data already available. In this way, manufacturers are able to expand their market without completing a full new, time and resource consuming, approval process. In this way, the FDA has the intention to spur competition between CDx assays, controlling prices and to ease patient access.

In addition to the factors proposed by Alonso (2017), the availability of a scientific base and the advances in research on pathology and biomarkers is perceived by respondents as key for future CDx development. Today, great variability in the availability of scientific base exists among diseases, resulting in inequalities in the presence of CDx between disease areas. The main focus of CDx application has so far been in the field of oncology, but research efforts in other disease areas can pave the way for the development of CDx for other indications. Gibson et al (2015) addresses possible applications of biomarkers, such as proteomics, genomics, microbiomics, imaging and bioinformatics in the field of rheumatology. An indication like rheumatology seems an obvious candidate for targeted healthcare and CDx development due to a high degree of heterogeneity among patients, number of treatment targets and even the presence of therapies with diverse mechanisms of action, but is the targeting of treatments to patients on the basis of laboratory measurements still limited. Rheumatology is an example of a disease area where CDx show great potential in clinical decision making and the prescription of effective treatments, but is the development of CDx assay inhibited by a lack of research on biomarkers and pathology. The majority of the respondents is convinced that investments in research projects focussed on pathology and biomarker discovery could lead to scientific breakthroughs and CDx feasibility in other disease areas than oncology. Therefore research projects, such as the Cancer Genome Atlas program, which catalogues and discovers genetic alterations that drive in cancer development (see Weinstein et al., 2013), are needed to identify new biomarkers to open up new possibilities for targeted therapy.

In contrast to the research of Luo et al., (2016), the factors, market size, competition and its related potential market share show a relationship with the motivation of diagnostic companies to invest in CDx development. Whereas a CDx assay is used by pharmaceutical companies as a tool to gain competitive advantage in specific patients populations, diagnostic companies strive to develop diagnostics for a large patient population as possible and is the motivation to develop a CDx assay fuelled by a potential monopoly position. Herein, seems to be misalignment between the manufacturers as market size seems to be more important for diagnostic manufacturers than for pharmaceutical companies. This misalignment can be explained by the observation in the article of Agarwal et al (2015) who indicates that pharmaceutical companies can count on a life time revenue from medicinal products developed for chronic diseases, whereas diagnostic companies only gets income per test, which are mostly conducted once per patient. Therefore, future CDx development by diagnostic companies seem to rely on the decision to include the use of a specific assay in the label of a medicinal products. Without the inclusion of specific assays in the label of medicinal products, CDx will lose its protective market and competitive advantage over complementary assays. Additionally, when not considered as being mandatory before prescribing a medicinal product, which is the main difference between CDx and complementary assays, an assay cannot be marketed as CDx assay at all, according to its definition. Questioning whether there is still a market for CDx left in the EU anyway when specific assays will not be included in the labelling of medicinal products.
The inclusion of assays in the label of the medicinal product in turn determine the degree healthcare professionals are restricted to use those assays referred to, overruling other variables mentioned by respondents important in the adoption process of diagnostic assays, such as compatibility, costs, complexity etc. However, the restricted use by labelling and the concept of only measuring a limited amount of biomarkers for the prescription of one specific medicinal product influences the

organization healthcare negatively if multiple assays need to be conducted before a medicinal products can be described, increasing need of much needed resources, such as time, money, space and materials. In this way the introduction of even more CDx can create resistance from health institutions. A potential solution articulated lie within merging all existing CDx assays and biomarkers relevant in clinical decision making into one assay, immediately providing an outcome on what medicinal product available will be most effective. The use of a so called ''composite assay'' is also mentioned in the article of Jørgensen & Hersom (2018). Not only because of problems related to organizational aspects, the discovery of new biomarkers requires for the supplementation of existing assays for optimal clinical decision making. Question in this respect lie within the distribution of revenues among CDx manufacturers, if the assays from different manufacturers are combined.

Limitations.

With respect to the methodology used, it can be argued that by identifying the views of manufacturers involved in CDx development, views and interests of other actors involved in the CDx system are excluded, providing a one-sided overview of factors important in the CDx development process. However, as this research aimed to identify the factors related to the development process, manufacturers are the only actors involved throughout the development process, whereas others have a role in a specific stage of the development process (e.g. payers, such as healthcare reimbursement companies; regulatory authorities; patients). However, this does not imply that other actors do not have relevant visions. Thereby, these actor groups have their own interests regarding CDx development, possibly different from the manufacturers. For further research, interviews with other actors than manufacturers are recommended to identify their views and interests. As poor alignment of (economic) incentives among stakeholders can result in an impediment of CDx development (Davis et al., 2009), these interest can be used to design an innovation system in such a way that CDx development can thrive while serving these interests as well as possible. The structural system analysis in section 5.3.8. can be used as a basis to identify actor groups and individual actors present in CDx development.

Not everyone approached agreed to do an interview as they had the idea they could not provide valuable input or could identify someone in the organization present that was able to. This issue was mostly applicable to commercial pharmaceutical and diagnostic manufacturers. Development decisions, partnerships, and regulatory affairs are mostly determined on a headquarters/global level. As a result, some respondents approached were involved in development processes and decision making on a local level, and felt not qualified to represent the company or had no or limited connections to people who could be helpful in this research. However, data saturation was obtained and no new insights were obtained in the last interviews. Furthermore, the opinion articles and position paper are written with permission of the members, in which no conflicting visions were found with the interviewees minimizing the possibility that visions of 'high-ranked' employees diverge from the identified factors.

Finally, due to the great resemblance between CDx and complementary diagnostics that also measure biomarkers for the safe and effective use of medicinal products, is that some factors and the consequences of the IVDR do not only apply to CDx specifically. Actually, for some factors (e.g. patents, some adoption variables) no specific information related to CDx or assays measuring biomarkers was found, showing great resemblance with the literature on diagnostics in general. Other factors could be more specified to assays measuring biomarkers (e.g. market size, resources, reimbursement) of which some had characteristics only relating CDx (e.g. competition based on label medicinal product, compatibility within health institutions, EMA involvement in market approval). The effect of this on the research is minimal as this implies that some of the identified factors can be applied to

complementary diagnostics, but some specific factors related to CDx development cannot be applied to the development of complementary diagnostics.

Outlook

Over the next few decades, the development of CDx can enable the creation of more targeted healthcare. Pharmaceutical companies show increasing effort in developing medicinal products for selected patient populations to gain competitive advantage, but also research efforts on pathology and biomarkers are needed to accelerate the development of these assays across more disease areas. If EU authorities include the use of a CDx assay in the label of medicinal products, CDx development still seems profitable for large diagnostic companies, despite the introduction of the IVDR. However, this labelling decision can create problems for the organization of healthcare in the long-run. The use of more mandatory assay demand for large amount of resources often not present within health institutions and the health system. In this way, the concept of prescribing a medicinal product on the basis of a limited amount of biomarkers threatens CDx own future. With the possible identification of more and more biomarkers, patients can be characterized even further. For optimal clinical decision making. future prospects, therefore, lie within merging those together in one assay.

References.

Abraham, J., Smith, H. L., & Smith, H. L. (2003). *Regulation of the pharmaceutical industry*. New York: Springer.

Acemoglu, D., & Linn, J. (2004). Market size in innovation: theory and evidence from the pharmaceutical industry. *The Quarterly journal of economics*, *119*(3), 1049-1090.

Agarwal, A. (2012). Do companion diagnostics make economic sense for drug developers?. *New biotechnology*, 29(6), 695-708.

Agarwal, A., Ressler, D., & Snyder, G. (2015). The current and future state of companion diagnostics. *Pharmacogenomics and personalized medicine*, *8*, 99.

Allan, C., Joyce, T. J., & Pollock, A. M. (2018). Europe's new device regulations fail to protect the public. *BMJ* 363

Alonso, M. M. (2017). Product Development and Commercialization of Diagnostic or Life Science Products for Scientists and Researchers. In *Molecular Profiling* (pp. 399-407). New York, NY: Humana Press.

Ansari, M. (2013). The regulation of companion diagnostics: a global perspective. *Therapeutic Innovation & Regulatory Science*, *47*(4), 405-415.

Barney, J. B. (1986). Strategic factor markets: Expectations, luck, and business strategy. *Management science*, *32*(10), 1231-1241.

Barney, J. B., & Arikan, A. M. (2001). The resource-based view: Origins and implications. *Handbook of strategic management*, 124-188

Bartlett, J. W., & Frost, C. (2008). Reliability, repeatability and reproducibility: analysis of measurement errors in continuous variables. *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *31*(4), 466-475.

Bergek, A., Jacobsson, S., Carlsson, B., Lindmark, S., & Rickne, A. (2008). Analyzing the functional dynamics of technological innovation systems: A scheme of analysis. *Research policy*, *37*(3), 407-429.

Bijker, W. E., Hughes, T. P., & Pinch, T. J. (Eds.). (1989). *The social construction of technological systems: New directions in the sociology and history of technology*. Cambridge:MIT press.

Blind, K. (2012). The influence of regulations on innovation: A quantitative assessment for OECD countries. *Research Policy*, 41(2), 391-400.

Braczyk, H. J., Cooke, P. N., & Heidenreich, M. (Eds.). (1998). *Regional innovation systems: the role of governances in a globalized world*. Hove, UK: Psychology Press.

Cain, M., & Mittman, R. (2002). *Diffusion of innovation in health care*. Palo Alto: Institute for the future.

Carlsson, B., & Stankiewicz, R. (1991). On the nature, function and composition of technological systems. *Journal of evolutionary economics*, 1(2), 93-118.

Chabner, B. A. (2011). Early accelerated approval for highly targeted cancer drugs. *New England Journal of Medicine*, *364*(12), 1087-1089.

Christensen, C. M. (2013). *The innovator's dilemma: when new technologies cause great firms to fail*. Cambridge, MA: Harvard Business Review Press.

Clemens, J. (2013). *The effect of us health insurance expansions on medical innovation* (No. w19761). National Bureau of Economic Research.

Cook, K., Shortell, S. M., Conrad, D. A., & Morrisey, M. A. (1983). A theory of organizational response to regulation: the case of hospitals. *Academy of Management Review*, 8(2), 193-205.

Cooke, P., Uranga, M. G., & Etxebarria, G. (1997). Regional innovation systems: Institutional and organisational dimensions. *Research policy*, 26(4-5), 475-491.

Cook-Deegan, R., Chandrasekharan, S., & Angrist, M. (2009). The dangers of diagnostic monopolies. *Nature*, *458*(7237), 405.

Cooper, R. G., & Kleinschmidt, E. J. (2011). *New products: The key factors in success*. Chicago: Marketing Classics Press.

Crafts, N. (2006). Regulation and productivity performance. *Oxford Review of Economic Policy*, *22*(2), 186-202.

Davis, J. C., Furstenthal, L., Desai, A. A., Norris, T., Sutaria, S., Fleming, E., & Ma, P. (2009). The microeconomics of personalized medicine: today's challenge and tomorrow's promise. *Nature reviews Drug discovery*, 8(4), 279-286.

De Bruijn, A. C. P., & Roszek, B. R. (2015). *In-huis ontwikkelde IVD testen: Gebruik en kwaliteitsborging.* Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu

Derksen, J. T. M., Staal, P. C., Ligtenberg, G. (2011). Medische tests (beoordeling stand van de wetenschap en praktijk) No. 293: College voor zorgverzekeringen.

DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, *47*, 20-33.

Dubois, P., De Mouzon, O., Scott-Morton, F., & Seabright, P. (2015). Market size and pharmaceutical innovation. *The RAND Journal of Economics*, *46*(4), 844-871.

Edquist, C. (Ed.). (1997). *Systems of innovation: technologies, institutions, and organizations.* London and Washington: Pinter/Cassell Academic.

Edquist, C. (2001, June). *The Systems of Innovation Approach and Innovation Policy: An account of the state of the art.* In DRUID Conference, Aalborg (pp. 12-15).

Edquist, C. (2004). *Systems of Innovations: Perspectives and Challenges,* in: Fagerberg, J. (2005). The Oxford handbook of innovation. Oxford: Oxford university press.

Edquist, C. and Johnson, B. (1997). *'Institutions and organisations in systems of innovation'*, in C. Edquist (ed.) Systems of Innovation: Technologies, Institutions and Organizations. London and Washington: Pinter/Cassell Academic.

Eichler, H. G., Pignatti, F., Flamion, B., Leufkens, H., & Breckenridge, A. (2008). Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nature Reviews Drug Discovery*, *7*(10), 818.

EMA (2019). Medical Devices. Latest retrieved 25-03-2018 from https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices

Enzmann, H., Meyer, R., & Broich, K. (2016). The new EU regulation on in vitro diagnostics: potential issues at the interface of medicines and companion diagnostics. *Biomarkers*, 10(12), 1261-1268.

European Parliament (2017). Regulation (EU) 2017/746 of the European Parliament and of the Council April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and 2010/227/EU Commission Decision. Volume 60. Latest retrieved 29-03-2019 from https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746&from=EN

FDA (2018a). Companion Diagnostics. Latest retrieved 25-03-2019 from https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm

FDA (2018b). Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products Guidance for Industry. Draft Guidance. Latest retrieved 19-04-2019 from https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm627805.pdf

Fineberg, H. V. (1978). Evaluation of computed tomography: achievement and challenge. *American Journal of Roentgenology*, 131(1), 1-4

Freeman, C. (1987). *Technology policy and economic policy: Lessons from Japan.* London: Pinter.

Fridlyand, J., Simon, R. M., Walrath, J. C., Roach, N., Buller, R., Schenkein, D. P., ... & Scher, H. I. (2013). Considerations for the successful co-development of targeted cancer therapies and companion diagnostics. *Nature Reviews Drug Discovery*, 12(10), 743-755.

Gagliardi, D., Ramlogan, R., Navarra, P., & Russo, C. D. (2018). Diffusion of complementary evolving pharmaceutical innovations: The case of Abacavir and its pharmacogenetic companion diagnostic in Italy. *Technological Forecasting and Social Change*, *134*, 223-233.

Gaultney, J. G., Sanhueza, E., Janssen, J. J., Redekop, W. K., & Uyl-de Groot, C. A. (2011). Application of cost–effectiveness analysis to demonstrate the potential value of companion diagnostics in chronic myeloid leukemia. *Pharmacogenomics*, 12(3), 411-421.

Gelijns, A. C., & Halm, E. A. (1991). The dynamics of medical device innovation: An innovator's perspective. In *The changing economics of medical technology*. Washington: National Academies Press.

Gibson, D. S., Bustard, M. J., McGeough, C. M., Murray, H. A., Crockard, M. A., McDowell, A., ... & Bjourson, A. J. (2015). Current and future trends in biomarker discovery and development of companion diagnostics for arthritis. *Expert review of molecular diagnostics*, *15*(2), 219-234.

Gilbert, R. (2006). Looking for Mr. Schumpeter: Where Are We in the Competition--Innovation Debate?. *Innovation policy and the economy*, *6*, 159-215.

Ginsburg, G. S., & McCarthy, J. J. (2001). Personalized medicine: revolutionizing drug discovery and patient care. *TRENDS in Biotechnology*, *19*(12), 491-496.

Gold, E. R., Kaplan, W., Orbinski, J., Harland-Logan, S., & Sevil, N. (2010). Are patents impeding medical care and innovation?. *PLoS medicine*, *7*(1), e1000208.

Grabowski, H. G., Vernon, J. M., & Thomas, L. G. (1978). Estimating the effects of regulation on innovation: an international comparative analysis of the pharmaceutical industry. *The Journal of Law and Economics*, *21*(1), 133-163.

Grabowski, H. (2002). Patents, innovation and access to new pharmaceuticals. *Journal of International Economic Law*, *5*(4), 849-860.

Hekkert, M. P., Suurs, R. A., Negro, S. O., Kuhlmann, S., & Smits, R. E. (2007). Functions of innovation systems: A new approach for analysing technological change. *Technological forecasting and social change*, *74*(4), 413-432.

Hill, R. G., & Rang, H. P. (2013). *Drug Discovery and Development: Technology in Transition*. London: Elsevier Health Sciences.

Hinman, L. M., Huang, S. M., Hackett, J., Koch, W. H., Love, P. Y., Pennello, G., ... & Webster, C. (2006). The drug diagnostic co-development concept paper Commentary from the 3rd FDA-DIA-PWG-PhRMA-BIO Pharmacogenomics Workshop. *The pharmacogenomics journal*, *6*(6), 375.

Hood, C., James, O., Jones, G., Scott, C., & Travers, T. (1998). Regulation inside government: where new public management meets the audit explosion. *Public Money and Management,* 18(2), 61-68.

Huttin, C., & Andral, J. (2000). How the reimbursement system may influence physicians' decisions results from focus groups interviews in France. *Health Policy*, *54*(2), 67-86.

Jørgensen, J. T. (2008a). Are we approaching the post-blockbuster era? Pharmacodiagnostics and rational drug development. *Expert review of molecular diagnostics*, *8*(6), 689-695.

Jørgensen, J. T. (2008b). From blockbuster medicine to personalized medicine. *Future medicine*, 55-63

Jørgensen, J. T. (2011). A challenging drug development process in the era of personalized medicine. *Drug discovery today*, 16(19), 891-897.

Jørgensen, J. T. (2012). Companion diagnostics and the drug–diagnostic codevelopment model. *Drug Development Research*, 73(7), 390-397.

Jørgensen, J. T. (2013). Companion diagnostics in oncology-current status and future aspects. *Oncology*, 85(1), 59-68.

Jørgensen, J. T. (2015). Companion diagnostics: the key to personalized medicine. *Expert review of molecular diagnostics*, 15(2), 153-156.

Jørgensen, J. T., & Hersom, M. (2016). Companion diagnostics—a tool to improve pharmacotherapy. *Annals of translational medicine*, *4*(24).

Jørgensen, J. T., & Hersom, M. (2018). Clinical and regulatory aspects of companion diagnostic development in oncology. *Clinical Pharmacology & Therapeutics*, *103*(6), 999-1008.

Kalia, M. (2013). Personalized oncology: recent advances and future challenges. *Metabolism*, 62, S11-S14.

Kremer, M. (2002). Pharmaceuticals and the developing world. *Journal of Economic Perspectives*, *16*(4), 67-90.

Kuhn, T. (1962) *The Structure of Scientific Revolutions*. Chicago, IL: University of Chicago Press.

Lanjouw, J. O. (2005). *Patents, price controls, and access to new drugs: how policy affects global market entry* (No. w11321). National Bureau of Economic Research.

Lundvall, B. A. (1992). *National systems of innovation: An analytical framework.* London: Pinter.

Lundvall, B. A. (2007). National innovation systems—analytical concept and development tool. *Industry and innovation*, *14*(1), 95-119.

Luo, D., Smith, J. A., Meadows, N. A., Schuh, A., Manescu, K. E., Bure, K., ... & Brindley, D. A. (2016). A quantitative assessment of factors affecting the technological development and adoption of companion diagnostics. *Frontiers in genetics*, *6*, 357.

Malerba, F. (2002). Sectoral systems of innovation and production. *Research policy*, *31*(2), 247-264.

Malerba, F. (Ed.). (2004). *Sectoral systems of innovation: concepts, issues and analyses of six major sectors in Europe*. Cambridge: Cambridge University Press.

Mansfield, E. (1986). Patents and innovation: an empirical study. *Management science*, *32*(2), 173-181.

MedTech Europe (2018). *The European Medical Tehcnology Industry – in figures 2018.* Latest retrieved 31-3-2019 from https://www.medtecheurope.org/wp-content/uploads/2018/06/MedTech-Europe_FactsFigures2018_FINAL_1.pdf

Milne, C. P., Bryan, C., Garafalo, S., & McKiernan, M. (2015). Complementary versus companion diagnostics: apples and oranges?. *Biomarkers in medicine*, *9*(1), 25-34.

Moore, M. W., Babu, D., & Cotter, P. D. (2012). Challenges in the codevelopment of companion diagnostics. *Personalized medicine*, *9*(5), 485-496.

Moors, E. H., Cohen, A. F., & Schellekens, H. (2014). Towards a sustainable system of drug development. *Drug discovery today*, 19(11), 1711-1720.

Naylor, S., & Cole, T. (2010). Companion diagnostics in the pharmaceutical industry part I. *Drug Discov World*, 11(2), 67-79.

Nelson, R. R. (Ed.). (1993). *National innovation systems: a comparative analysis*. Oxford: Oxford University Press on Demand.

Nelson, R. R., & Winter, S. G. (1977). In search of a useful theory of innovation. In *Innovation, economic change and technology policies* (pp. 215-245). Birkhäuser, Basel.

Nooteboom, B. & Stam, E. (2008) *Micro-foundations for Innovation Policy.* Amsterdam: Amsterdam University Press.

OECD (2003). *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies.* Paris: OECD Publishing.

Olsen, D., & Jørgensen, J. T. (2014). Companion diagnostics for targeted cancer drugs–clinical and regulatory aspects. *Frontiers in oncology*, *4*, 105.

Palomeras, N. (2003). Sleeping patents: any reason to wake up. IESE Research Papers No D/506.

Phillips, K. A., Van Bebber, S., & Issa, A. M. (2006). Diagnostics and biomarker development: priming the pipeline. *Nature reviews Drug discovery*, *5*(6), 463.

Pignatti, F., Ehmann, F., Hemmings, R., Jonsson, B., Nuebling, M., Papaluca-Amati, M., ... & Rasi, G. (2014). Cancer drug development and the evolving regulatory framework for companion diagnostics in the European Union. *Clinical Cancer Research*, 20 (6) 1458-1468.

Pindyck, R. S., & Rubinfeld, D. L. (2013). *Microeconomics* (8th ed). New Jersey: Pearson

Porter, M. E. (1990). *Competitive advantage of nations: creating and sustaining superior performance.* New York: Palgrave Macmillan.

Puntmann, V. O. (2009). How-to guide on biomarkers: biomarker definitions, validation and applications with examples from cardiovascular disease. *Postgraduate medical journal*, *85*(1008), 538-545.

Roberts, P. W. (1999). Product innovation, product–market competition and persistent profitability in the US pharmaceutical industry. *Strategic management journal*, *20*(7), 655-670.

Rogers, E. M. (2003). *Diffusion of innovations* (5th ed). New York: Simon and Schuster.

Sanson-Fisher, R. W. (2004). Diffusion of innovation theory for clinical change. *Medical journal of Australia*, *180*, S55-S56.

Scannell, J. W., Blanckley, A., Boldon, H., & Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. *Nature reviews Drug discovery*, 11(3), 191-200.

Scherf, U., Becker, R., Chan, M., & Hojvat, S. (2010). Approval of novel biomarkers: FDA's perspective and major requests. *Scandinavian Journal of Clinical and Laboratory Investigation*, *70*(sup242), 96-102.

Schmookler, J. (1966). *Invention and economic growth*. Cambridge, MA: Harvard University Press

Schreyögg, J., Bäumler, M., & Busse, R. (2009). Balancing adoption and affordability of medical devices in Europe. *Health policy*, *92*(2-3), 218-224.

Schumpeter, J. (1934). *The Theory of Economic Development*. Cambridge, MA: Harvard University Press.

Schumpeter, J. (1950). *Capitalism, Socialism and Democracy.* New York: Harper.

Smits, R., & Kuhlmann, S. (2004). The rise of systemic instruments in innovation policy. *International journal of foresight and innovation policy*, *1*(1-2), 4-32.

Stark, N. J., & Jaeger, V. (2011). *Reimbursement Strategies for New Technologies.* Retrieved 29-12-2018 from http://clinicaldevice.typepad.com/cdg_whitepapers/2011/05/reimbursement-strategies.html

Stern, A. D. (2017). Innovation under regulatory uncertainty: evidence from medical technology. *Journal of public economics*, *145*, 181-200.

Teece, D., & Pisano, G. (1994). The dynamic capabilities of firms: an introduction. *Industrial and corporate change*, *3*(3), 537-556.

Teece, D. J., Pisano, G., & Shuen, A. (1997). Dynamic capabilities and strategic management. *Strategic management journal*, *18*(7), 509-533.

Thomas, L. G. (1990). Regulation and firm size: FDA impacts on innovation. *The RAND Journal of Economics*, 497-517.

Tidd, J., & Bessant, J., (2005). *Managing innovation integrating technological, market and organizational change*. West Sussex: John Wiley and Sons Ltd.

Trusheim, M. R., & Berndt, E. R. (2015). The clinical benefits, ethics, and economics of stratified medicine and companion diagnostics. *Drug discovery today*, *20*(12), 1439-1450.

Walsh, J. P., Arora, A., & Cohen, W. M. (2003). Working through the patent problem. *Science*, *299*(5609), 1021-1021.

Weinstein, J. N., Collisson, E. A., Mills, G. B., Shaw, K. R. M., Ozenberger, B. A., Ellrott, K., ... & Cancer Genome Atlas Research Network. (2013). The cancer genome atlas pan-cancer analysis project. *Nature genetics*, *45*(10), 1113.

Wernerfelt, B. (1984). A resource-based view of the firm. *Strategic management journal*, *5*(2), 171-180.

Wieczorek, A. J., & Hekkert, M. P. (2012). Systemic instruments for systemic innovation problems: A framework for policy makers and innovation scholars. *Science and Public Policy*, *39*(1), 74-87.

Wiggins, S. N. (1983). The impact of regulation on pharmaceutical research expenditures: a dynamic approach. *Economic Inquiry*, *21*(1), 115-128.

Woolthuis, R. K., Lankhuizen, M., & Gilsing, V. (2005). A system failure framework for innovation policy design. *Technovation*, *25*(6), 609-619.

Appendix I: Regulatory requirements for the approval of commercial developed IVDs under the IVDR.

For the approval of CDx under the IVDR, commercial manufacturers must submit a performance evaluation report in which the scientific validity, analytical and clinical performance of the device must be demonstrated. Additionally, manufacturers must establish a comprehensive post-marketing surveillance plan and quality management system (Ansari, 2013; European Parliament, 2017; Pignatti et al., 2014).

A. 1.1. Performance evaluation report.

The performance evaluation of a device is *''a continuous process by which data are assessed and analysed to demonstrate the scientific validity, analytical performance and clinical performance of that device for its intended purpose as stated by the manufacturer''* (European Parliament, 2017, p. 321). This definition implies that even after marker approval the manufacturer has the responsibility to actively gather and asses data to improve the performance of the assay. This is largely part of the post-marketing surveillance plan, explained in A.1.2. The intended purpose is also defined in the IVDR and quite similar to the definition of CDx: ''*CDx is used for the safe and effective use of a corresponding medicinal product to: (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product''* (European Parliament, 2017, p. 13). The performance evaluation report covers three main pillars: scientific validity, analytical performance and clinical performance (figure 12).

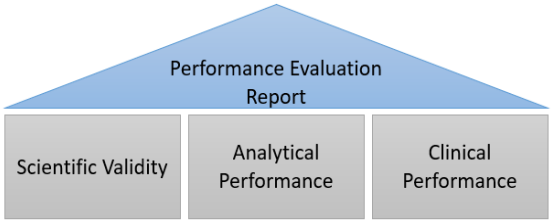

Figure 12: The three main pillars in the performance evaluation report that shall be demonstrated by the manufacturer of the CDx assay: scientific validity, analytical performance, and clinical performance. Authors own compilation

A. 1.1.1. Scientific validity.

Scientific validity is defined as ''*the association of an analyte with a clinical condition or a physiological state*'' (European Parliament, 2017, p. 15). In other words, scientific validity provides an indication on of the why it is makes sense to measure a specific analyte for a specific condition and what it means when a certain level of this biomarker is measured. In the case of CDx, the analyte measured is often a biomarker associated with the pathophysiology of a (dub)condition or with the susceptibility to develop this condition. The scientific validity is not assay specific, enabling the manufacturer to demonstrate the scientific validity of a biomarker on the basis of data that is already available, such as scientific literature, results from other clinical performance studies or proof of concept studies (European Parliament, 2017).

A. 1.1.2. Analytical performance.

The analytical performance of an assay means *''the ability of an assay to correctly detect or measure a particular analyte''* (European Parliament, 2017, p. 15). In the IVDR different analytical characteristics are described (see p.95 and p. 99-100 in the IVDR for more details) that should be tested and verified by the manufacturers to demonstrate analytical performance (table 8).

Table 8: Overview of analytical characteristics of an assay that should be tested and verified. Definitions and explanations from European Parliament, 2017; Barlett & Frost, 2008

Analytical performance characteristic	Definition & explanation

Accuracy	Accuracy is a product of the trueness and precision of an assay.
	• Trueness: difference between the test result and the actual ''true'' value. Actual true value is provided by an certified reference method
	• Precision is reflected by the assay's repeatability and reproducibility.
	  ○ Repeatability: the variation in repeat measurements made on the same subject under identical conditions
	  ○ Reproducibility: the variation in measurements made on a subject under changing conditions

Analytical sensitivity	The ability of an assay to identify the presence of a target marker associated with a particular disease or condition
Analytical specificity	The ability of an assay to recognise the absence of a target marker associated with a particular disease or condition
Predictive value	The probability that a person with a positive device test result has a given condition under investigation, or that a person with a negative device test result does not have a given condition
Positive predictive value	The ability of a device to separate true positive results from false positive results for a given attribute in a given population
Negative predictive value	The ability of a device to separate true negative results from false negative results for a given attribute in a given population

The analytical sensitivity and specificity are determined by a certain threshold, i.e. limit of detection, programmed by the manufacturer. The limit of detection is the starting point of a measuring range. All values within this measuring range can be measured by the assay. The manufacturer must describe and justify a certain cut-off value that separates the test positives and test negatives within this measuring range. In the ideal situation having the highest predictive value (figure 13, upper picture) the chosen cut-off value of a CDx assay perfectly identifies the patients for which the medicinal product will be effective/responders (green curve) and the patients for which the medicinal product will not be effective/non-responders (blue curve) (Trusheim & Berndt, 2015). Unfortunately, in a more realistic scenario, lower picture, the chosen cut-off value does not perfectly separate the responders and non-responders; there is overlap between the two patient populations, resulting in false positives i.e. patients with a positive test result for which the medicinal product is not effective and false negatives i.e. patients with a negative test result for which the medicinal product is effective. To increase the certainty that only the patients that will benefit from

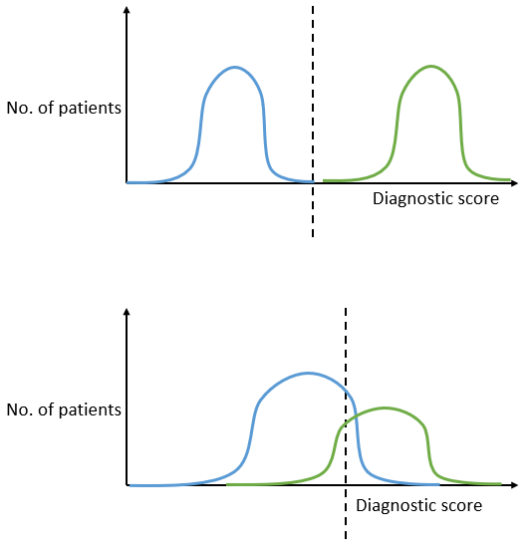

Figure 13: Situation with an ideal cut-off value (upper picture) and in which there is overlap between the responders and non-responders with a given cut-off value (lower picture). Adapted from Trusheim & Berndt, 2015

the medicinal product will get the medicinal product, the manufacturer must demonstrate the positive and negative predictive value of the assay.

A. 1.1.3. Clinical Performance.

The clinical performance of an assay is *''the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user''* (European Parliament, 2017, p. 15). In order words, manufactures must demonstrate the relevance and usefulness of the CDx assay in clinical decision making and must its demonstrate usefulness in patientcare against the state-of-the-art medicine (Jørgensen, 2012; European Parliament, 2017). To demonstrate clinical utility for new assay, clinical performance studies must be conducted. For CDx, clinical performance studies are used to demonstrate that the CDx assay can predict the treatment outcome of individual patients and thus separate the patients for which the medicinal product is likely to be effective or not (Olson and Jørgensen, 2014). When developed in conjunction with the medicinal product, the CDx assay is most likely incorporated in the clinical studies of the medicinal product, testing both the analytical performance of the CDx assay as well as the effectiveness of the medicinal product. Two different clinical study designs are proposed in the literature to prove the clinical utility of the CDx assay and the corresponding medicinal product: the enrichment design and the stratification design (figure 14). In the enrichment design only the patients that are tested positively are enrolled in the clinical study and get after randomization the targeted 'new' medicinal product or the standard/reference therapy that is already available (Jørgensen, 2012; Olson and Jørgensen, 2014; Scherf et al., 2010). This design provides only insight in the effectiveness of medicinal product in the test positive group, excluding the test negative group (Olson and Jørgensen, 2014; Scherf et al., 2010). In the stratification design also the group that is tested negatively is randomized and will get the new drug or the standard therapy, allowing the manufacturer to calculate the positive predictive value (number of true positives/number of positive calls), but also the negative predictive value (number of true negative/number of negative calls), sensitivity (true positive rate) and specificity (true negative rate) of the CDx assay. This stratification design is preferred over the enrichment design as it allows the manufacturer and authorities to compare the effectiveness of the medicinal product in the test positive and test negative group. When the effectiveness is equal in both group, a CDx assay is not of added value in prescribing the medicinal product. This is, however, not demonstrated by the enrichment design.

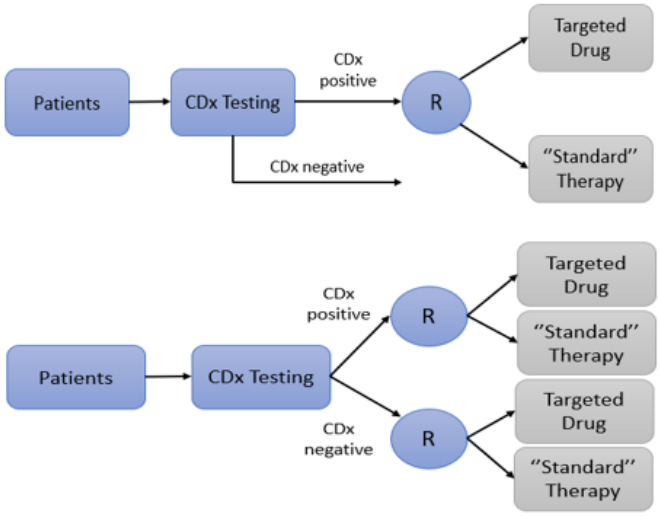

Figure 14: Overview of different clinical trial designs used to demonstrate clinical utility of the CDx assay. Upper picture is enrichment design, lower picture is stratification design. Adapted from Jørgensen, 2012; Olson and Jørgensen, 2014; Scherf et al., 2010

A. 1.2. Post-marketing surveillance plan.

In the IVDR post-marketing surveillance is defined as *''all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any*

necessary corrective or preventive actions'' (p. 17). Manufactureres need to systematically gather, record and analyse data on the quality, performance and safety of the assay throughout its lifetime in post-market performance follow-up (PMPF) studies with the aim to identify needs to improve usability, performance and safety of the device (European Parliament, 2017 (article 78)). This data needs to be published annually by the manufacturer in a so called periodic safety update report (PSUR) allowing authorities to assess data of the real-life performance of the assay and call for actions or remove the assay from the market if satefy or effeicacy issues appear.

A. 1.3. Quality management system.

CDx manufacturers must also establish a quality management system, which covers ''*all parts and elements of a manufacturer's organisation dealing with the quality of processes, procedures and devices. It shall govern the structure, responsibilities, procedures, processes and management resources required to implement the principles and actions necessary to achieve compliance with the provisions of this Regulation''* (European Parliament, 2017, p. 22). Manufacturers must be transparent in their development and manufacturing processes by providing NBs insight in organisational structures, procedures for monitoring, verifying, validating and controlling the performance of the assay, and risk and solution management (European Parliament, 2017). Additionaly manufacturers and their suppliers and distributors can be inspected at any time by NBs or other supervision authorities.

Appendix II: CDx development stages in the Drug-Diagnostic Codevelopment model.

In general the development process of a diagnostic assay is defined as *'the development process from initial design or [biomarker] discovery to the finished diagnostic including implementation and post-marketing surveillance'* (Philips et al., 2006, p. 463).

Philips et al (2006) stated that one of the key differences between medicinal product and diagnostic assay development is that diagnostic assays incorporate technologies that are rather designed than discovered. However, in the case of CDx, the identification and discovery of molecular biomarkers, does play a major role in the development of CDx and requires, similar to drugs, a thorough understanding of the underlying pathophysiology of the (sub)disease for which the CDx is developed for (Jørgensen, 2012). It is among the molecular characteristics of the underlying pathology that potential predictive and selective biomarkers should be identified. Selecting the right biomarker(s) and potential drug candidate(s) are crucial, because if biomarkers and/or drug candidates are selected having no relation with each other the project will likely fail (Jørgensen, 2012). In sum, extensive research activities on the underlying pathophysiology and genome variability of diseases are needed to identify potential drug targets or biomarkers.

When after the feasibility studies the biomarker(s) appears promising a prototype assay is developed during the pre-clinical and phase I studies of the medicinal product (Jørgensen, 2012). During the pre-clinical and phase I studies the candidate medicinal product is first tested in computer models, animals and a small group of healthy subjects to test the safety and tolerability (Hill & Rang, 2012). During the clinical phase II studies the assay is analytical validated. The most critical part in this process is to determine and select the clinical cut-off value in series of experiments (see figure x and x). If the correlation between the measured biomarker and clinical effectiveness is to weak, it becomes difficult to establish a cut-off value separating responders and non-responders and will be problematic to continue to phase III clinical trials (Jørgensen, 2012).

During the phase III clinical trials, the correlation between the biomarkers measured and the effectiveness is actually tested and validated. A CDx assay is only considered to be useful in clinical decision making it is able to provide information that is helpful in discriminating the responders and non-responders to the medicinal product under development. To test the correlation the enrichment design and/or the stratification design as explained in AI can be used.

Although not specifically mentioned in the drug-diagnostic codevelopment model in the articles by Jørgensen (2012; 2013), Jørgensen & Hersom (2018), and Olson & Jørgensen (2014), the CDx assay and the corresponding medicinal product follow a specific diffusion and adoption trajectory after regulatory approval. The article of Gagliardi et al (2018) is the first that explored the diffusion process of a medicinal product and its CDx assay. The diffusion starts with getting the support of healthcare professionals and organizations, such as hospitals, by highlighting the advantages of the new CDx assay and its corresponding medicinal product. Whilst this might seem straightforward, the deployment and integration of an additional test can be complex as practitioners and laboratory staff members need to change their routines and learn new clinical guidelines (Gagliardi et al., 2018). In the case described by Gagliardi et al (2018) the diffusion of the CDx assay was significantly accelerated by the introduction of guidelines in which the use of the CDx assay was highlighted as a mandatory component in the clinical routine. Additionally, the CDx assay and the medical product also need commitment from other parties than healthcare professionals, such as the state and third-party payers/healthcare reimbursement companies (Gagliardi et al., 2018). The diffusion of any medical innovation will only be successful if the test or medicinal will be reimbursed; reimbursement plays an important role for healthcare professionals when choosing between tests or therapies (Schreyögg et al., 2009).

Appendix III: Overview of diagnostic companies involved in CDx development.

Table 9: Overview of diagnostic companies found, including their focus in CDx development and potential collaboration agreements.

Company name	Focus CDx Development	Collaboration agreements with:	Company present in Europe?
20/20 GeneSystems	- Biomarker discovery & development - Essay development	-	No
Abbott Molecular, Inc. or Abbott Laboratories	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Pfizer (2009) - Biocartis (2014) - Biogenex Laboratories - Janssen Biotech (2013 and 2018) - Merck (2012)	Yes
Agendia BV	- Biomarker discovery & development	-	Yes
Agilent Technologies	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	-	Yes
Allegro Diagnostics (acquired by Veracyte)	- Biomarker discovery & development	- Loxo Oncology (2018)	No
Almac Group	- Biomarker discovery & development - Essay development	- OncoMed Pharmaceuticals, Inc (2015)	Yes
ArcherDx	- Biomarker discovery & development - Essay development	- Merck (2018) - Ignyta - Celgene	No
ARUP Laboratories	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Labceutics (2015)	No
AssuerRx Health	- Biomarker discovery & development	-	No
Avant diagnostics	- Biomarker discover7 & development	-	No
Axial Biotech	- Biomarker discovery & development	-	Closed
Beckman Coulter	- Biomarker discovery & development - Essay development	- Transgene (2011)	Yes
BioCartis	- Biomarker discovery & development - Essay development	-	Yes

BioCurex	- Biomarker discovery & development	-	No
Biodesix	- Biomarker discovery & development - Essay development with partner	- Checkmate pharmaceuticals (2018) - Aveo Oncology	No
Biogenex Laboratories, Inc.	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Abbott Molecular (end in 2013)	Yes, but no physical building
Biomarker Strategies	- Biomarker discovery & development - Essay development	-	No
bioMérieux Inc	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Bioaster (2016)	Yes
Brain Resource Company Ltd	- Biomarker discovery & development	-	No
Bruker Daltonics	- Biomarker discovery & development	-	Yes
Cangen Biotechnologies	- Biomarker discovery & development	-	No
Caprion Biosciences	- Biomarker discovery & development	-	Yes
CardioDx	- Biomarker discovery & development	-	No
Caris Life Sciences	- Biomarker discovery & development	-	Yes
Celera Diagnostics (acquired by Quest Diagnostics)	- Biomarker discovery & development - Essay development	- Janssen Biotech	No (Celera itself does not exist anymore)
Clarient Inc (acquired by NeoGenomics)	- Biomarker discovery & development	-	No
Corgenix	- Biomarker discovery & development - Essay development	- Lilly (2013)	No
Crescendo Bioscience	- Biomarker discovery & development	-	No
Cytocore, Inc	- Biomarker discovery & development	-	No
Dako North America, Inc or Dako Denmark A/S (acquired by Agilent Technologies company)	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Merck (2015 - Pfizer (2015) - Amgen (2015)	Yes
Decisive Diagnostics	- Biomarker discovery & development	-	No
deCode Genetics	- Biomarker discovery & development	-	No

DiaDexus	- Biomarker discovery & development	-	Closed
Diagnocure	- Biomarker discovery & development	-	No
DxS Limited (acquired by Qiagen)	- Biomarker discovery & development - Essay development	- Amgen - Boehringer Ingelheim -AstraZeneca -Roche Diagnostics -Merck	Yes
EDP Biotech	- Biomarker discovery & development	-	No
Epigenomics	- Biomarker discovery & development - Essay development	- Companion Dx Reference Lab (2012)	Yes
EXACT Sciences Corp	- Biomarker discovery & development	-	No
Exagen Diagnostics	- Biomarker discovery & development	-	No
Foundation Medicine, Inc. (Part of Roche group)	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Pfizer (2018) - Merck (2018) - AstraZeneca (2016)	No
GeneDX	- Biomarker discovery & development	-	No
Genesis Genomics	- Biomarker discovery & development	-	No
Genomas	- Biomarker discovery & development	-	No
Genomic Health	- Biomarker discovery & development	-	No
Health Discovery Group	- Biomarker discovery & development	-	No
Hologic **Tepnel Pharma Services**	- Biomarker discovery & development - Essay development (assisting)	-	Yes
Ikonisys	- Biomarker discovery & development	-	No
Illumina, Inc	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Bristol-Myers Squibb (2018) - Loxo Oncology (2018) - Almac (2015)	Yes
InterGenetics	- Biomarker discovery & development	-	No
Invivoscribe Technologies, Inc.	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Astellas Pharma (end in 2018) - Thermo Fischer Scientific (2017)	Yes
LabCorp	- Biomarker discovery & development - Essay development	- Unilabs (2018)	No

Leica Biosystems	- Biomarker discovery & development - Essay development	- Synthon Biopharmaceuticals - Bristol-Myers Squibb (2014) - Bayer (2016) -Merrimack Pharmaceuticals (2016)	Yes
Life Technologies Corporation (acquired by Thermo Fischer Scientific)	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Bristol-Myers Squibb (2012) - Merck (2013)	Yes
LineaGen	- Biomarker discovery & development	-	No
Luminex	- Biomarker discovery & development	-	Yes
Molecular MD corporation	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Illumina (2016) - Novartis (2014) - ARIAD (2011)	No
Monogram Biosciences	- Biomarker discovery & development - Essay development	- Pfizer (2006)	No
Myriad Genetic Laboratories, Inc.	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- AstraZeneca (2018) - Beigene (2017)	Yes
Nodality	- Biomarker discovery & development		Closed
OncoMethylome Sciences (new name: MDxHealth)	- Biomarker discovery & development - Essay development	- Pfizer (2011)	Yes
On-Q-ity	- Biomarker discovery & development	-	Closed
OPKO Health	- Biomarker discovery & development		No
Orion Genomics	- Biomarker discovery & development	-	No
Panacea Pharmaceuticals	- Biomarker discovery & development - Essay development	-	No
ParagonDx	-Biomarker discovery & development	-	No
Power3 Medical Products	- Biomarker discovery & development	-	Closed
Prognomix	- Biomarker discovery & development - Essay development	-	No
Prometheus Laboratories	- Biomarker discovery & development	-	No
Proventys	- Biomarker discovery & development	-	No
Provista Diagnostics	- Biomarker discovery & development	-	No

R-Biopharm AG	- Biomarker discovery & development - Essay development	- Merck (2016)	Yes
Resonance Health Analysis Services Pty Ltd	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- BlackFort Analysis (2018)	Yes
Roche Molecular Systems, Inc or Roche Diagnostics (Part of Roche group)	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Five Prime Therapeutics (2018) - AstraZeneca (2014) - Merck (2011)	Yes
Qiagen Manchester, Ltd	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- SRL (2018) - Lilly (2014)	Yes
Rosetta Genomics	- Biomarker discovery & development	-	Closed
Saladax biomedical	- Biomarker discovery & development - Essay development	- Bristol-Myers Squibb (2012)	No
Savyon Diagnostics	- Biomarker discovery & development	-	No
Seegene	- Biomarker discovery & development	-	Yes
SenSei Biotherapeutics	- Biomarker discovery & development	-	No
Siemens Healthineers	- Biomarker discovery development - Essay development	- Pfizer (2013)	Yes
Singulex Inc	- Biomarker discovery & development	-	Yes
Source MDx	- Biomarker discovery development - Essay development	- Pfizer (2007)	No
TcLand Expression	- Biomarker discovery & development - Essay development	-	Yes
Thermo Fisher Scientific	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Blueprint Medicines (2017) - University Hospital Basel (2017)	Yes
Transgenomic	- Biomarker discovery & development	-	No
TrimGen	- Biomarker discovery & development	-	No
Tyrian Diagnostics	- Biomarker discovery & development	-	No
Ventana Medical Systems, Inc. (Part of Roche group)	- Biomarker discovery & development - Essay development - Approved CDx essay on the U.S. market	- Boehringer Ingelheim (2013) - Loxo Oncology (2017) - Immunogen (2014)	Yes

Appendix IV: Overview of health institutions developing in-house CDx.

Table 10: Overview of health institutions in the EU developing CDx for in-house use.

Name Health Institution	Focus CDx development	European country	Collaboration agreements with:
Antoni van Leeuwenhoek Hospital	- Biomarker discovery	The Netherlands	-
Ghent University Hospital	- Biomarker discovery - Assay development	Belgium	MDxHealth (2010)
Erasmus MC	- Biomarker discovery - Assay development	The Netherlands	-
Maastricht UMC+	- Biomarker discovery	The Netherlands	-
Oxford University Hospital	- Biomarker discovery	United Kingdom	-
Radboud UMC	- Biomarker discovery - Assay development	The Netherlands	TcLand Expression (2011)
University Hospital Basel	- Biomarker discovery	Switzerland	ThermoFisherScientific (2017)
University of Groningen	- Biomarker discovery	The Netherlands	
University of Leeds	- Biomarker discovery	United Kingdom	
Vrije Universiteit Hospital	- Biomarker Discovery	The Netherlands	

Appendix V: Overview of FDA approved medicinal products with a CDx assay.

Table 11: Overview of FDA approved medicinal products having a CDx assay.

Medicinal product name	Indication	Pharmaceutical company	Pharmaceutical company present in EU?	Approved CDx Essay	Manufacturer CDx Essay
Lynparza (olaparib)	Breast cancer & ovarian cancer	AstraZeneca	Yes	- BRACanalysis CDx	- Myriad Genetic Laboratories, INC.
Talzenna (talzoparib)	Breast cancer	Pfizer	Yes	- BRACanalysis CDx	- Myriad Genetic Laboratories, INC.
Rubraca (rucaparib)	Ovarian Cancer	Clovis Oncology	Yes	- BRACanalysis CDx - FoundationFocus CDxBRCA Assay	- Myriad Genetic Laboratories, INC. - Foundation Medicine, Inc
Iressa (gefitinib)	Non-small cell lung cancer	AstraZeneca	Yes	- FoundationOne CDx - Oncomine Dx Target Test - therascreen EGFR RGQ PCR Kit - cobas® EGFR Mutation Test (v2)	- Foundation Medicine, Inc. - Life Technologies Corporation - Qiagen Manchester, Ltd. - Roche Molecular Systems, Inc.
Gilotrif (afatinib)	Non-small cell lung cancer	Boehringer Ingelheim	Yes	- FoundationOne CDx - therascreen EGFR RGQ PCR Kit	- Foundation Medicine, Inc. - Qiagen Manchester, Ltd.
Vizimpro (dacomitinib)	Non-small cell lung cancer	Pfizer	Yes	- therascreen EGFR RGQ PCR Kit	- Qiagen Manchester, Ltd.
Tarceva (erlotinib)	Non-small cell lung cancer	Genentech (part of Roche)	Yes	- FoundationOne CDx - cobas® EGFR Mutation Test (v2)	- Foundation Medicine, Inc. - Roche Molecular Systems, Inc.
Tagrisso (osimertinib)	Non-small cell lung cancer	AstraZeneca	Yes	- FoundationOne CDx - cobas® EGFR Mutation Test v2	- Foundation Medicine, Inc. - Roche Molecular Systems, Inc.
Keytruda (pembrolizumab)	Non-small cell lung cancer, gastric	Merck & Co	Yes	- PD-L1 IHC 22C3 pharmDx	- Dako, North America, Inc.

	adenocarcinoma, cervical cancer				
Tecentriq (atezolizumab)	Non-small cell lung cancer	Genentech (part of Roche)	Yes	- PD-L1 (SP142)	- Ventana Medical Systems, Inc
Tibsovo (ivosidenib)	Acute myeloid leukemia	Agios Pharmaceuticals	No	- Abbott RealTime IDH1	- Abbott Molecular Inc
Tasigna (nilotinib)	Chronic myeloid leukemia	Novartis	Yes	- MolecularMD MRDx® BCR-ABL Test	- MolecularMD Corporation
Alecensa (alectinib)	Non-small cell lung cancer	Roche	Yes	- FoundationOne CDx - VENTANA ALK (D5F3) CDx Assay	- Foundation Medicine, Inc. - Ventana Medical Systems, Inc.
Xalkori (crizotinib)	Non-small cell lung cancer	Pfizer	Yes	- VYSIS ALK Break Apart FISH Probe Kit - VENTANA ALK (D5F3) CDx Assay - Oncomine Dx Target Test - FoundationOne CDx	- Abbott Molecular Inc - Ventana Medical Systems, Inc. - Life Technologies Corporation - Foundation Medicine, Inc.
Zykadia (ceritinib)	Non-small cell lung cancer	Novartis	Yes	- FoundationOne CDx - VENTANA ALK (D5F3) CDx Assay	- Foundation Medicine, Inc. - Ventana Medical Systems, Inc.
Tafinlar (dabrafenib)	Melanoma	Novartis	Yes	- FoundationOne CDx - THxID™ BRAF Kit - Oncomine Dx Target Test	- Foundation Medicine, Inc. - bioMérieux Inc. - Life Technologies Corporation
Zelboraf (vemurafenib)	Melanoma	Roche	Yes	- FoundationOne CDx - COBAS 4800 BRAF V600 Mutation Test	- Foundation Medicine, Inc. - Roche Molecular Systems, Inc
Mekinist (trametinib)	Non-small cell lung cancer	Novartis	Yes	- FoundationOne CDx - THxID™ BRAF Kit - Oncomine Dx Target Test	- Foundation Medicine, Inc. - bioMérieux Inc. - Life Technologies Corporation
Herceptin (trastuzumab)	(mainly) breast cancer	Genentech (part of Roche)	Yes	- INFORM HER-2/NEU and INFORM HER2 DUAL ISH DNA Probe Cocktail	- Ventana Medical systems - Abbott Molecular Inc

				and PATHWAY antiHer2/neu (4B5) Rabbit monoclonal Primary Antibody - PATHVYSION HER-2DNA Probe Kit - INSITE HER-2/NEU KIT - SPOT-LIGHT HER2 CISH Kit - Bond Oracle Her2 IHC System - HER2 CISH PharmDx Kit and HER2 FISH PharmDx Kit - HERCEPTEST and HER2 CISH pharmDx kit and HER2 FISH pharmDx kit - - FoundationOne CDx	- Biogenex Laboratories Inc - Life Technologies Inc - Leica Biosystems - DAKO Denmark A/S - Foundation Medicine, Inc.
Perjeta (pertuzumab)	Breast Cancer	Genentech (part of Roche)	Yes	- HERCEPTEST and HER2 FISH PharmDx Kit - FoundationOne CDx	- Dako Denmark A/S - Foundation Medicine, Inc.
Kadcyla (adotrastuzumab emtansine)	Breast cancer	Genentech (part of Roche)	Yes	- HERCEPTEST and HER2 FISH PharmDx Kit - FoundationOne CDx	- Dako Denmark A/S - Foundation Medicine, Inc.
Erbitux (cetuximab)	Colorectal cancer	Imclone Systems (part of Lilly)	Yes	- FoundationOne CDx - The cobas® KRAS Mutation Test - DAKO EGFR PharmDx Kit - therascreen KRAS RGQ PCR Kit	- Foundation Medicine, Inc. - Roche Molecular Systems, Inc. - Dako North America, Inc. - Qiagen Manchester, Ltd.
Vectibix (panitumumab)	Colorectal cancer	Amgen	Yes	- FoundationOne CDx - The cobas® KRAS Mutation Test - DAKO EGFR PharmDx Kit - therascreen KRAS RGQ PCR Kit - Praxis Extended RAS Panel	- Foundation Medicine, Inc. - Roche Molecular Systems, Inc. - Dako North America, Inc. - Qiagen Manchester, Ltd. - Illumina, Inc.
Idhifa (enasidenib)	Acute myeloid leukemia	Celgene	Yes	- Abbott Realtime IDH2	- Abbott Molecular, Inc.

Rydapt (midostaurin)	Acute myeloid leukemia	Novartis	Yes	- LeukoStrat® CDx FLT3 Mutation Assay	- Invivoscribe Technologies, Inc.
Xospata (gilterinib)	Acute myelogenous leukemia	Astellas	Yes	- LeukoStrat® CDx FLT3 Mutation Assay	- Invivoscribe Technologies, Inc.
Venclexta (venetolax)	Chronic lymphocytic leukemia	Abbvie	Yes	- VYSIS CLL FISH PROBE KIT	- ABBOTT MOLECULAR, INC
Gleevec (imatinib)	Agressive systemic mastocytosis, myelodyplastic syndrome and gastrointestinal stromal tumors	Novartis	Yes	- *KIT* D816V Mutation Detection by PCR and *PDGFRB* FISH - DAKO C-KIT PharmDx	- ARUP Laboratories - Dako North America, Inc.
Exjade (deferasirox)	Non-transfusion-dependent thalassemia	Novartis	Yes	- Ferriscan	- Resonance Health Analysis Services Pty Ltd
Glivec (imatinib mesylate)	Gastrointestinal stromal tumors	Novartis	Yes	- DAKO C-KIT PharmDx	- Dako North America, Inc.
Cotellic (cobimetinib)	Melanoma	Genentech (part of Roche)	Yes	-cobas 4800 BRAF v6000 Mutation Test	- Roche Molecular systems

Appendix VI: Interview template commercial CDx manufacturer and medicinal product manufacturer.

Please note: The interviews can be held in Dutch, as respondents can be native Dutch speakers.

Introduction

- The researcher introduces herself and indicates the research topic: The influence of regulation on innovation activities concerning CDx and actors and their relation that determinants are important to the development of CDx.
- Field of study: Innovation Sciences at Utrecht University.
- Indicate that the interview will be recorded for analyzing the transcripts. Ask for permission for the recording of the interview, ensuring that the full transcripts and data will not be made available to any other than the researcher and will be anonymized.
- Ask if the interviewee has any questions beforehand.

Personal Questions

- Who are you?
- What is your function in -name manufacturer-?

Content Related Questions

- Are you familiar with the definition of Companion Diagnostics (CDx)?
  [indicate whether or not this complies with definition used in this research and explain what definition is used in this research]

- What is your stance on the development of CDx? Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
- Why is it for -name manufacturer- interesting to be involved in the development of CDx?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What is the role of -name manufacturer- in the development process of CDx?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Is -name manufacturer- involved in partnerships with other organizations to develop CDx? If yes, how do these partnerships look like and what is the role of -name manufacturer- in this partnership?
    - Are there any preferences for -name manufacturer- when choosing a partner? If yes/no, why is this important?

  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

Questions related to the new regulatory demands.

- Are you aware that new regulations in the European Union are introduced concerning the approval of CDx (Regulation 2017/746 on IVD approval)?

[If the interviewee is not aware, explain the major change in the regulatory framework: introduction clinical trials, a quality management system and comprehensive post-marketing surveillance program]

- Do you advocate the introduction of the new regulations? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - Do you think the quality of the IVDs will be improved? If yes or no, why?
      [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What are the implications of these new regulatory demands on the development of CDx in -name manufacturer-?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Is it for -name manufacturer- possible to comply with the new regulations?
    - Will -name manufacturer- change to other product areas?

  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Although new regulations are introduced, is it still interesting for -name manufacturer- to develop CDx? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- IVDs and CDx already on the market need to be re-approved under the new regulations. Do you think this will pose any problems for -name manufacturer-?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Do you think other organizations now developing CDx will experience any problems with the new regulations?
    - Do you think these organizations will change their strategy? If yes, why and what do you think is the new strategy?

  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Overall and looking at the industry as a whole, do you think that the new regulations impede or stimulate the development of CDx? Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Do you think the market composition will change as a result of these new regulations?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- In the new regulations the use of in-house developed assays is impeded over commercial developed assays if patients need can be met by the commercial assay. Do you advocate this new requirement? If yes/no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - What do you think are the implications for health institutions?
    - What do you think are the implications for healthcare systems?

Determinants affecting the development of CDx.

- Apart from regulations, what is/are important determinant(s) for you/-name developer- when developing a CDx? Why is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - How does/do this/these determinant(s) influence the development of CDx?

- Is the intellectual landscape (patents) an important determinant for developing a CDx? Why and how is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Does the end-user, healthcare professional, play an important role when developing a CDx essay? Why and how is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Is the market size or amount of patient important in deciding to develop a CDx assay? Why and how is it important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Is the existence of other (competing) technologies important in deciding to develop a CDx assay? Why and how is it important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Does reimbursement play a role in (deciding to develop) developing a CDx assay? Why and how is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - Does -name developer- perceives difficulties for granting reimbursement for CDx?

- Are resources, such as human, physical and capital resources, important for developing a CDx assay? Why and how is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - Are certain resources more important for developing a CDx assay than others? Why?

- A CDx essay is developed for or together with a specific corresponding medicinal product. In what way does the development of the medicinal product play a role in the development of the CDx essay.
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
  - What is important in this co-development process?
  - Are there any difficulties in this co-development process? If yes, what are the difficulties and why is this difficult?

- Are there other determinants for -name developer- when developing a CDx assay?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
  - Why is that factor important when developing a CDx assay?
  - How does the factor affect the development of a CDx assay?

Interventions

- In light of the new regulations, do you think new interventions or policy is needed to maintain of increase the development of CDx? If the answer is yes or no: why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

  If yes:

- On industry level, what kind of interventions are needed to stimulate the development of CDx? Why?
  - How do you think is the development of CDx affected by these interventions?
  - Who should introduce these interventions?
    [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- On firm level, How can the development of CDx within -name developer- be stimulated?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
  - How do you think is the development of CDx affected by these interventions?
  - Who should introduce these interventions?

Ending

- Thank the respondent for its cooperation and time.
- Ask for potential other persons who might be interested.

Appendix VII: Interview template non-commercial/health institution CDx manufacturer.

Please note: The interviews can be held in Dutch, as respondents can be native Dutch speakers.

Introduction

- The researcher introduces herself and indicates the research topic: The influence of regulation on innovation activities concerning CDx and actors and their relation hat determinants are important to the development of CDx.
- Field of study: Innovation Sciences at Utrecht University.
- Indicate that the interview will be recorded for analyzing the transcripts. Ask for permission for the recording of the interview, ensuring that the full transcripts and data will not be made available to any other than the researcher and will be anonymized.
- Ask if the interviewee has any questions beforehand.

Personal Questions

- Who are you?
- What is your function in -name manufacturer-?

Content Related Questions

- Are you familiar with the definition of Companion Diagnostics (CDx)?
  [indicate whether or not this complies with definition used in this research and explain what definition is used in this research]

- What is your stance on the development of CDx? Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - What is the stance of the healthcare professionals within -name manufacturer/hospital- on CDx? Why?

- Is it very common to use a CDx in -name health institution- to prescribe a specific treatment?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What are the reason(s) that -name health institution- develops its own IVDs and/or CDx?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Why is it for -name health institution- interesting to be involved in the development of CDx?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - Are the CDx developed used by your specific hospital only, or is it the intention to put them on the market?

- Is -name health institution- involved in partnerships with other organizations to develop CDx?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Are there any preferences for -name health institution- when choosing a partner? If yes/no, why is this important?

- What is the role of -name health institution- in the development process of CDx?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

Questions related to the new regulatory demands.

- Do you advocate the introduction of the new regulations? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
  - Do you think the quality of the IVDs will be improved? If yes or no, why?
    [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What do you think are the implications of these new regulatory demands on the development of CDx in -name health institution-?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Are you aware that the new regulations demand the use of commercial developed devices (if possible) over in-house developed diagnostics?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
  - Do you advocate this new demand? If yes/no, why?
  - What do you think are the consequences for health institutions of this new demand?
  - Are there any consequences for the healthcare system as a whole?

- Is it for -name health institution- possible to comply with the new regulations?
  - Will -name manufacturer- change to other product areas?

  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Although new regulations are introduced, is it still interesting for -name health institution- to develop CDx? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Commercial developers also face regulatory changes. What do you think are the implications of these requirements on CDx development of commercial manufacturers. [In case respondents is not aware of the new regulations for commercial developed assays, explain the need to demonstrate scientific validity, analytical and clinical performance by conducting clinical trials and the set-up of a post-market surveillance programme and quality management system]
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Do you think commercial organizations now developing CDx will change their strategy? If yes, why and what do you think is the new strategy?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Overall and looking at the industry as a whole, do you think that the new regulations impede or stimulate the development of CDx? Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Do you think the market composition will change as a result of these new regulations?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

Determinants affecting the development of CDx.

- Apart from regulations, what is/are important determinant(s) for you/-name health institution- when developing a CDx? Why is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - How does/do this/these determinant(s) influence the development of CDx

- Is the intellectual landscape (patents) an important determinant for developing a CDx? Why and how is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Is the market size or amount of patient important in deciding to develop a CDx assay? Why and how is it important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Is the existence of other (competing) technologies important in deciding to develop a CDx assay? Why and how is it important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Does reimbursement play a role in (deciding to develop) developing a CDx assay? Why and how is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - Does -name developer- perceives difficulties for granting reimbursement for CDx?

- Are resources, such as human, physical and capital resources, important for developing a CDx assay? Why and how is this important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - Are certain resources more important for developing a CDx assay than others? Why?

- A CDx essay is developed for or together with a specific corresponding medicinal product. In what way does the development of the medicinal product play a role in the development of the CDx essay.
    - What is important in this co-development process?
    - Are there any difficulties in this co-development process? If yes, what are the difficulties and why is this difficult?

  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Are there other determinants for -name developer- when developing a CDx assay?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - Why is that factor important when developing a CDx assay?
    - How does the factor affect the development of a CDx assay?

Interventions

- In light of the new regulations, do you think new interventions or policy is needed to maintain of increase the development of CDx? If the answer is yes or no: why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

  If yes:

- On industry level, what kind of interventions are needed to stimulate the development of CDx? Why?
    - How do you think is the development of CDx affected by these interventions?
    - Who should introduce these interventions?
      [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- On firm level, How can the development of CDx within -name developer- be stimulated?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - How do you think is the development of CDx affected by these interventions?
    - Who should introduce these interventions?

Ending

- Thank the respondent for its cooperation and time.
- Ask for potential other persons who might be interested.

Appendix VIII: Interview template regulatory experts.

Please note: The interviews can be held in Dutch, as respondents can be native Dutch speakers.

Introduction

- The researcher introduces herself and indicates the research topic: The influence of regulation on innovation activities concerning CDx and actors and their relation hat determinants are important to the development of CDx.
- Field of study: Innovation Sciences at Utrecht University.
- Indicate that the interview will be recorded for analyzing the transcripts. Ask for permission for the recording of the interview, ensuring that the full transcripts and data will not be made available to any other than the researcher and will be anonymized.
- Ask if the interviewee has any questions beforehand.

Personal Questions

- Who are you?
- What is your function in relation to the new IVDR?

Content Related Questions

- Are you familiar with the definition of Companion Diagnostics (CDx)?
  [indicate whether or not this complies with definition used in this research and explain what definition is used in this research]

Questions related to the new regulatory demands.

- Do you advocate the introduction of the new regulations? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - Do you think the quality of the IVDs will be improved? If yes or no, why?
      [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What are the main regulatory changes for commercial manufacturers to comply with. In other words what should commercial manufacturers need to establish or deliver to get market approval under the IVDR?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary] [validation question]

- Do you think it is possible for manufacturers to comply with the new regulations? If yes or no, why?
    - Do you think manufacturers will change to other product areas or pursue other strategies? If yes or no, why?
    - Do you think the market composition will change as a result of these new regulations?

  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Although new regulations are introduced, do you think that it is still interesting for commercial manufactures to develop CDx? If yes or no, why?

[ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- IVDs and CDx already on the market need to be re-approved under the new regulations. Do you think this will pose any problems for manufacturers, both diagnostic and pharmaceutical companies? Yes/No, Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What do you think are the consequences of demanding commercial assays over LTDs for health institutions? And for healthcare systems?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

    - Do you think commercial developers advocate this new regulatory demand? If yes/no, why?

- Notified Bodies will get a greater role in the approval of CDx, do you expect any challenges in this? What kind of challenges and why are they a challenge?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Do you expect any difficulties with the EMA being consulted in CDx approval ? If yes/no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Do you see any other challenges in relation to the implementation of the IVDR? What kind of challenges and what do they impose?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Do you think the development of CDx will be hampered by the new regulations? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

Interventions

- In light of the new regulations, do you think new interventions or policy is needed to maintain of increase the development of CDx? If the answer is yes or no: why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

If yes:

- On industry level, what kind of interventions are needed to stimulate the development of CDx? Why?
    - How do you think is the development of CDx affected by these interventions?
    - Who should introduce these interventions?

[ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- On firm level, How can the development of CDx within -name developer- be stimulated? [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
    - How do you think is the development of CDx affected by these interventions?
    - Who should introduce these interventions?

Ending

- Thank the respondent for its cooperation and time.
- Ask for potential other persons who might be interested.

Appendix IX: Interview template medicinal product approval authority.

Introduction

- The researcher introduces herself and indicates the research topic: The influence of regulation on innovation activities concerning CDx and actors and their relation that determinants are important to the development of CDx.
- Field of study: Innovation Sciences at Utrecht University.
- Indicate that the interview will be recorded for analyzing the transcripts. Ask for permission for the recording of the interview, ensuring that the full transcripts and data will not be made available to any other than the researcher and will be anonymized.
- Ask if the interviewee has any questions beforehand.

Personal Questions

- Who are you?
- What is your function in -name manufacturer-?

Content Related Questions

- Are you familiar with the definition of Companion Diagnostics (CDx)?
  [indicate whether or not this complies with definition used in this research and explain what definition is used in this research]

- What is the stance of -name authority- on the development of CDx? Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- When approving a medicinal product, does -name authority- look at what medicinal products are already on the market? Does -name authority- compare the effectiveness of the new product to the effectiveness of the products already on the market and is this information used in the approval of a new medicinal product?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What is the current role of -name authority- in the development process/regulatory approval of CDx?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Does -name authority- at this moment demand/stimulate pharmaceutical companies to define specific patient populations for their drugs to increase effectiveness for these drugs? Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What is the stance of -name authority- on the introduction of these new regulations? Do you think the new regulations are needed/not necessary or good/bad? Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Although new regulations are introduced, do you think it still interesting for diagnostic manufacturers to develop CDx? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- For the approval of CDx, clinical studies need to be conducted to prove safety, analytical performance and clinical utility. Often, in these studies (phase III) also the effectiveness of the medicinal products is assessed. Do you think that it is possible that this data can be used for both the approval of the medicinal product and the CDx? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- What is important for -name authority- when approving a medicinal product in combination with a CDx assay. What (specific) requirements does the CDx assay needs to fulfil to satisfy the -name authority- ? Why are these requirements important?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Although new regulations are introduced, do you think it still interesting for pharmaceutical manufacturers to develop CDx? If yes or no, why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- IVDs and CDx already on the market need to be re-approved under the new regulations. Do you think this will pose any problems for manufacturers, both diagnostic and pharmaceutical companies? Yes/No, Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Overall and looking at the industry as a whole, do you think that the new regulations impede or stimulate the development of CDx? Why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Do you think the market composition will change as a result of these new regulations?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

Implications for -regulatory authority-

- What do you think are the most important implications of the new regulations for -name authority-?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- When looking at the new approval process for CDx and its tight relationship with the drug, Notified Bodies need to consult medicinal approval authorities. Do you think that there any challenges for -name authority- in this new role.

[ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- Is the decision to approve a medicinal product still separated from the decision to approve the CDx?
- What happens if or the Notified Body or -name authority- does not approve the CDx or the medicinal product?

- In light of the new regulations do you think that -name authority- needs to build up expertise to assess CDx (in combination with the drug)?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]

- At this moment there is in the diagnostic industry great concern about the low amount of Notified Bodies (which also may not have the expertise needed) that is willing to assess under the new regulations. What do you think are the implications of this on the approval process of CDx?
  - Does this also pose a problem for -name authority-? If yes, how and why?

- In light of the new regulations, do you think new interventions or policy is needed to maintain or increase the development of CDx? If the answer is yes or no: why?
  [ask the respondent to elaborate on the answers given if not properly understood, ask additional questions if necessary]
  - What can -name authority- do to smoothen the process of CDx and medicinal product approval.
  - What should the manufacturers do to smoothen the process of CDx and medicinal product approval.

Ending

- Thank the respondent for its cooperation and time.
- Ask for potential other persons who might be interested.

Appendix X: Overview of interest organizations representing actors involved in CDx development.

Table 12: Overview of interest organizations present in the EU or its member states representing actors involved in CDx development.

Name Association	Representing what actor in CDx system?	Website	Amount of articles retrieved
Europe			
MedTech Europe (formed by European Diagnostic Manufacturers Association (EDMA) and European Confederation of Medical Devices Associations (EUCOMED))	Representing in-vitro diagnostic companies.	http://www.medtecheurope.org	24
EuropaBio – European Association for Bioindustries	Representing biotechnology pharmaceutical companies	http://www.europabio.org/	0
European Biopharmaceutical Enterprises (EBE)	Representing biotechnology pharmaceutical companies	https://www.ebe-biopharma.eu/	5
European Federation of Pharmaceutical Industries and Associations	Representing pharmaceutical companies	https://www.efpia.eu/	2
Health First Europe	Representing patients, healthcare professionals, healthcare experts and in-vitro diagnostic companies	http://www.healthfirsteurope.org	2
The European Association for Medical Devices of Notified Bodies (Team NB)	Representing Notified Bodies	http://www.team-nb.org	2
Austria			
Austromed	Representing in-vitro diagnostic companies	http://www.austromed.org/	0
Fachverband der Chemischen Industrie Österreichs (FCIO)	Representing pharmaceutical companies	http://www.fcio.at/	0
Belgium			

Bio.be	Representing (bio)pharmaceutical companies	http://www.essenscia.be/en/bio.be	0
Pharma.be	Representing pharmaceutical companies	https://pharma.be/nl/	0
beMedTech (was UNAMEC)	Representing in-vitro diagnostic companies	https://www.bemedtech.be/?lang=nl	0
Croatia			
Cromed	Representing in-vitro diagnostic companies	http://cromed.hr/	0
Inovativna farmaceutska inicijativna	Representing pharmaceutical companies	http://ifi.hr/	0
Cyprus			
Cyprus Association of Research and Development Pharmaceutical Companies	Representing pharmaceutical companies	http://kefea.org.cy/	0
SAIEEK	Representing in-vitro diagnostic companies	http://www.saieek.com/index.php/en/	0
Czech Republic			
CZedma	Representing in-vitro diagnostic companies	http://www.czedma.cz/index.php	0
Denmark			
DANSK BIOTEK	Representing biotechnology pharmaceutical companies	https://danskbiotek.dk/	0
DiaLab (was Danish Diagnostic & Laboratory Association (DADIF))	Representing in-vitro diagnostic companies	https://www.dialab.dk/en/	0
Medico Industrien	Representing in-vitro diagnostic companies	https://www.medicoindustrien.dk/	0
Finland			
Pharma Industry Finland	Representing pharmaceutical companies	http://www.pif.fi/en	0
Sailab - MedTech Finland	Representing in-vitro diagnostic companies	https://www.sailab.fi/	0

France			
Comité Interprofessionnel des Fournisseurs du Laboratorie (CIFL)	Representing in-vitro diagnostic companies and laboratories	https://cifl.com/	0
France Biotech	Representing biopharmaceutical companies	http://www.france-biotech.fr/	0
Les Enterprises du Médicament	Representing pharmaceutical companies	https://www.leem.org/	0
SIDIV	Representing in-vitro diagnostic companies	https://www.sidiv.fr/	0
Germany			
Bio Deutschland	Representing biopharmaceutical companies	https://www.biodeutschland.org/en/home.html	0
VDGH Verband der Diagnostica-Industrie eV	Representing in-vitro diagnostic companies	https://www.vdgh.de/	1
Verband Forschender Arzneimittelhersteller	Representing pharmaceutical companies	https://www.vfa.de/	0
Greece			
Hellenic Association of Pharmaceutical Companies	Representing pharmaceutical companies	https://www.sfee.gr/	0
SEIV	Representing in-vitro diagnostic companies	http://www.seiv.gr/	0
Hungary			
Association of Innovative Pharmaceutical Manufacturers	Representing pharmaceutical companies	http://aipm.hu/en	0
HIVDA	Representing in-vitro diagnostic companies	https://hivda.hu/english/	0
Ireland			
Biopharmachem Ireland	Representing bio-pharmaceutical companies	https://www.biopharmachemireland.ie/sectors/bpci/bpci.nsf/vpages/home?opendocument	0

Irish Pharmaceutical Healthcare Association (IPHA)	Representing pharmaceutical companies	https://www.ipha.ie/	0
Irish MedTech Association	Representing in-vitro diagnostic companies	https://www.irishmedtechassoc.ie/Sectors/IMDA/IMDA.nsf/vPages/Home?OpenDocument	1
Italy			
Assobiomedica	Representing in-vitro diagnostic companies	https://www.assobiomedica.it/it/index.html	0
Associazione delle impresse del farmaco	Representing pharmaceutical companies	https://www.farmindustria.it/	0
Norway			
LabNorge	Representing in-vitro diagnostic companies	http://labnorge.no/	0
Legemiddelindustriforeningen	Representing pharmaceutical companies	https://www.lmi.no/	0
Poland			
Employers Union of Innovative Pharmaceutical Companies	Representing pharmaceutical companies	http://en.infarma.pl/	0
MedTech Polska	Representing in-vitro diagnostic companies	https://ipddl.pl/	0
Portugal			
Apifarma	Representing pharmaceutical and in-vitro diagnostic companies	https://www.apifarma.pt/Paginas/Home.aspx	0
Romania			
AFPM (ASOCIAŢIA FURNIZORILOR DE PRODUSE MEDICALE)	Representing in-vitro diagnostic companies	http://www.afpm.ro/	0
Slovenia			
Forum of International Research and Development Pharmaceutical Industries	Representing pharmaceutical companies	https://www.farmaforum.si/en	0
SIEDMA	Representing in-vitro diagnostic companies	https://www.siedma.si/	0
Slovakia			

SEDMA	Representing in-vitro diagnostic companies	https://www.sedma-ivd.sk/	0
Slovak Association of Innovative Pharmaceutical Industry	Representing pharmaceutical companies	http://www.aifp.sk/sk/	0
Spain			
Farmaindustria	Representing pharmaceutical companies	http://www.farmaindustria.es/web/	0
Federacion Española de Empresas de Technologia Sanitarial (FENIN)	Representing in-vitro diagnostic companies	http://www.fenin.es/	0
Sweden			
Swedish LabTech	Representing in-vitro diagnostic companies	http://swedishlabtech.se/	0
The Swedish Association of the Pharmaceutical Industry	Representing pharmaceutical companies	https://www.lif.se/	0
Switzerland			
Interpharma	Representing pharmaceutical companies	https://www.interpharma.ch/	0
SVDI/ASID	Representing in-vitro diagnostic companies	https://www.svdi.ch/	0
Swiss Biotech Association	Representing biopharmaceutical companies	https://www.scienceindustries.ch/	0
The Netherlands			
Diagnostica Associatie Nederland (DIAGNED)	Representing in-vitro diagnostic companies	https://www.diagned.nl/	2
Vereniging Innovatieve Geneesmiddelen (VIG) (Innovative medicines association)	Representing pharmaceutical companies	https://www.verenigginnovatievegeneesmiddelen.nl/homepage	1
United Kingdom			
Association for Clinical Biochemistry	Representing medical laboratories	http://www.acb.org.uk/	0
BioIndustry Association (BIA)	Representing pharmaceutical and biotechnology companies	https://www.bioindustry.org/	0

British In Vitro Diagnostics Association (BIVDA)	Representing in-vitro diagnostic companies	https://www.bivda.org.uk/	1
British Medical Association (BMA)	Representing healthcare professionals	https://www.bma.org.uk/	0
The association of the British Pharmaceutical Industry	Representing pharmaceutical companies	http://www.abpi.org.uk/	1

Appendix XI: Roles actors present in CDx innovation system.

In the CDx system there are actors present operating on a European level i.e. within the boundaries of the European Union (table 13) (actors within the blue dashes, figure 11) and actors operating on a National level i.e. within the boundaries of a nation or country (table 14) (actors within the green dashes, figure 11).

Table 13: Overview of role(s) actors operating at an European level.

Actor	Main role(s) in the CDx system
European Parliament	Ability to amend, reject or accept new legislation proposed by the European Commission that affects the development, production, market authorization and use of CDx.
European Commission	Ability to propose new legislation that affects the development, production, market authorization and use of CDx.
European Patent Office (EPO)	Examination of patent applications and the grant of European patents.
European Medicines Agency (EMA)	Conducting the approval process, including market authorization decision making, of drugs and biological products in the European Union.
Manufacturers of medicinal products	Conducting research, developing and producing medicinal products.
Manufacturers of CDx assays	Conducting research, developing and producing CDx assays.
Notified bodies	Conducting the approval process, including market authorization decision making, of CDx in the European Union according to the directive 98/79/EC.

Table 14: Overview of role(s) actors operating at an National level.

Actor	Main task(s) in the CDx system
Ministries (of Health)	Local ministries are held accountable and responsible for good health and healthcare. To do so, ministries develop policies and measurements to promote the health of its citizens.
Advisory bodies	Institutes or public organizations that conduct research with the aim to provide information and policy support to local governments.
Inspection & supervision bodies	Institutes or public organizations that aim to ensure public health by evaluating therapies, drugs, medical tests and supervise the quality and accessibility of health services and medical products.
National patent offices	Examination of patent applications and the grant of national patents.
Knowledge institutes & service organizations	Institutes, organizations or universities that conduct research to develop knowledge which can be used in the development of healthcare products or provide other services.
Patients and patient organizations	Patients are the actual customers or users of healthcare products. Patient organizations represent the interests of patients and provide support by giving information and helping them in healthcare decision making.
Healthcare providers and professionals	Organizations or individuals that offer healthcare services to patients.
Healthcare reimbursement companies	A healthcare insurance company funds the medical and healthcare related expenses of patients that have a contract, in which the care that is funded is described, with this company.