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Institutionalisation of markets: The case of personalised cancer medicine in the Netherlands

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ABSTRACT

The article aims to understand the institutionalisation process of markets for innovative products. To pursue this study of market formation, we analysed the introduction of innovative personalised medicines products: Herceptin® (trastuzumab) for breast cancer and Tarceva® (erlotinib) for lung cancer, which were introduced successively in the Netherlands between 2000 and 2012. We apply the technological innovation system (TIS) approach to understand the development, implementation and diffusion of new markets, including new roles for users and producers, new forms of regulation and novel user practices regarding innovative health technologies. We show that market access became institutionalised as part of the technological innovation system of the first-mover personalised medicine, i.e. the market was formed, paving the way for the later personalised medicine products.

1. Introduction

Sociotechnical transitions are necessary to sustain economic welfare and societal well-being, as well as to tackle grand societal challenges like demographic changes and increasing pressures on public welfare services (EC, 2013; OECD, 2010). Healthcare is one of the areas of society facing challenges associated with high levels of complexity, high stakes and heterogeneity of involved stakeholders. In particular, the pharmaceutical system is in the middle of a transition. For decades, pharmaceutical companies have been successful in developing new drugs, promoting patients' health and increasing shareholder value. The current system of drug development, however, has reached its limits: it is more costly and difficult to develop products that are at least as good, in terms of safety and efficacy, as what is already on the market (Scannell et al., 2012). This leads to the introduction of less-needed products and higher drug prices (e.g., Drummond and Towse, 2014; Kaitin, 2010; Pammolli et al., 2011). At the same time, there is an accelerating demand for healthcare products and technologies, due to ageing populations and increase in chronic diseases in the Western world. To ensure high quality healthcare in the future, there is a need for innovative solutions and even new business models in the pharmaceutical industry (Downs and Velamuri, 2016; Munos, 2009). Stakeholders in healthcare need to rethink how healthcare is organised, regulated and delivered. This makes studying the transition towards a more sustainable healthcare system, in which healthcare is affordable and accessible for everyone in need, highly relevant (Moors et al., 2014).

One technological driver of transitions in the pharmaceutical sector is personalised (or precision) medicine, i.e. tailoring diagnosis and therapy to individual patients based on their predicted response to therapy or risk of disease (Collins and Varmus, 2015). It is expected that tailoring leads to improved treatment efficacy and safety. Despite these high expectations, the developments in personalised medicine has been slower than expected (Joyner and Paneth, 2015; Kukk et al., 2016).

Part of the explanation for the slow advancement lies in the unforeseen scientific and technological challenges related to personalised medicine. The institutional context of the pharmaceutical sector and the market activities of companies, regulators, hospitals, patient organisations in the sector also seem to play a key role (Morlacchi and Nelson, 2011; Nelson et al., 2011). Such a socio-technical-institutional perspective on innovation and transition is well covered by the innovation system framework. An innovation system consists of actors that contribute to the innovation process in various ways, e.g., through knowledge development, supply of financial resources, standardisation and the application of innovation. The actors are constrained and enabled in their actions by the structure of the innovation system that consists of network characteristics, technological artefacts and institutions (Hekkert and Negro, 2009). Since we focus on the emergence of personalised medicine as a specific technological field, we use the concept of technological innovation system (TIS) (Carlsson and

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Stankiewicz, 1991). A TIS framework covers actors, networks and institutions that contribute to the generation, development, diffusion and use of new technologies (Edquist, 1997).

Until now, TIS studies have focused more on the knowledge generation of technologies than on the diffusion, development and implementation of new user practices (Dewald and Truffer, 2012; 2011; Grabher et al., 2008). The institutionalisation of markets and regulations for the use of personalised health technologies has not been explored in depth (Kukk et al., 2016). Earlier work has already focused on healthcare transitions, in which the institutional character of radical innovations in healthcare systems and the importance of institutions in market formation were put on the agenda (Kukk et al., 2015). But more detailed insights on how market formation exactly takes place are still missing in the TIS literature. Taking this into account, our aim is to further unpack the market formation component of TIS, and to gain more insight in the institutionalisation process of market formation over time.

In terms of market formation, TIS literature originally focused on characterising the potential target groups and measures needed to create niches in which new technologies can mature, protected from institutional pressures (Hekkert et al., 2007; Hekkert and Negro, 2009). Local markets have also been perceived as being important testing grounds for new technologies (Bergek et al., 2008), or as a way to stimulate certain industry activities by creating 'lead markets' (Edler and Georghiou, 2007). The aim of this paper is to further specify these market formation processes and as such, it builds on recent work in three ways. First, we build on recent advances in the TIS framework and specifically address the current emphasis on the interaction of a TIS and geographical contexts (Bergek et al., 2015; Coenen and Truffer, 2012). Several aspects of the emergence of a TIS have a transnational character, such as knowledge production and entrepreneurial activities. These global activities need to be implemented in national, pre-existing structures and institutions. In terms of market formation, this 'embedding' in local contexts is often depicted as pushing or transferring technologies to new markets (e.g. Moulaert and Sekia, 2010), or being dependent on simple market-pull policies such as public subsidies (Dewald and Truffer, 2011). We elaborate on work by Dewald and Truffer (2012) who emphasise the influence of local contexts by taking a micro-perspective on market formation. This paper adds to their conceptualisation and empirical studies of market formation by unpacking market formation processes while following new, emerging technologies over time. Second, we do not perceive the introduced technology as a standalone product. Often, and especially in the medical sector, validation of the value of a pharmaceutical product is just as important as the compound itself. The data package that validates the use of the product should be regarded as part of the innovation (Steinberg et al., 2015). This is even more prominent in the context of personalised medicine, which concerns more tailor-made and localised data production. Without these data, the product is worthless to potential users: regulation prescribes the necessity of these data for personalised medicine, and medical doctors require personalised medicine products that are proven safe and efficacious. Often users like medical specialists play an active role in the production of these data (DeMonaco et al., 2006; Smits and Boon, 2008). As such, market formation becomes intertwined with activities like knowledge production and gaining legitimacy on a local level. These localised TIS activities that support market formation in the context of emerging technologies have not been studied so far. Third, until now the TIS framework has been mostly applied and developed in the sustainability and energy sectors (e.g. Binz et al., 2014; Hekkert et al., 2007; Negro et al., 2008; Suurs and Hekkert, 2009; Truffer et al., 2012). We contribute to the TIS literature by using the TIS approach to clarify the emergence of technologies and market formation in the healthcare sector. Particularly in the highly regulated healthcare field, institutions play a crucial role. Institutional boundaries and institutional change processes around innovative medical technologies, such as personalised medicines, might play a bigger role in the effective functioning of a TIS than they do in other sectors, such as energy or transport technologies. Market formation is also a salient issue with regard to personalised medicine as this field is a transnational endeavour, where science and big pharmaceutical companies operate on a global scale. Markets for personalised medicines, on the contrary, are organised on a national or local level. This emphasises the significance of better understanding market formation in the national uptake of personalised medicine.

In line with this, the following research question is answered: How does the market formation of personalised medicine innovation systems occur over time?

In order to better understand market formation of personalised medicine innovation systems, we follow two personalised cancer medicines that entered the Dutch healthcare market between 2000 and 2012. Our goal is to understand how market formation of Herceptin® – one of the first medicinal products that was characterised as personalised, produced by Roche and used in breast cancer treatment – has occurred and paved the way for a follow-up personalised medicine product Tarceva® – also produced by Roche and used in lung cancer treatment in the Netherlands.

The outline of the paper is as follows: Section 2 focuses on the development of personalised cancer medicines. It discusses the theoretical background of technological innovation systems (TIS). And it details the process of market formation of personalised cancer medicines. Section 3 presents the methodology. Section 4 applies the TIS approach to the personalised medicine field in order to understand the specific dynamics of health-related market formation in technological innovation systems. It presents the results of the two cases (Herceptin® and follow-up product Tarceva®). Finally, Section 5 discusses the results and gives concluding remarks.

2. Theoretical background

2.1. Personalised medicine

Personalised medicine represents an emerging innovative technology field in biomedical innovations that is based on major advances in genomics, proteomics and metabolomics (Meadows et al., 2015). Personalised medicine is especially promising in the field of oncology. Multiple genetic mutations are present within tumours which cause uncontrollable cell growth (Bates, 2010). Every tumour has a different combination of mutations, which make each of them unique. Increased understanding of how these mutations' combinations contribute to the origin and development of cancer leads to knowledge about targets for new personalised cancer medicines (Greshock et al., 2010). Because patients vary in their genetic make-up and thus in their expression of molecular pathways, targeted therapies only work for a subset of the population. Potentially, personalised medicine enables more effective treatment options with fewer adverse effects and has the potential to reduce the cost of cancer care (Schilsky, 2010).

2.2. Technological Innovation System

Earlier studies in the field of energy transitions (Negro et al., 2007; Suurs and Hekkert, 2009) have shown that the success of a new technology is not only determined by technological characteristics, but also by the surrounding social system that develops, diffuses, implements or rejects new technologies (Jacobsson and Bergek, 2004). Hekkert et al. (2007) label this sociotechnical system as a Technological Innovation System (TIS). The basic assumption is that a well-functioning TIS is required for the dexterous development, diffusion and implementation of the technology in question (Hekkert et al., 2007).

Accordingly, the TIS approach pursues studying the development of the innovation system that supports an emerging technology (Negro et al., 2008). The approach takes into account a wide variety of actors, institutions and networks that contribute to the diffusion and

Table 1
Description of the system functions of the innovation system.
Adapted from Kukk et al., 2015; Wieczorek et al., 2013).

System functions	Description
Entrepreneurial activities (F1)	Entrepreneurs are essential for a well-functioning innovation system. Their role is to turn the potential of new knowledge, networks, and markets into concrete actions to generate – and take advantage of – new business opportunities.
Knowledge development (F2)	Mechanisms of learning are at the heart of any innovation process, where knowledge is a fundamental resource. Some indicators are R&D projects, patents and investments in R&D.
Knowledge diffusion (F3)	Relevant knowledge needs to be exchanged between actors in the system, such as via workshops, meetings and conferences.
Guidance of the search (F4)	Guidance of the search processes lead to a clear development goal for the new technology based on technological expectations, articulated user demand and societal discourse.
Market formation (F5)	This process refers to the creation of markets for the new technology: niche markets, tax regimes and new standards to create a competitive advantage for novel technologies.
Resource mobilisation (F6)	Financial and human resources are necessary to make knowledge production possible for a specific technology. Without these resources, all processes are hampered.
Creation of legitimacy (F7)	Interest groups and their lobby activities can create legitimacy for a new technology, by agenda setting, lobbying for resources and favorable tax regimes, with investments, etc.

implementation of this emerging technology, by fulfilling several key processes, called system functions (Table 1).

These system functions are necessary to build-up the innovation system's structure, consisting of institutional settings, technological artefacts and networks. When this structure is in place, diffusion and implementation of innovation becomes easier. Important features of systems are the strong complementarities that commonly exist between the components and system functions within a system. The system functions are not independent of each other and can either reinforce or weaken each other, and therefore either block or slow down the performance of the entire system (Hekkert et al., 2007; Jacobsson and Bergek, 2011).

Various scholars, however, have criticised that the TIS approach only focuses on structures and system functions on the meso-level, without giving deeper insight in micro-level processes (e.g. Farla et al., 2012; Markard and Truffer, 2008). In this paper, we aim to take a micro-perspective on the market formation system function. We emphasise the influence of local contexts on the development of markets for personalised medicine.

2.3. Market formation of personalised cancer medicines

The transition to a healthcare system that is (partially) based on personalised medicine emphasises several aspects that are particular to the pharmaceutical sector. This directly affects market formation by limiting the consumer's or patient's choice (Grit and Dolfsma, 2002). The first particularity is that drug development is strongly science-based, integrating a variety of cognitive disciplines (Pisano, 2006) and characterised by profound and persistent uncertainty and complexity. This leads to extensive product development timelines (Hill and Rang, 2013) and an R&D process characterised by high failure rates. In turn, this results in increasing development costs (DiMasi et al., 2015, 2010). Second, the pharmaceutical sector is highly regulated. Pharmaceutical products need a license to enter the market with the aim to safeguard public health in the form of safety, efficacy and product quality. For innovative personalised medicine, these licenses are often obtained on a European level. Third, innovations in diagnostic tools are also important, especially for personalised medicine. Molecular diagnostics enable the detection of diseases before symptoms appear (Schulman et al., 2009). Innovation dynamics in the diagnostics sector differ from those in the pharmaceutical sector: drugs are subject to strict approval procedures and regulation, while diagnostics regulation requires a CE Marking.[1] This results in shorter timelines and less resources needed for diagnostics (Ito and Demers, 2004; Regenold, 2011). Fourth, once a product has obtained a license to enter the market, the usage and reimbursement of these products is regulated, often on a national level. Reimbursement agencies compile evidence about the safety, effectiveness and cost-effectiveness of these products and determine whether they are valuable enough to become standard care (and as such covered by basic insurance packages). Medical specialists decide in the context of their professional associations what the position of the novel drugs will be in their diagnostic and therapeutic guidelines. Local patient groups negotiate with national governments and regional hospitals for access to healthcare budgets for reimbursement of cancer medicines. After all, differences in local resources and different application policies at individual hospitals cause inconsistencies in access and delivery of innovative drugs and corresponding diagnostics. This illustrates that market formation has a strong national character in medical innovation practices, due to national regulations and local reimbursement schemes. These four particularities contribute to a sector-specific way of market formation that will also apply to (and in turn be influenced by) the advent of personalised medicine.

In this vein, this study focuses on unpacking the market formation part of the technological innovation system of personalised medicine. Such a market-side perspective emphasises specific conditions, such as the availability of locally specific institutional structures (e.g. reimbursement) or legitimacy of the new personalised medicine products by patient groups and healthcare users, which requires deliberation about, for example, new guidelines, data protection and privacy, patient surveillance, treatment compliance and user acceptance of the new personalised medicine (e.g., Gonzalez-Angulo et al., 2010; Swan et al., 2007; Weldon et al., 2012). Following this, and reflecting on the contributions introduced in the first section, we emphasise three theoretical aspects.

First, Fligstein (1996) states that markets are constructed through interplay between key actors, e.g., suppliers, consumers and regulators. Market formation thus means contestation and construction involving building powerful coalitions that are able to dictate rules and develop control. Building on Fligstein's sociological and constructivist notion of market formation, and emphasising local forms of market formation, Dewald and Truffer (2012) differentiate market formation into three sub-processes: (1) the formation of market segments, that is the formation and differentiation of market related actors, networks and institutions, (2) market transactions, that is communicating and competing to establish an exchange relationship between suppliers and customers and (3) end-user profiles, that is the constructive part on the side of the users, including determining consumer images, use patterns and preference structures. We use Dewald and Truffer's conceptualisation because it defines market formation as build up from three sub-processes, which start from the position that although technological emergence is a global dynamic, contextualisation is needed on a local level.

[1] CE = *Conformité Européenne*, a mandatory conformity marking, signifying that products sold in the European Economic Area (EEA) have been assessed to meet high safety, health, and environmental protection requirements (EC, 2016).

Second, in the formation of markets, the active role of users should be taken into account. We build on the work of Fligstein (1996), who noted that the perspective of producers shaping markets dominates, however other actors such as consumers should not be neglected. Earlier work showed that users, such as patients, pharmacists, physicians, insurers and governmental bodies indeed play an important role in pharmaceutical innovations (e.g. Smits and Boon, 2008). Under influence of regulations as well as professional codes, users like medical specialists aim to co-produce guidelines and use practices. For this they are in a need of knowledge production on effectiveness in real-life and local settings in order for the guidelines and eventual professional codes to be legitimised. The co-production is thus not limited to market formation but critically extends to other system functions like knowledge production and gaining legitimacy. This leaves questions about how these functions are fulfilled and in what order, what the roles and responsibilities are of users and other actors, and how these local activities relate to global activities in the context of personalised medicine.

Third, the local activities that include market formation, but extend to other functions, should be regarded as part of a learning process (Neij et al., 2017). Activities are performed, repeated and adjusted, and routines are developed. We are interested in what extent the introduction of a personalised medicine (as a first-mover) product influences the way in which a subsequent (second-mover) product is implemented.

3. Methodology

3.1. Case selection

We focus on market formation in one particular national healthcare innovation system, the Netherlands. The Netherlands is one of the smaller countries in Europe, with a total healthcare expenditure of more than €80 billion in 2011 (Frost and Sullivan, 2011). The Netherlands has an excellent research and healthcare performance and infrastructure and a very well developed biomedical research sector (CWTS, 2010).

The local specificity is demarcated by national borders because decisive elements of the pharmaceutical market, such as reimbursement, are organised on a national level, rather than by technology boundaries as done in previous studies (e.g., Negro et al., 2008). Additionally, hospital policies with regard to expensive medicines and reimbursement are very often being locally determined (Boon et al., 2014).

The focus on oncology is supported by the fact that cancer is the number one cause of death in the Netherlands (CBS, 2014) and results of cancer treatments have so far been modest (Haber et al., 2011). Furthermore, developments in genetics and genomics have led to more efficient and personalised treatment approaches, which until now were mostly used in the field of oncology (Andre et al., 2013). The focus lies in particular on breast cancer[2] and lung cancer,[3] as these diseases are among the first for which personalised medicine products were developed (Herceptin® and Tarceva® respectively, both produced by Roche). Herceptin® as an early stage breast cancer drug is an illustrative first case of purposive change processes in personalised cancer medicine developments. The case is a relatively well-documented example where various reimbursement struggles took place in the Netherlands. Therefore, interesting market formation dynamics regarding the activities in the TIS are expected. We also wanted to study whether the same strategies were apparent for market introduction of subsequent personalised drugs in the Netherlands, i.e. Tarceva® as a first line personalised lung cancer drug. We focus our analysis on the time period 2000–2012, when the major TIS development took place for both personalised cancer medicines. This eventually led to successful market uptake in the Netherlands for Herceptin® in 2005 and for Tarceva® in 2012. These two personalised medicines thus illustrate successive cases, which allow us to inductively explore (Eisenhardt, 1989) how the market formation processes around Herceptin® actually paved the way for Tarceva® later on.

3.2. Data collection

The data was collected making use of different sources, such as scientific literature, professional journals, 'grey' literature (industry reports, policy papers and books) and various websites –among others – online databases,[4] government bodies (EMA, CVZ, VWS), professional journals, professional groups (Diagned, NVMO) and patient organisations (NFK, BVN).[5] Search terms comprised the following words either on their own, or in combination: 'Herceptin' or 'Tarceva' or 'erlotinib' or 'trastuzumab' or 'personalised medicine' or 'breast cancer' or 'non-small-cell lung carcinoma (NSCLC)' or 'the Netherlands' or 'Dutch'.

In addition, we conducted 11 semi-structured interviews with experts from different stakeholder groups, such as industry, academia and research, the non-profit sector and intermediary organisations, drug regulators and policy makers (Table 2). A semi-structured research approach was used, because this allows covering a broad spectrum of relevant topics and at the same time highlighting a particular topic based on the responses of the interviewee (Lindlof and Taylor, 2002). The interviewed experts were purposefully selected: the majority of our interviewees were identified from personal contacts, scientific articles and policy papers through the criteria of being involved in, or having profound knowledge of the diffusion process of personalised medicine in the Dutch context. Interviews lasted on average from 1 to 2 h. We customised the interview guide for experts based on their area of expertise. We asked the experts a series of questions about the history of market formation of personalised medicines and the regulatory environment of the market in the Netherlands in general, and about Herceptin® and Tarceva® in particular. We asked them to identify the main stakeholders involved in the diffusion process of personalised medicines, the obstacles they had encountered and how they were overcoming these issues.

The interviews have been anonymised and are referred to as interview A, B, C, etc. to mask the identities of the experts.

3.3. Data analysis

A qualitative event history analysis was performed to systematically analyse different key processes essential for personalised medicine innovations over time, to identify mechanisms that hamper or stimulate these innovation processes, and in particular to gain insight into the dynamics of market formation processes in the Dutch healthcare context. The event history analysis method has been initially developed by Poole et al. (2000) and Van de Ven (1990) to analyse in a structured way complex data by gathering information as a sequence of different events that unfold over time. An event can be defined as "the smallest meaningful unit in which change can be detected. Hence development and change can be studied in the sequence of events an entity participates in or experiences" (Poole et al., 2000: p5). In an event history analysis, system-level events were identified that were influential to the development and diffusion of Herceptin® and Tarceva® in the

[2] In the Netherlands, breast cancer is the most frequent type of cancer in women, about 1 in every 8 women are diagnosed with breast cancer (VWS, 2015).

[3] Lung cancer is one of the most frequent types of cancers worldwide, and next to breast cancer, it has the highest rate of mortality (Peters et al., 2012). In the Netherlands, almost 11,000 new patients are diagnosed with lung cancer each year (KWF, 2011).

[4] Examples of literature sources: LexisNexis database, Web of Science, Scopus, PubMed; 'grey' literature: annual reports and press releases of Roche; websites: www.clinicaltrials.gov, www.trialregister.nl.

[5] EMA (European Medicine Agency),CVZ (Health Insurance Board), VWS (Ministry of Health Welfare and Sports), NVMO (Dutch Society for Medical Oncology), NFK (Dutch Federation for Cancer Patient Associations), BVN (Dutch Breast Cancer Association).

Table 2
List of interviewees.

ID	Type of actor
A	Medical oncologist and clinical assessor for the Dutch Medicines Evaluation Board (MEB)
B	Researcher at Centre for Personalised Cancer Treatments (CPCT)
C	Financer from the 'Rabobank Bioscience' division, advises on market trends and risks
D	Representative of Dutch diagnostic company and member of the 'Personalised Medicine' taskforce
E	Policy officer at the Dutch Federation of Cancer patient organisations (NFK)
F	Business development manager at diagnostics company
G	Medical doctor and senior medical advisor for health insurance company
H	Policy officer at Royal Dutch Pharmacists Association (KNMP)
I	Pharmacist and Research coordinator Scientific Affairs at National Institute for Public Health & Environment (RIVM)
J	Manager Science and Technology of Dutch diagnostic company
K	Clinical pharmacologist and senior clinical assessor for the Dutch Medicines Evaluation Board (MEB)

Netherlands from 2000 until 2012, and systematically allocated to specific system functions in the innovation system. We chronologically ordered the events over these twelve years into a database. Each event was allocated to one of the seven system functions, according to key functions as defined in Table 1 in the theory section, and categorised them accordingly to healthcare related indicators. Table 3 provides the operationalisation of the seven system functions of the TIS, with a specific emphasis on the market formation processes.

The collected interview data complemented and triangulated our narrative and analysis of the Herceptin® and Tarceva® TIS developments over time.

4. Results

In order to understand which factors influence the market formation of personalised cancer medicine innovations over time, this section presents the developments and diffusion of two consecutive personalised cancer medicines (Herceptin® and Tarceva®) and their corresponding companion diagnostics in the Netherlands from 2000 until 2012.Two episodes are discerned. The first episode (Section 4.1) starts with the introduction of the first personalised breast cancer medicine, Herceptin® to the Dutch market from 2000 until 2006, followed by the second episode (Section 4.2), of the personalised lung cancer medicine Tarceva® from 2006 until 2012. The episodes are described chronologically to follow how the dynamics of events changed over time sequentially and how the market formation processes evolved. Section 4.3 compares the market formation of Herceptin® and Tarceva® in these episodes.

4.1. First episode: market formation of personalised breast cancer medicine Herceptin®

4.1.1. Background

Herceptin® (brand name for trastuzumab) is the first personalised cancer medicine that entered the Dutch market, after its approval by the European Medicines Agency (EMA) in 2000 (EMA, 2011). It is a humanised monoclonal antibody, designed to target and block the function of the protein produced by the oncogene Human Epidermal Growth Factor 2 (HER2),[6] with breast cancer-causing potential when it is over-expressed (Slamon et al., 2001). The mode of action of Herceptin® activates the body's immune system and suppresses HER2, signalling that the tumour should be targeted and destroyed. It is administered on its own as monotherapy, as well as in combination with, or following, chemotherapy. Eligibility for Herceptin® treatment is determined by a diagnostic test, identifying those patients who would derive the greatest benefits (Roche, 2013).

4.1.2. Market introduction of Herceptin®

Herceptin® entered the Dutch market as a late stage breast cancer drug in 2000. Vital to the emergence of Herceptin® was the simultaneous introduction of the HercepTest® from the Danish diagnostic manufacturer DAKO on the Dutch (and European) market. DAKO was granted a license from Genentech to develop this test (Bioprocess Online, 1998; Genentech, 1998). The introduction of diagnostic tests, such as the DAKO test, served as an incentive for Dutch biotechnology companies to focus their activities on personalised medicine and diagnostics development.

At that time knowledge about personalised medicine was low and knowledge diffusion in general was not well developed in the Netherlands. One interviewee observed that "*Development of personalized medicine for cancer is slower than was expected right after the completion of the Human Genome Project in 2003*" (Iv E). Knowledge development and diffusion related to personalised medicine in general, and Herceptin® in particular, took off in the Dutch context with publications about the 'new' Her2Neu receptor in 2001. These first studies on Herceptin® focused on addressing appropriate testing methods for the HER2 receptor. In 2001, numerous Dutch cancer researchers published on this topic (Bijker et al., 2001; Pender et al., 2001; Vijver, 2001). Most of this early Dutch research was done by large established academic medical centres (i.e., UMCU, LUMC, AMC, ErasmusMC)[7] and the Netherlands Cancer Institute (NKI/Av).[8] Or, as Interviewee J, spelled out:"*Doctors from academic medical centers have knowledge about personalized medicine, but doctors in other hospitals could benefit from more conferences and meetings in the Netherlands*" (Iv J). The introduction of Herceptin® occurred in a period of rising interest in personalised medicine. There were a number of (policy) initiatives at the Dutch national level that supported further knowledge diffusion and creation of legitimacy about personalised medicine in parallel with Herceptin® market introduction in Europe in 2000. New alliances and partnerships between different cancer research organisations were formed to focus on the area of cancer and genomics. This contributed heavily to *diffusion of knowledge* about personalised medicine and *creation of legitimacy* to this new type of cancer treatment. These alliances mostly encompassed research and *resource allocation activities*. Later on, the Netherlands Genomic Initiative (NGI) was started in 2002. NGI received a budget of €195 million to set up the genomics infrastructure in the Netherlands. As part of this infrastructure, the Cancer Genomics Centre (CGC) was awarded a five-year grant of €15 million. In addition, in 2003, NGI founded the Netherlands Bioinformatics Centre and the Netherlands Proteomics Centre with €86 million coming from the BSIK 'Investment Grants for Knowledge Infrastructure'[9] (Kloet et al., 2012).

Alongside the rise of personalised medicine R&D, related genomics *entrepreneurial activities* took place and start-ups specialising in personalised cancer treatments were founded in the Netherlands. A prominent example is the diagnostic company Agendia that developed the Mammaprint® diagnostic kit in 2002, for identifying breast cancer metastasis risks and Targetprint® for determining HER2 over-expression (Agendia, 2013).

Our results indicate that between 2000 and 2002, *knowledge development* and *entrepreneurial activities* took off quite well in the Netherlands regarding personalised medicine. These factors positively

[6] The oncogene Human Epidermal Growth Factor 2 (HER2) is present in 10–30% of breast tumours, in which this gene is amplified (Slamon et al., 2001). This leads to increased numbers of receptor proteins on the surfaces of the cell, so called HER2 over-expression. The HER2 over-expression causes cells to receive increased signalling, resulting in stimulated cell growth, that is, tumour development (Bazell, 1998).

[7] UMCU (Utrecht University Medical Center), LUMC (Leiden University Medical Center), AMC (Academic Medical Center), ErasmusMC (Erasmus University Medical Center).

[8] NKI/AvL (Nederlands Kanker Instituut/Antoni van Leeuwenhoek Ziekenhuis).

[9] In Dutch: BSIK = Besluit Subsidies Investeringen Kennisinfrastructuur.

Table 3
Operationalisation.

System functions	Indicators
Entrepreneurial activities	Number of clinical trials and new entrants
Knowledge development	Scientific publications
Knowledge diffusion	Workshops, conferences, meetings, networks formation
Guidance of the search	Regulations, guidelines
Market formation	Formation of market related networks, institutions, actors; market transactions; end-user profiles, e.g. market approval, reimbursement policies, guideline development, consumer images, use patterns, preference structures.
Resources mobilisation	Financial investments, funding programmes
Creation of legitimacy	Media coverage, lobby activities

affected *market formation* because the growing number of R&D programmes and new firms assured that personalised medicines should be taken seriously and Herceptin® served as the first emblematic example. However, in that period market formation was hampered due to the fact that personalised drugs served small patient populations, leaving pharmaceutical companies with the task to recoup their R&D spending with higher prices. Hence, Herceptin® was an expensive cancer drug which caused potential problems for reimbursement.

4.1.3. Market segmentation

The Dutch government had already gained experience in dealing with expensive cancer medicines: since the introduction of the chemotherapy drug Taxol® in 1995, constant signals of under-treatment emerged. The principal actors that exerted pressure on the Dutch Ministry of Health were first and foremost patient organisations from patients who did not receive Taxol® and demanded equal access to healthcare (Boon, 2008). The ministry created a set of initiatives and policy measures to address this issue, including specific subsidies, a 'policy rule' that dictated reimbursement of drugs in hospital settings and a dedicated medical commission that had the task to assess reimbursement of these drugs. As such, reimbursement of expensive cancer medicines started to become slowly institutionalised via special policy initiatives (Boon, 2008) creating a specific market segment for these medicines in hospitals. Herceptin® was covered by such an initiative.

The Dutch Federation of cancer patient organisations NFK and the Dutch Breast Cancer Association BVN put the issue of equal availability of, and access to, Herceptin® in the Netherlands on the political agenda (Iv E). Their lobbying activities were effective, partially because they successfully collaborated with the medical specialists in these activities: "…*The lobby for Herceptin was* […] *one of our great achievements*…, *as we really have acted together with the professional groups*…" (Iv E).The patient organisations as well as the medical specialists and their representative organisations acted as intermediary groups between the knowledge production around personalised medicine and the formation of markets.

4.1.4. Market transactions: reimbursement issues with Herceptin® for early-stage usage

In 2005, new clinical evidence for Herceptin® use was reported. At the Annual Meeting of the American Society of Clinical Oncology (ASCO), Roche presented the results from their HERA-study (Piccart-Gebhart et al., 2005; Tuma, 2005). These results showed that besides late-stage breast cancer, Herceptin® was also effective on early-stage HER2 positive breast cancer patients. Based on these results, Dutch oncologists actively pursued including early-stage use of Herceptin® in their medical guideline, as such making use of Herceptin® common medical practice. However, the medical guideline route sidestepped regulatory authorisation, since Herceptin® was only registered for late stage breast cancer in 2005. As a result, Herceptin® could not be included in a reimbursement scheme for early stage cancer, creating a dilemma for oncologists in the Netherlands. As one of interviewed experts explained:

"*Current regulation for clinical trials and registration is too strict for personalised medicine for cancer*" (Iv K).

On the one hand, they wanted to adhere to the state-of-the-art healthcare for patients; on the other hand, unlicensed drugs were not automatically reimbursed. So, formation of market segments took place: Herceptin® only being reimbursed for late stage breast cancer patients, and only for patients having a specific breast cancer profile. In other words, a reimbursed Herceptin® use profile became visible.

As a result, when Herceptin® started to be used for early stage breast cancer, Dutch hospitals had to reimburse all new treatments from their hospital budget, which had not been adjusted to the rise of these expensive new cancer drugs. Hospitals with sufficient financial reserves were able to offer the new treatment to their patients, but hospitals with little or no financial reserves were not able to provide their patients the new treatment. This created differences between regional areas in access to the drug. This was called 'area code[10] healthcare' (Boon, 2008), leading to further market segmentation.

4.1.5. Unequal access to Herceptin®

The Dutch Breast Cancer Association (BVN) quickly acted to articulate the unequal access to Herceptin®. They published a report that presented the differences between regions in the Netherlands (BVN, 2005). Accordingly, the report led to fierce reactions in the media and in politics, even in the form of questions to parliament. So, by 2005, the issue of unequal access to Herceptin® had led to increased pressure on, and questions to, members of parliament, and received a great deal of media attention. In 2006, the Dutch Minister of Health decided to change the reimbursement policy, while the BVN continued its actions by presenting the Ministry of Health with 14 concrete cases of undertreated patients (Boon, 2008). Although the Ministry of Health changed the reimbursement policy in 2006 leading to directly financing expensive drugs that are used in hospitals, the reimbursement issues were not totally solved. They continued to be publicly discussed by patient advocacy and medical professional groups, e.g., the Dutch Federation of Academic Medical Centres (NFU) and the Dutch Association of Hospital Apothecaries (NVZA) (SFK, 2010).

In summary, *legitimacy* was *created* mostly through a strong combination of patients and medical specialists' initiatives. In several instances, their representative organisations acted together leading to coordinated efforts. This patient-specialist collaboration formed a strong driver in translating knowledge of personalised medicine to application and subsequently to *market formation*. This market formation was based on predefined rules and regulations, e.g., regarding reimbursement, medical practice and market access, which took care of transactions and interactions on the healthcare market. At the same time, our research shows how, in this episode, idiosyncratic institutional solutions were introduced as well.

[10] In Dutch: postcode.

4.2. Second episode: market formation of personalised lung cancer medicine Tarceva® and further development of personalised cancer medicine

4.2.1. Background

Similar to Herceptin®, Tarceva® (brand name for erlotinib) is a new type of personalised cancer medicine. It is a small molecule drug that inhibits a specific molecular target EGFR-TK[11] that causes lung cancer tumour cells growth.[12] This molecular target is over-expressed in around 15% of non-small-cell lung cancer patients' tumour cells (Rosell et al., 2012), and can only be recognised using a specific diagnostic test. In 2005, Tarceva® was approved in Europe as a second line treatment for all advanced non-small-cell lung cancer patients (Roche, 2005).

4.2.2. Market introduction of Tarceva®

In the years after the introduction of the policy rule on expensive drugs in 2006, expenditure on drugs was monitored, and various studies showed that the new policy was helpful (e.g., SFK, 2010). Tarceva® benefited from it and the reimbursement of Tarceva® differed from the reimbursement principles of Herceptin®. Already in 2006, the Health Insurance Board (CVZ) advised the Dutch Ministry of Health to include Tarceva® in the reimbursement scheme after an appraisal period of five months. Because Tarceva® is administered extramurally (outside the hospitals), and considered to have a therapeutic surplus value, the drug could be 100% reimbursed by the Exceptional Medical Expenses Act in the Netherlands.

At the same time, in 2006, the Dutch Centre for Translational Molecular Medicine (CTMM) was initiated. It focused on innovations in molecular diagnostics and molecular imaging technologies that enable determination of predisposition, early diagnosis, and personalised treatment of patients. It has been a public-private partnership with 119 partners including Philips, Organon, DSM, 30 small and medium-size enterprises and several universities. (CTMM, 2013). Especially with the projects arising from the so-called 'Top Sector Life Sciences and Health', which started in 2011, the Dutch government aimed to increase the cost effectiveness of Dutch healthcare by supporting personalised therapeutics. These included projects related to personalised cancer treatments: molecular diagnostics for developing companion diagnostics, pharmacotherapy for developing targeted drugs, and enabling technologies and infrastructure for providing an infrastructure that improves the efficiency of translational biomarker research (Regiegroep Life Sciences and Health, 2012). All these initiatives further supported the entire personalised medicine data package (therapeutic, diagnostic test, data infrastructure), and enlarged the personalised medicine basic knowledge infrastructure in the Netherlands.

According to the Web of Science research, from the market approval of Tarceva® as treatment for lung cancer in 2005 onwards, the number of Dutch publications on lung cancer and personalised medicine increased annually, indicating growth in *knowledge creation and diffusion* on Tarceva®. The number of publications about the EGFR mutation showed exponential growth after 2008 (Schellen, 2013). As the interviewed experts clarified (Iv A,B,C):

> "*An explanation for the focus on molecular mechanisms* (*e.g., EGFR functioning*) *could be that the Netherlands has been enjoying a world-leading position in genetics since the 1970s*" (Iv B).

Furthermore,

> "*The Netherlands has one of the largest collections of clinical material* (*biobanks*) *and patient databases*" (Iv C).

Accordingly,

> "*Cancer research in the Netherlands does not focus on finding new drugs, but on finding new targets for existing drugs or potential leads for new drug development*" (Iv A).

Compared to the first years after market introduction of Herceptin® in the beginning of 2000s, when there were only a few conferences on the topic of personalised medicine, *knowledge diffusion* about personalised medicine cancer drugs improved significantly over time. From 2007 onwards, for example, the conference 'Personalised Therapeutics' ('Therapie op Maat') has been organised every two years in the Netherlands (Schellen, 2013).

4.2.3. Growing legitimacy of personalised medicine

In 2010, Roche obtained a license from Genzyme Corporation in the USA and at the same time collaborated with OSI Pharmaceuticals to develop a companion diagnostic test for Tarceva®. In 2011, Roche launched its Cobas 4800 EFGR mutation test as a companion diagnostic for Tarceva® (Roche, 2011a, 2011b). Accordingly, the *entrepreneurial activities* of large players regarding personalised lung cancer therapeutics have mainly taken place at the international level.

At the same time, in 2010, the three largest cancer centres in the Netherlands combined forces in the Centre for Personalised Cancer Treatment (CPCT). The NKI/AVL, Erasmus MC Daniel den Hoed Oncologisch Medisch Centrum, and University Medical Centre Utrecht (UMCU) participated in this centre. This centre focuses on determining the genetics of individual tumours to guide treatment (CPCT, 2013; Iv D). Increased network activities were also visible between diagnostics manufacturers and the pharmaceutical industry. By 2011, the number of collaborations had also increased between the Dutch locations of Roche Pharmaceuticals and Roche Diagnostics.

> "*By combining their activities, the different areas of expertise required for the successful implementation of personalised medicine had been put together*" (Iv F).

Also, when Tarceva® entered the market it could enjoy very positive expectations about personalised medicine. This was not the case for Herceptin® in 2001 as back then the general knowledge and legitimacy of personalised cancer drugs was still low. These positive expectations were describing the promise of new cancer therapeutics. Most events focused on personalised cancer treatment in general, as opposed to the specific drugs Herceptin® or Tarceva®. This explains the hype and the very high expectations around these personalised cancer therapies in general. The main negative expectations around Herceptin® and Tarceva® were about the high cost of therapies and the related concerns that personalised drugs would make healthcare unaffordable if too many drugs would enter the market (Schellen, 2013). Not everyone shared the optimism that within a few decades, most forms of cancer would be regarded as chronic instead of life threatening diseases (AD, 2013). According to interviewed experts, making cancer a chronic disease in a few decennia would be a huge challenge, but in the coming years, a huge improvement in the survivability of some types of cancer is expected (Iv F, Iv H). Personalised cancer treatments benefited from this hype and more resources were mobilised. This had a positive effect on creation of legitimacy, as more funding became available for cancer research and private companies were encouraged to dedicate and mobilize more resources into the oncology business branch, both for drugs and diagnostics. In 2008, the Netherlands Genomics Initiative (NGI) was granted additional funds of €280 million from the Dutch government for its second phase (Kloet et al., 2012). The NGI awarded the Cancer Genomics Centre (CGC) an additional grant of €24 million for the period 2008–2012 (Kloet et al., 2012; Nanotechnology Marketing and News, 2015).

4.2.4. Market transactions and use profiling: problems with reimbursement of oncolytics

However, in 2013, oncolytics, including Tarceva®, were transferred to the hospital setting. This meant that from 2013, the same conditions

[11] EGFR-TK = Epidermal Growth Factor Receptor Tyrosine Kinase.

[12] Treatment of lung cancer is difficult because it is a heterogeneous disease characterised by many genetic mutations.

for the reimbursement of Herceptin® and Tarceva® apply. From then on, Dutch hospitals had to negotiate reimbursement of Tarceva® with insurers instead of being 100% reimbursed. As IV K quotes: "*The problem to be tackled now is how the reimbursement for genetic testing will be dealt with*" (*Iv K*). Diagnostics are not financed per individual action in the Netherlands. Under the current Dutch Diagnosis-Treatment-Combination macro financing, diagnostics are reimbursed in several ways. For example, "*The contractual agreement between genetic specialists and insurers often does not fully cover the diagnostic test*" (IV B).

Using other cash flows, such as cash flows for academic research, the remaining deficits are eliminated. This implies that the reimbursement system for companion diagnostics has not been working correctly and diagnostics could not be reimbursed on their actual costs. Accordingly, companion diagnostics are treated the same way as other kinds of diagnostics. The business models of pharmaceutical companies and diagnostic companies are misaligned, partly due to different reimbursement principles (e.g. Boon and van Merkerk, 2008; Mittra and Tait, 2012). Surprisingly, we did not observe events that would relate to the development of *market formation* regarding companion diagnostics. No specific actions took place to correct this issue, although large-scale use of companion diagnostics could prevent unnecessary and expensive cancer treatments. We observe a misalignment between the pharmaceutics and diagnostics market formation of personalised cancer medicine, such as Tarceva®.

4.3. Comparison between the cases

The main difference in market formation between Herceptin® and Tarceva® was that Herceptin® was reimbursed inside the boundaries of the hospital ('intramurally'). Hospitals were only receiving 75% reimbursement). Tarceva® was reimbursed outside the boundaries of the hospital ('extramurally'), for which separate reimbursement systems were developed. As Tarceva® was fully reimbursed by the Exceptional Medical Expenses Act, it put no additional pressure on hospital budgets. In 2005, five years after market introduction, around 50% of eligible patients received treatment with Herceptin® (BVN, 2007). The same holds for Tarceva® in 2011 (Uyl-de Groot, 2011). So, also for Tarceva®, formation of specific extramural market segments took place.

For Tarceva®, we observed much less lobby activity and legitimacy creation in the period 2006–2012. The reason for this could be that the reimbursement of Tarceva® differed from Herceptin®. Tarceva® was already 100% reimbursed, so no cost issues were involved regarding availability for patients. Another reason for the low lobbying activities of Tarceva® compared to Herceptin® is that the Dutch Breast Cancer Association (BVN) is a much larger organisation and the breast cancer lobby in general is much more prominent and powerful compared to the patient organisation Lung Cancer Netherlands (Iv E).

5. Discussion and concluding remarks

In order to better understand how the market formation of personalised medicine innovation systems occurred over time, we followed two personalised cancer medicines that entered the Dutch healthcare market between 2000 and 2012: Herceptin® as a first-mover personalised breast cancer medicine and Tarceva® as a second-mover personalised lung cancer drug.

Based on our analysis we conclude that within the technological innovation system of the first-mover Herceptin®, market access became institutionalised, tentatively preparing for the second-mover Tarceva®. Tarceva® benefited from Herceptin® as the Dutch knowledge infrastructure on genomics, biomarkers and personalised medicine in general was much better developed over time. After the introduction of Herceptin® to the Dutch market, the personalised cancer treatment system became in place, the medical community knew about testing, reimbursement was on the policy agenda and high prices for personalised medicine were not a surprise anymore. At the same time, stakeholders around lung cancer encountered problems with creation of legitimacy for access to personalised lung cancer treatment since the disease is stigmatised (smoking causes lung cancer) and because the lung cancer patient lobby is much weaker than the breast cancer lobby.

Theoretically, the two episodes of personalised cancer medicine development, as described in Section 4, support and further develop earlier work of Dewald and Truffer (2012, 2011), who theorised on market formation processes in the energy sector. These processes include the formation of market segments, market transactions, and end-user profiles that enable a better understanding of market formation within a technological innovation system. Our paper zooms in on the same sub-processes and shows how two personalised cancer drugs formed *market segments* in the healthcare field that consist of a basic network and infrastructure of medical practices. These networks are composed of actors such as medical specialists and researchers who have the resources to assess and utilise new pharmaceuticals. In a way, these resources were strengthened at that time by dedicated, large-scale knowledge impulse programs. The institutional context started from the business-as-usual rules about medicine authorisation, medical practices and reimbursement, but gradually changed to create room for personalised drugs.

Regarding *transactions* in the newly created market segments, we observe several parties being heavily involved in co-designing ways to organise the exchange of products, such as Dutch oncologists pursuing inclusion of early-stage use of Herceptin® in medical guidelines. In this case, much depends on regulation: improving medical guidelines, as produced by medical specialists, and on reimbursement rules. The creation of these rules (e.g., policy rules on expensive drugs) led to institutionalisation of markets which made it possible to create a level playing field and ensured a decrease in variation over geographical locations.

The local preferences regarding personalised medicines and the way in which they organised the implementation of these treatments in the local setting (i.e. one hospital) very much depended on the involvement of the end-users – i.e. medical specialists and patients – and how they developed their preferences when exposed to new products. The medical specialists differed in their expertise and viewpoints on personalised medicine between different Dutch regions. This might have been created through the relations they maintained with frontier science as well as the way in which they prioritised drugs like Herceptin® in their local practice. With regard to the patients, personalised medicine is associated with a highly visible and clear *user profiling*: personalised medicine products (and companion diagnostics) dictate subsets of patients, as not every patient is eligible anymore for general cancer treatments. In the end, end-user profiles became codified over time by inclusion in medical professional guidelines, in that way also creating fewer differences between distinct local practices.

Following Dewald & Truffer and others' work on the geography of transitions (e.g., Binz et al., 2014), we find differences between locations in these market formation processes, as indicated by the diversity in resources and expertise over hospitals that eventually led to stratified 'postcode lottery' reimbursement of personalised drugs in the Dutch healthcare system. Thus, geographical differences in institutional work, network building and actor resources (i.e., hospital budgets) can lead to strong spatial variation of market segment formation, which lead to stratified access to personalised cancer drugs. Finally, our findings from the healthcare sector are strongly in line with earlier studies and show that classical TIS studies with national boundaries can easily overlook the importance of subnational dynamics and that local scale resources matter.

Our main observations regarding institutionalisation of markets are:

First, we observed dynamics in forming market segments, transactions, and user profiles. At the same time, these three sub-processes were very much interlinked in our study: institutions that create market segments also influence the formation of transaction practices. Market segmentation is closely related to patient profiles regarding eligibility

to early- and late-stage cancer treatments. In market formation processes, we found co-dependencies among personalised cancer medicines and their companion diagnostics, for example diagnostics following a different reimbursement scheme than medicinal products. In addition, the involved actors are co-dependent, medical specialists, being the designers of new medical guidelines and the intermediary between patients and hospital reimbursement procedures. Also, as our study shows, the activities around market formation of a personalised medicine innovation system are highly co-dependent. We have witnessed how first mover Herceptin® paved the reimbursement pathway for second-mover product Tarceva®. Theoretically, we thus claim that a TIS analysis should be further refined, taking these co-dependencies among technologies into account (Kukk et al., 2016).

Second, there seems to be a move from geographical divergence to geographical convergence in practices and market formation processes. The initial geographical differences could be explained by the variety in market formation sub-processes. The subsequent convergence is spurred by exchange of practices and rules, e.g. through national-level codification in medical guidelines and reimbursement rules that lead to further convergence at the regional level.

Third, market formation dynamics are supported and influenced by close interactions with the knowledge production side of the technology-related innovation system. This includes the large-scale genomics research programs in the Netherlands that started in parallel with the market introduction of Herceptin® and Tarceva®. We illustrate how a dedicated knowledge infrastructure becomes a necessary precondition for market formation to take place, especially with regard to highly-specialised innovative products, such as personalised cancer medicine. Knowledge development in the pharmaceutical sector mainly takes place at the international level in association with entrepreneurial activities and business development of large pharmaceutical companies being also internationally oriented. When clinical testing starts, medical knowledge creation can be regarded as a co-evolutionary process (e.g. Metcalfe et al., 2005; Nelson et al., 2011) distributed over a large range of countries; knowledge creation in clinical settings informs decision making on drug licensing and reimbursement as well as in clinical guideline development.

Fourth, gaining legitimacy is an important activity for innovative technologies. Locally, medical specialists needed to convince their hospital boards to reserve finances for personalised medicine. Nationally, medical specialists and patient representative organisations worked hard to convince media, parliament and others to change the rules and guidelines. Following Fligstein (1996), markets can indeed be seen as institutions that are constructed and legitimised by a wide variety of actors. Therefore, a TIS analysis should pay more attention to legitimation processes related to institutional change (e.g. Garud et al., 2007; Leca et al., 2008; Maguire et al., 2004), especially in highly-regulated markets, such as healthcare.

Fifth, it seems that the build-up of the technological innovation system of the first-mover personalised breast cancer medicine Herceptin® provided lessons for the second-mover personalised lung cancer medicine Tarceva®. The Dutch knowledge infrastructure on genomics, biomarkers and personalised medicine was improved over time. Personalised cancer treatment systems were in place, the medical community knew and learned about testing, routines were built, and consequently the cost of personalised medicine was no longer a surprise, and the legitimation of subsequent personalised medicine grew over time. Notions from the innovation ecosystems literature highlights the significance of technological co-dependency and product complementarity on system development (e.g. Adner, 2006; Holmström Olsson and Bosch, 2014; Mantovani and Ruiz-Aliseda, 2016; Mercan and Göktas, 2011). This study indicates that the context of new technologies, especially regarding medical technologies, has a strong impact on system-building and market formation strategies of innovative actors (Kukk et al., 2016).

5.1. Practical implications

This study has shown how demographic factors and differences in local resources and reimbursement policies cause inconsistencies in access to, and delivery of, innovative drugs and diagnostics. National-level policies need to be better adapted to address these regional or local-level inequalities.

This study also illustrates how pharmaceutical (reimbursement) policy is not only a political decision but is being shaped and strongly influenced by end-user profiles and perspectives. We conclude, therefore, that it is important for policy makers to be aware and supportive of the contextualisation activities needed for a product to become part of a national market. This especially applies to cases of innovative products for which no market boundaries, regulations, exchange mechanisms, etc. exist. Pharmaceutical companies should be more aware that when their products are radically-new, more attention is needed for creating markets on local (national) levels. This means more outreach to and education of medical specialists and policymakers, even emphasising that the product is different from previous products in need for new institutions. Competition is fierce in the pharmaceutical sector and being second-in-class detrimental to product diffusion (Schulze and Ringel, 2013), but in the case of radical innovation and markets still to be formed there might be a case for cooperation with competitors. Since healthcare managers and medical professionals are the principal players, they could take the lead in the creation of markets; in defining market segments, transaction mechanisms and user profiles. The latter has become apparent in recent discussions on the reimbursement of expensive drugs: medical scholars and governments are more aware of the need to know more about who should get a drug and when. Finally, patient organisations did already perform well in the two cases in lobbying for market regulations favorable to access to medicines. They should cherish being key players in legitimating market institutions, and ensure not being captured by un-intended, non-patient interests.

5.2. Limitations and suggestions for future research

In literature there is discussion about how to delineate the TIS geographically (Bergek et al., 2015). In this study it is difficult to set the geographical boundaries that would serve the best purpose of a TIS analysis of medical innovations. Entrepreneurial activities of companies involved in personalised cancer medicine have mainly taken place internationally by the multinational pharmaceutical companies. At the same time, market formation has a strong national character in medical innovation, due to national regulations and high institutionalism (e.g., local reimbursement schemes) in the Netherlands. In order to take the particular geographical context into account and to better understand the specific roles from Dutch policy makers in market formation, a future fine-grained analysis of Dutch policy design would be helpful. Also, more attention to the specific role of regulation (including further operationalisation of regulatory activities) in analysing health care innovation systems is important.

This study showed how a first-mover personalised cancer medicine prepared the ground for a second mover cancer medicine. It is interesting to analyse whether the pattern of market formation carries on with upcoming third-mover personalised cancer products. Furthermore, the personalised lung cancer medicine Tarceva® is rather a special case with regard to stigmatisation. Further research should also focus on the market formation of second- and third-mover personalised breast cancer medicines introduced in the Netherlands.

This paper builds on previous works (Dewald and Truffer, 2011, 2012) and demonstrates that the further conceptualisation of market formation into three sub-processes works well to unpack the market formation function also in other sectors outside of the energy field with different characteristics and dynamics. Our work further shows that the sub-processes of market segments, market transactions, and user-

profiles are interlinked. We identified a number of co-dependencies among innovation system building activities over time. Especially, the knowledge development function proves to be a necessary precondition for market formation. We also find spatial variations in market formation. By zooming in on infrastructural, regulatory and user legitimisation dimensions of market formation, this study showed the increased institutionalisation of personalised medicine markets over time, in which first-mover personalised medicine prepared the ground for subsequent personalised products. Therefore, we recommend that future research should focus on further operationalisation, refinement and quantitative studies of these sub-processes, identifying actors, strategies and activities that hinder or promote market formation processes in different settings, so as to analyse whether typical patterns emerge.

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