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Genomics as a new research regime? Evidence from the Netherlands

Abstract

Social scientists commenting on developments in the life sciences have suggested that the rise of genomics in the field of human genetics does not only involve a shift in the research agenda from relatively rare monogenetic disorders to multifactorial, common diseases, but also involves a transformation on the institutional level of research regimes. In the (Dutch) genomics landscape, in which such research regimes are embedded, increasingly dominant values and objectives exert pressures on researchers to collaborate with industrial partners and to valorize knowledge results. To assess how these pressures are actually taken up and transforming research regimes, a multi-level approach is developed and applied in two case studies in which regimes are characterized in terms of the identities of actors, the knowledge and products exchanged and the principles that coordinate these exchanges. We describe the dominant regime in a typical genomics research field (Alzheimer's Disease) as compared to the regime in a typical clinical genetics research field (Duchenne Muscular Dystrophy) and show whether and how these research regimes are transforming in response to landscape pressures. The analysis shows that the AD regime has not been transformed against the background of changing landscape expectations and that the DMD regime did change, but under the condition of maturation. Developments on the level of genomics research regimes follow a dynamics of their own more than reflecting a changing genomics landscape.

Keywords: Genomics, multi-level approach, research regime, university-industry relations

Introduction

Does genomics represent a new type of biomedical research system? This is the question that Martin (2001) raised to draw attention to changing arrangements in networks of actors involved in the production, use and commercial exploitation of human genetic data. Historically, biomedical knowledge production occurred in biochemistry-based networks of basic scientists, clinical researchers, pharmaceutical companies and patient groups. Since the 1980s, the development of biological drugs and gene-based technologies have brought molecular biologists, geneticists and newly formed biotechnology companies into the center of the biomedical knowledge production system. Until about 2000, however, these developments took place in strongly aligned networks of laboratories and clinics, with close cooperation between researchers and clinicians and a strong focus on the demands of patients and patients' families (Hopkins, 2004, 2006a; Rabeharisoa, 2003; Callon and Rabeharisoa, 2008). In the Netherlands, for example, regional clinical genetics centres played an important part as nodes linking genetic laboratory research and diagnosis with clinical patient care and counselling (Nelis, 1998; Stemerding, 1993; Boon, 2008). Characteristic for this early genetic research system were the absence of large firms as leading actors, informal self-regulation, ad-hoc funding, and bottom-up initiatives. Hence, this research system can be conceived as being governed by an 'internal regime' (Hopkins 2009).

In contrast, Hopkins (2009) argues that in recent years, research in medical genomics is more and more governed by an 'external regime' including laws, regulations, social norms and involving wider groups, like biotechnology companies, policy makers and funding agencies. One of the most prominent organizational features of this new type of research system is the accommodation and intensification of university-industry linkages in several respects. Firstly, various technology transfer initiatives and the creation of a large number of academic spin-offs reflect the increased collaboration in terms of knowledge production and uptake. Secondly, companies specialising in research tool development and contract genotyping services exploit the commercial opportunities offered by the increased use of large datasets. Thirdly, while

genetic databases are usually funded by the state and set up by academic researchers in collaboration with clinical actors, biotechnology firms and pharmaceutical companies involved in testing and drug development are eager to get access and may even be prepared to co-sponsor them (Coriat et al., 2003; Hopkins, 2006b; Martin, 2001; Martin and Kaye, 2000; Mayrhofer and Prainsack, 2009). The rise of medical genomics, thus, not only brings a new research agenda (from rare monogenic diseases to common multifactorial diseases) but also new methodological approaches (high-throughput technologies and large biobanks) accompanied by new social relations and institutional arrangements in the biomedical research system.

The pattern of development in medical genomics has also been described in the broader contexts of (i) the biotechnology industry, a growing science-based industry characterized by large multinational companies that conduct in-house research and dedicated biotechnology firms that are financially independent by virtue of their intellectual property, even without delivering commercial products (Coriat et al., 2003), and (ii) the knowledge society as a changing contract between science and society, fostering an increase of academic researchers' orientation towards the production of 'relevant' knowledge, i.e. the solution of societal problems and support for innovations and economic growth (Hessels, 2010; Berman, 2008; Slaughter & Rhoades, 1996). These patterns are supported by powerful and continuous state interventions. New advisory committees and funding agencies are founded to stimulate, facilitate and co-ordinate university-industry collaborations. Science and technology policy instruments include research funding programmes, support for technology transfer, financial and technical support for start-up firms and regional clusters, R&D tax credits, and a focus on funding applicable research. Substantial public investments are reserved in order to gain advantages in this key area of the knowledge economy.

The emergence of genomics as a new type of research system takes place in the broader context of a knowledge economy that is itself changing. However, it is unclear what the relations between changes at different levels are. The central research question therefore reads: how do changes pertaining to genomics (as an emerging science field) relate to changes of the

biotechnology sector and the knowledge society in general? Is the emergence of a new type of research system in medical genomics an autonomous, internally-driven development or does it (also) reflect responses to broader developments? In terms of the foregoing distinction between 'internal' and 'external' regimes: is the new government by an external regime in medical genomics a result of increased landscape pressure or of a voluntary externalization and formalization of the internal regime.

By addressing this question we contribute to an ongoing debate in research policy studies about university-industry relations. Gibbons et al. (1994) and Nowotny et al. (2001) argue that modern science systems are shifting from academic, investigator-initiated and discipline-based (mode 1) knowledge production towards problem-focused, interdisciplinary, and societally relevant (mode 2) knowledge production. Intensified science-industry relations are an integral part of this macro-level process in which society is 'speaking back' to science (Gibbons, 1999, 2000). According to Etzkowitz et al., (2008) entrepreneurial universities play an increasingly central role where state interventions and university initiatives are converging. Others note, however, that supporting evidence for this development is soft (Gibbe and Hannon, 2008; Hessels, 2010). Whether scientists indeed listen to society-speaking-back is often contingent upon the local work environment, for example whether or not others in their research group, preferably the chair, are active in technology transfer (Bercovitz and Feldman, 2008).

Bonaccorsi (2008) takes another position in the debate in his analysis of search regimes in new research systems. He has introduced the notion of technical complementarity to denote the dependence of researchers on specific equipment or infrastructure to perform their research. He argues that new sciences like genomics are increasingly dependent on the production of advanced technology to manipulate and observe phenomena at micro and nano level. Intensified science-industry relations are then a result of increased technical complementarity within sciences rather than a new problem orientation of the science system in general. This reference to research-internal drivers also brings to mind a third explanation from 'finalization theory' developed by the Starnberger group in the 1970s (Böhme et al., 1973, 1983). They argued that

any science goes through three phases of theory maturation. After the second phase, when its theoretical program has come to organize the field, science starts to absorb external goals of research. Science-industry relations occur in this third phase.

The emergence of genomics as a new type of research regime is a multifaceted and complex process with diverse drivers. In this article we develop a *multi-level approach* to conceptualize this process. The approach distinguishes between transformation processes at different empirical levels: the 'landscape' and the 'regime' level. We use this approach as a starting point for an empirical investigation of developments at these different levels. From this perspective we have studied the rise of genomics in the Netherlands as an example of an innovation landscape in transition. In the Netherlands, a major initiative was the foundation of the Netherlands Genomics Initiative (NGI) in 2002, allocating 580 million Euros for genomics research and innovation between 2002 and 2012. Countries like the UK, Canada and Belgium (Flanders) have programs in place that are to some degree comparable to the Dutch NGI. NGI is interesting for its decentralized organization of valorization[1] activities. In this sense, NGI is most similar to Genome Canada: both programs strongly aim at integrating valorization in the whole research organization by requiring researchers to incorporate valorization activities into their research projects. For an international comparison, see Boekholt, Meijer and Vullings (2007).

In this article we claim that developments on the level of the Dutch *genomics landscape* indeed represent a more general transformation involving a 'changing contract' between science and society and the promise of a science-based biotechnology industry. Developments on the level of *genomics research regimes*, however, mainly follow a dynamics of their own showing aspects of technical complementarity and maturation. Mature regimes are more likely to develop relations with industry. To support these claims, we compare two research regimes: one

[1] Valorization is a Dutch science policy concept for what is elsewhere called science impact or the third mission of universities (see below).

is a typical case of new genomics research and the other is rooted in the early clinical genetics regime.

A multi-level approach of innovation

Based on existing literature, we have developed a multi-level approach to conceptualize complex, multifaceted transformation processes in systems of innovation. Callon's concept of techno-economic networks (TEN) is used as a starting point (Callon, 1991; Callon et al., 1992). Our approach shows how TEN can be tailored to study multi-level processes.

A TEN is "a coordinated set of heterogeneous actors – laboratories, technical research centres, industrial companies, financial organizations, users, and public authorities – which participate collectively in the development and diffusion of innovations, and which via many interactions organize the relationships between scientific and technical research and the marketplace" (Callon et al., 1992, p. 220). Networks are organized around poles, which are characterized by the kinds of objects which actors in different network positions produce and exchange. We distinguish four different poles of the genomics innovation system (Figure 1)[2]:

- Science: research contributing to the knowledge base of scientific fields
- Industry: R&D oriented at commercial applications
- Clinic: activities of clinicians, patients, patient groups and reimbursement agencies oriented at prevention, diagnosis, prognosis and therapy.
- Public policy: regulatory and funding activities of actors professionally occupied with the governance of innovation, including activities of patient organizations.[3]

[2] See De Laat (1996) for a similar modification of the original figure (Callon et al., 1992).
[3] Rabeharisoa (2003) gives a clear example of how funding scientific and clinical research granted the French Muscular Disease Organization a partnership role in decisions about the direction of future research. In addition, Callon and Rabeharisoa (2008) convincingly show that the support by patient (parents) groups in turn led to the construction of stabilized identities, goals, interests and preferences of these groups. They argue that the emergence of such groups is often driven by shared concern of patients with rare diseases who are not taken into account in prevailing configurations of science, technology and markets. The relation to rare (monogenetic) diseases explains the strong involvement of patient groups in clinical genetics.

<<Figure 1 about here>>

Using the concept of a TEN it is possible to distinguish between developments at the level of the genomics landscape and at the level of genomics research regimes. This distinction also enables investigating the interaction between developments on these levels. The *genomics landscape* is situated at the level of poles. Each of these poles are characterized by their own activities and coordination mechanisms, such as scientific norms, technical standards, or clinical guidelines. Poles are conceived as networks themselves, but historically established ones with their own traditions and dynamics. Callon (1991) uses the term 'punctuation' to refer to the past institutionalization of network configurations. Thus, poles are punctuated networks with a relatively strong internal coherence, irreversibility and autonomy, but still need continuous reproduction. In addition, intermediary poles facilitate the exchange of products or knowledge between poles (Callon et al., 1992). A technology transfer pole is characterized by services to stimulate the use of certified knowledge for product development and vice versa the use of technological instruments for scientific purposes. The institutionalization of technology transfer at universities reflects the emergence of such an intermediary pole (Miller et al., 2009). Between other poles, similar intermediary mechanisms are conceivable. For example, clinical genetics centers in the Netherlands, founded in the 1980s, serve as a bridge between laboratory research and clinical use of genetic testing. So, the emergence of intermediary poles can be seen as a manifestation of 'new contract' relations between science and society: they concern changing structures of exchange relations on a societal level. On this level, the genomics landscape exists as the external context of genomics research and innovation. Relatively long-

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Interestingly, Callon and Rabeharisoa speculate that the stratification of common disorders into many genetic variants by genomics research will produce many more rare diseases and henceforth similar concerns.

term trends, like the increased significance of strategic science or the institutionalization of technology transfer, may put pressure on research networks.

Embedded in the genomics landscape are specific *genomics research regimes*. Poles represent worlds apart, but in research regimes these poles may be linked via interactions in which objects or knowledge are exchanged between researchers and actors representing other poles. Knowledge produced in one pole can pass to other poles to serve a different purpose, for example when scientific insights give rise to new ideas for product development. The notion of 'regime' refers to the rules and routines that coordinate these exchanges. Examples of coordination rules are shared visions and divisions of labor, which coordinate interactions of researchers with other researchers, clinicians, patients, commercial firms, and funding agencies. Increased sharing of rules may lead to the crystallization of 'regime' relations connecting actors from different poles. A regime can thus be defined as "complexes of (more or less) shared rules on how to act and to interact, and to a system of corresponding interdependencies between (groups of) actors" (Deuten, 2003, p. 31).[4]

Van de Poel (1998) distinguishes between more abstract and generative rules on the one hand and more concrete or tacit rules on the other. Guiding principles are the most abstract rules that relate research activities to core values shared by all actors and that are constitutive of a regime. Examples of guiding principles in genomics research are 'understanding the hereditary component of a disease' or 'developing (gene) therapy'. Guiding principles are used to legitimize more concrete rules, such as the promises and expectations inscribed in research programs, the labor divisions governing the relations between actors, and the proven heuristics, taken-for-granted concepts, techniques, skills and routines, and the possibilities and limitations of equipment and platforms that guide the daily practice of scientific research.

[4] To avoid confusion: Hopkins's (2009) distinction between an internal and an external regime does not coincide with the regime and landscape level. An internal regime refers to informal routines and ad-hoc rules; an external regime to structural and formalised rules. Although external rules that connect actors from different poles (e.g. contracts) are often anchored at the landscape level (e.g. IPR legislation) they still apply at the regime level.

In this article, we focus on the interaction between the landscape level and the regime level. Regimes may shift or transform in response to landscape pressures (Smith et al., 2005). Van de Poel (1998) defines a regime shift as a change of one or more of its core or constitutive rules. This implies that researchers not only develop new activities and relations, but also start legitimizing activities and interactions in different terms. The regime analysis thus highlights how researchers conform to landscape pressures within their research activities.

Empirical analysis: medical genomics in the Netherlands

On the basis of our multi-level approach, we will describe the emergence of genomics in The Netherlands at the landscape level and then turn to the comparative analysis of two case studies at the regime level. The landscape analysis is mainly based on key policy documents and five in-depth interviews with high-profile actors involved in genomics policy making and evaluation. Interviews were tape-recorded and transcribed and used to select the most relevant policy documents and to understand the impacts of documents and policies and the dynamics of policy making and execution. Interviewees held strategic positions in an interdepartmental task-setting group, a national executive body for genomics policy and an external evaluation committee. They were selected according to their capacity to oversee main events and developments in the changing genomics landscape.

Research regimes, we will describe in terms of five dimensions: scientific collaborations, relations with the clinic, relations with industry, relations with public policy, and coordination rules. Table 1 provides an operationalization of these dimensions.

<<Table 1 about here>>

We conducted two case studies to analyze and compare medical genomics (Alzheimer's disease) and clinical genetics (Duchenne Muscular Dystrophy) research regimes. Alzheimer's disease is an example of a complex condition with multiple genetic as well as environmental

causes. To understand its heredity, research is focusing on different areas of the human genome simultaneously. For this reason genetic research into AD did not really take off until more comprehensive approaches and techniques became available that were developed in the context of the Human Genome Project. In our analysis we contrast this case with Duchenne Muscular Dystrophy. Due to its specific monogenetic characteristics (inherited via the mother and expressed only in sons) the genetic cause of DMD was found relatively early and with traditional genetic techniques. Subsequent efforts focused on the diagnostic application of this knowledge in the clinic and on the understanding of the pathological mechanism of DMD.

In each study, we took a collection of scientific output in the last decade (2000-2010) as the empirical starting point. The collection for the first case study (AD) is derived from the ISI Web of Knowledge database (which includes the PubMed database) from which we selected articles with 'Alzheimer' as topic and within subject area 'genetics & heredity'. Based on a map of co-author relations we identified several clusters of co-author networks. The largest cluster comprised all Alzheimer genomics research conducted in Rotterdam, reflecting a large research program that is part of the Center for Medical Systems Biology (CMSB) funded by the Netherlands Genomics Initiative. After delimitation[5] and fine-tuning[6] of this cluster we isolated a set of 57 articles. This set is considered as the output of a dense network of collaborating Alzheimer genomics researchers, whose activities are assumed to be coordinated by a genomics regime.

Data collection for the second case study (DM) followed the same methodology. Within the 'genetics & heredity' subject area, we used 'Duchenne' as topic and 'Leiden' as address-

[5] When searching for collective coordination rules, it does not make sense to include unconnected or peripheral scientific networks in one case study. Therefore, we limited our case studies to the largest clusters in the overall maps. In the case of AD, we used 'Rotterdam' as a keyword for institutional address, which appeared to be a very precise intervention to delimit the largest cluster from most smaller ones in the total data-set.

[6] Of the 70 remaining articles, a small number (13) still appeared to be unconnected or peripheral to the main cluster in the co-author map. Since we were interested in the rules governing interactions between the core of researchers, we only included articles co-authored by one of the top-10 most publishing researchers (who were all part of the core cluster).

keyword (52 articles).[7] After exclusion of small unconnected networks, one dense core network remained (44 articles) . The case studies are based on an analysis of these data. For each case we constructed a database with selected articles and all possible information these articles displayed pertaining to the variables specified in table 1. Three in-depth interviews with prominent researchers (one in DMD and two in AD research, all central in co-author maps) and one with an official of the Leiden Technology Transfer Office were conducted, tape-recorded, transcribed and used to triangulate and interpret the data. Project descriptions, progress reports and patents referred to in these reports were also used as secondary data sources.

The rise of a genomics landscape in the Netherlands

The history of clinical genetics in the Netherlands is strongly related to the development of prenatal diagnosis, based on chromosome analysis, which was introduced in the clinic from the early 1970's. The role of the Dutch government was limited to the establishment of a number of specialized Clinical Genetics Centers in the 1970s, which had the task to develop and offer clinical testing and counselling. The focus was on rare single gene disorders like Duchenne Muscular Dystrophy and Huntington's Disease (Nelis 1998).

While a clinical genetics research regime developed, and continued to exist, in the context of an established landscape of Clinical Genetics Centers with little government intervention, a differently institutionalized genomics landscape emerged next to it. Inspired by the expectations and prospects raised in the Human Genome Project, the Dutch government strongly stimulated genomics from early 2000 through a series of initiatives with the aim to establish a leading position in the field (Van Lente, 2006). At that time, scientists, industry representatives and policy-makers began to promote genomics in the Netherlands as an exciting new and promising field which needed special support from the government (interviews policy makers). In response to these promotional activities, the Dutch government established, in November 2000,

[7] 'Leiden' research represents the largest cluster in the overall co-author map (compare note 3). Dutch DMD genetics research is very much concentrated at the Leiden department of Human and Clinical Genetics, a leading research group in this field worldwide.

the Temporary Advisory Committee Knowledge Infrastructure Genomics (the Wijffels Committee). The committee had the task to advise the Minister of Education, Culture and Science about the way in which the knowledge infrastructure in the field of genomics might be strengthened.

In its advice, the committee made clear that genomics unmistakably was one of the new scientific 'frontiers' with strategic relevance for Dutch society (Wijffels, 2001). In this context, the committee also referred to the ambition of the Dutch government to play a prominent role in the European knowledge and innovation agenda as it had been proclaimed during the EU Lisbon and Stockholm Summits in 2000 and 2001. Thus, a 'national strategy' for genomics was proposed which should cover the complete innovation chain from fundamental research to product development, including the protection of intellectual property and measures which should stimulate the commercial exploitation of knowledge. In this way, according to the committee, additional investments in genomics could indeed benefit society as fast as possible.

The proposed national strategy strongly emphasized the need for new forms of institutionalization of genomics, concentrating research activities in a few centres of excellence, which should be able to connect to current economic strengths and to important international developments in the field. Special incentives for the 'valorization' of research were also needed according to the committee in order to advance the flow of knowledge from science to practical application. Active involvement in public-private collaboration and active support of knowledge protection and transfer were seen as crucial in this respect.

In line with the advice of the Wijffels Committee, a Netherlands Genomics Initiative (NGI) was founded in 2002, which involved the establishment of several centres of excellence under the umbrella of a National Directorate Genomics and which was supported on a five-year basis by significant additional funding from the government. According to its mission statement, the NGI should "develop a world class knowledge infrastructure within five years, which is firmly embedded in society and in which pioneering and innovative research can be performed with a view to yielding a continuous influx of new commercial applications" (NGI, 2002, p. 2). To

achieve that aim, the NGI developed, in the first five years of its existence, a policy in which valorization managers were made responsible for facilitating the commercialization of results in each centre, thus also creating a change of mindset among its researchers towards valorization of research (interviews NGI).

Although NGI's role generally was perceived as successful in this respect, it was also concluded, at the start of its next five-year period, that for the realization of a truly optimal valorization infrastructure, a significant further effort would be required (NGI, 2007). For the next period a significant amount of funding was reserved for valorization activities and all NGI genomics centres explicitly had to include valorization targets in their business plans (interview NGI). Moreover, as part of the current NGI valorization policy, valorization targets are clearly set in terms of quantifiable output indicators, including numbers of invention disclosures, patents, licenses, spin-off companies, and industrial collaborations (NGI, 2007). Strengthening technology transfer offices in the field of the life sciences and a start-up support programme, offering coaching, financing and networking to young entrepreneurial scientists, are two other core focus areas in the current NGI valorization strategy (interview NGI).

The way in which genomics in the past decade has been institutionalized in the Netherlands, clearly reflects the changing contract between science and society which we have described as a more general development at the landscape level of the innovation system. In this context, valorization is introduced as a mode of governance which strongly promotes entrepreneurial activities of value creation. As the authors of a recently published future vision for genomics in the Netherlands observe, a country which has the ambition to become or remain one of the top bioregions of the world has to act aggressively in order to stay ahead of its competitors (Laane and Besteman, 2009). In other words, with the institutionalization of genomics as a new and promising strategic science, genomics researchers more and more have to face the pressure of policy initiatives to reform and shape links between different poles of the innovation system, in particular stimulating collaborations between science and industry. How then are genomics researchers dealing with this challenge at the level of genomics research regimes?

Genomics research into Alzheimer's Disease

Alzheimer's Disease (AD) is being studied in a typical genomics research regime: a multifactorial disease as research object, the use of large population studies and high-throughput technology, genome wide association studies as an important approach, and funded by the Netherlands Genomics Initiative.

Alzheimer's disease (AD) is the most frequently occurring form of dementia among frontotemporal dementia (FTD), Lewy body dementia and vascular dementia. Usually a distinction is made between Early-Onset AD and Late-Onset AD. Research in the 1980s and 1990s into EOAD revealed that mutations that account for a heritable component of EOAD. Little is known about the importance of genetic factors for developing LOAD, except that a mutation on the APOE gene, found in 1991, increases the risk of getting LOAD in a set of patients.

This section describes the regime in which the research of the past decade has been taking shape, paying attention to relations within the science pole and between science and clinic, industry and public policy using indicators specified in table 1.

A co-author map of the set of articles selected according to the abovementioned methodology reveals three sub-networks, which broadly correspond with three different population studies underlying the Alzheimer's genomics research in Rotterdam: a EOAD patient population study, the Rotterdam Study and the Erasmus Rucphen Family Study (figure 2).

<<Figure 2 about here>>

Science-science collaborations

Sub-network I is the oldest (until 2005) and represents a strong Rotterdam-Antwerp collaboration, which was based on hypothesis-driven candidate gene association studies using a population-based epidemiological study of EOAD within metropolitan Rotterdam and the four northern provinces of The Netherlands (Van Duijn et al., 1994). According to the established division of labor between collaborating researchers in these studies, sample collection and statistical analysis were done by the Rotterdam epidemiologists and genotype analysis by molecular geneticists in Antwerp.

Sub-network II comprises articles from 2004 to 2010. The research reported in these articles is based on the Rotterdam Study, a prospective cohort study ongoing since 1990 and set up by the epidemiologists in Rotterdam (Hofman et al., 2007). The cohort comprises 8,000 (diseased as well as healthy) subjects aged 55 years or over that have been followed for 12 years. The large number of subjects and the variety of collected clinical data enabled researchers to study associations between (incident) Alzheimer's disease, genes involved and a number of intermediary factors (brain volumes, white matter lesions).

Sub-network III comprises articles from 2002 to 2010 that report findings from the Genetic Research in Isolated Populations (GRIP) program. Within this program the Erasmus Rucphen Family (ERF) Study includes 2800 subjects who are related to 30 founding couples from an isolated community living in the period 1850-1900. Because of familial relationships, 400 to 800 markers suffice to genotype the full genome of these subjects. In addition, clinical data were collected including anthropometrical measurements, cardiovascular assessments, and cognitive function tests (CMSB, 2003, 2008a). Most of the researchers involved are affiliated with the department of Clinical Genetics or the department of Epidemiology & Biostatistics in Rotterdam. These departments collaborate in the Genetic Epidemiology unit, founded halfway the first decade of the 21st century.

Noteworthy is that the increased interest in genome-wide association studies around 2005 involves an emergent change in configuration of research teams. According to an AD

researcher, the increased scale of research (from less than 500 to about 3000 subjects) makes it ever more difficult to do every research step within one's own small group. Research is increasingly conducted in large consortia (e.g. the ENGAGE consortium), enabling a new kind of logistic and labor division in order to process large amounts of data efficiently. Moreover, it is becoming increasingly important to replicate findings and combine different studies to increase the reliability of published results (interview). The Rotterdam Study, for example, is being used as a resource in an international research project that exploits the power of aggregated data (the Epistasis Project) (Combarros et al., 2009).

Science-clinic collaborations

Relations between researchers and clinical practitioners are very much one-way traffic in all sub-networks. The recruitment of AD patients for the first population study (I) happened by asking clinicians in nursing homes, psychiatric institutions, social-geriatric services, neurologic departments, and CT facilities in these areas to provide names of dementia patients (Hofman et al., 1989). For the Rotterdam Study (II) participants were interviewed at home and had extensive examinations in a specially built research facility, which were repeated every 3-4 years. Over 500 participants underwent MRI investigations and the total cohort was continuously monitored for incident dementia through computerized linkage with existing clinical records (Hofman et al., 2007). The clinical work in the ERF Study (III) comprised the foundation of a health center in the village of Sprundel, where 3h examinations took place and blood was drawn (Van de Leemput, 2004). So, the clinic is important for providing input for research. Reversely, however, the direct relevance of the research for clinical practice has been very limited overall. With few exceptions, the articles point to the fact that genetic effects on AD pathology, if observed at all, are very small and occur via largely unknown pathways. They mainly urge for further research (cf. Mihaescu et al., 2010).

Science-industry collaborations

Unlike what one might expect in light of a changing genomics landscape, relations with industry are absent except when it comes to the purchase of machines and assays from commercial manufacturers for in-house genotyping of blood samples (eg. Van Oijen et al., 2007). An Alzheimer researcher explains:

> "It is a practical question. We have done things ourselves, also GWA studies. But even in those cases, if it could have been done cheaper elsewhere, then we would have outsourced it. By then, it just wasn't cheaper" (interview).

The same researcher notes a change in this regard. In a very recent whole genome sequencing project, genotyping is outsourced to a Chinese company that has all the equipment in place. But, he adds, it is simply a practical cost-benefit decision.

In terms of industrial sponsoring, patents and spin-off companies, we did not observe any university-industry collaborations. The researchers explain that, by now, it is not-done to file a patent on a gene. Moreover, patents from the past have not yielded any revenues. There is very little testing on Alzheimer susceptibility genes, because their effects are small and hardly predictive. Neither is there any commercial interest in the biobanks developed by the Rotterdam groups. Researchers believe that industry might be curious for major research results, but not for getting direct access to the samples from the biobanks (interviews).

Science funding

Funding is acquired from a large number of different agencies and foundations, such as Fund for Scientific Research Flanders (Belgium), Netherlands Organization for Scientific Research, International Alzheimer's Research Foundation, and the Alzheimer's Association (eg. Dermaut et al., 2003). In addition, the Rotterdam Study is funded by the medical center and university of Rotterdam, the municipality of Rotterdam, ministries of health and science, the European Commission and councils for scientific research and health research (eg. Van Oijen et al.,

2007). In contrast to the Netherlands Genomics Initiative (NGI), none of these funding agencies prioritizes or demands collaboration with industry or economic valorization.

One of the centers of excellence funded by NGI is the Center for Medical Systems Biology (CMSB). In this center, Alzheimer genomics is one of the spearheads. Especially, the collection of clinical data and biological material in the Erasmus Rucphen Family Study (III) and some research conducted in the context of the Rotterdam Study (II) has been made possible by NGI funding (eg. Sleegers et al., 2007; Vasquez et al., 2004). We expected articles acknowledging this funding to reveal more intensive university-industry collaboration and different coordination rules, because economic valorization is a central performance criterion for NGI-funded ressearch. However, there does not seem to be a relation between funding criteria and collaboration patterns in Dutch Alzheimer genomics.

Guiding principles

The research in all three sub-networks of authors is of a very academic nature and justified in academic terms. Agenda statements expressed in publications are for example: "we show that […] might be a genetic risk factor for EOAD" (Dermaut et al., 2003, p. 412) or "to provide clues about the aetiology of AD" (Roks et al., 2000, p. 2130). Over time, the explanation of the heredity percentage remains a very prominent research objective (eg. Liu et al., 2008). Although, in the CMSB business plans, the intention is expressed "to enter into partnerships after value has been created, especially in the form of validated targets for diagnosis, prognosis, therapy or prevention in a particular disease domain" (CMSB, 2003, p. 6), Alzheimer genomics is ultimately justified in terms of the heredity gap: "These developments leave the disease unexplained in more than 82% of the patients" (CMSB, 2003, p. 7) and "still 30-50% of the patients remain unexplained" (CMSB, 2008a, p. 5).

These agenda statements reveal a common interest among collaborating scientists in *understanding* the relation (association or linkage disequilibrium) between particular

(candidate) genes and Alzheimer disease. Researchers confirm this interpretation of academic legitimization:

> "I am fundamentally interested in causes. My motivation is to understand why one person gets it and another one does not. I think, if we do not have fundamental knowledge about how it develops, then treatment will remain trial and error. With such knowledge, a treatment can be directed much more precise" (interview).

Accordingly, AD researchers admit that there is little to valorize as yet. "We made progress in the past decade, but this progress was not of a kind that it yields a patent" (interview). Another researcher makes a comparison with Duchenne research:

> "That was one of the fields in which it was possible. It should be noted that the trajectory towards exon skipping … we are talking about a disorder of which the gene has been known for thirty years. It is fine to hold researchers accountable for their valorization. It is crazy to think that that is possible in five years" (interview).

Similar explanations are also reported in progress meetings with the Netherlands Genomics Initiative "valorization with regard to multifactorial disorders is difficult by definition: the research is in its very early stage and patents and the like are relatively rare" (bi-annual meeting, May 2006). Researchers thus attribute the lack of valorization to the explorative phase of AD genomics.

Conclusions Alzheimer case

Alzheimer genomics research takes place in a genetic-epidemiology-oriented research regime established in the 1990s. It is a multidisciplinary regime in which epidemiologists and statisticians collaborate with geneticists. Large international consortia with access to multiple biobanks and conducting replication studies and meta-analyses seems to be a trend for the near future of Alzheimer genomics research. Relations between science and the clinic are unidirectional. While patients are recruited for research, the research promises little in return. Relations between science and industry are also thin. Companies are not very interested in

knowledge of genes with small effects. Commercial potential, presupposed in the literature about (resisting) pressures of commercialization (e.g. Bercovitz and Feldman, 2008; Berman, 2008), is absent in the case of Alzheimer genomics. Somewhat more dynamic are relations on the research equipment market, because genotyping platforms need to be kept up-to-date (cf. Bonaccorsi, 2008). Whereas genotyping is generally done in-house, the increasing costs of high-throughput equipment is now forcing researchers to outsource the work to commercial firms offering cheaper genotyping services. This substitutes part of the work done previously by academic molecular geneticists. Statistical analysis develops in a similar vein. Although the genetic epidemiology unit uses its own biostatistical software, the rise of genomics has lead to the blossoming of a bioinformatics sector comprising firms that develop statistical softwares for large studies (Fujimura, 2010). With regard to relations with public policy, research is funded by agencies that basically support academic research with the exception of the Netherlands Genomics Initiative (NGI). NGI-funding, however, does not affect the type of Alzheimer research, even though the overall program proposal submitted to NGI does promise knowledge valorization. Guiding principles of Alzheimer genomics research are scientific by nature. Figure 3 illustrates this scientific orientation of Alzheimer genomics. In conclusion, even though some developments indicate a changing research regime, there is a clear discrepancy between research practices and landscape expectations.

<<Figure 3 about here>>

Genetic research into Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is a single-gene disorder, that has been object of research in a clinical genetics regime since around 1984. The emergence of this regime and its typical characteristics, like close links between research and clinical practice and strong patient involvement, have been described in detail by Nelis (1998). Her analysis shows that this regime

developed in the relative absence of landscape pressures; an institutionalized genomics landscape did not exist until the 2000s. This article presents a follow-up of her analysis and highlights a number of more recent developments in DMD research: a strong focus on therapeutic interventions and the involvement of commercial actors. Although some prominent DMD researchers do have projects funded by the Netherlands Genomics Initiative, DMD research itself is not funded by the NGI. Therefore, DMD research has developed independent from landscape pressures channeled through NGI's valorization policy and, as we will show, recent developments are mainly driven by an internal dynamics of the regime and more general patterns of change in the life science sector. Indeed, DMD is not only interesting as a comparative case study because it represents the characteristics of the traditional clinical genetics regime, but also because it shows a different dynamics that has resulted in intensive university-industry collaborations in this clinical genetics regime.

Duchenne muscular dystrophy (DMD) is a metabolic disease affecting one in 3500 males. It is characterized by rapid muscle degeneration, leading to death at the age of twenty on average. DMD research was one of the first areas in which human geneticists made use of DNA markers. Because DMD only affects males (with very rare exceptions) who inherit the cause of the disease from their mother, the mutation must be localized on the X-chromosome. In the mid-1980s research groups in Leiden, London and Freiburg succeeded to develop markers with which a prenatal genetic test could be offered, predicting the chance of a newborn with DMD with 97% certainty. Subsequent research focused on the role of dystrophin deficiency in muscle degeneration, the identification and characterization of the dystrophin gene, the deletions and duplications that cause dystrophin deficiency, improved diagnostic methods, etc.

Since the mid-1980s, DMD research and related diagnostic and counseling activities have been embedded in a co-evolving clinical genetics regime, which developed in the institutional context of Dutch Clinical Genetic Centers (Nelis, 1998). Characteristic for this regime was the

strong involvement of patient organizations. In the case of DMD, they urged for research, provided funding and helped recruiting subjects for research. The diagnostic practice of the Leiden CGC was also crucial for research. While from the patient perspective the Duchenne test was merely the result of research, from a scientific perspective the tests were the main source of data. In this context important steps have been taken since with several implications for the way research is organized.

Science-science collaborations

Most of the research published in the period we studied (2000-2010) is application oriented: it either deals with techniques, classifications or standards for improved diagnosis and genetic counseling (eg. Helderman-van den Enden et al., 2009; White et al., 2003), or with the development of a therapy aimed at the restoration of dystrophin expression by inducing specific exon skipping (eg. Aartsma-Rus et al., 2007; van Deutekom et al., 2001). First authors are generally affiliated with the Center for Human and Clinical Genetics of the Leiden University Medical Center (LUMC) and mostly collaborate with departments elsewhere in the Netherlands or abroad. The articles do not reveal clear patterns of frequently occurring science-science collaborations, which indicates that the choice of scientific partners is rather based on incidental complementarities and interdependencies than on established relations.

Science-clinic relations

Relations with the clinic continue to be very close. Clinical researchers frequently participate in DMD research, patient organizations are very active in fundraising for research,[8] and in some research projects DMD patients and families are actively involved (eg. Dent et al., 2005). Reversely, the research promises several clinically relevant outcomes. Improved techniques and standards for testing offer possibilities for reliable prenatal diagnosis and genetic counseling

[8] The Duchenne Parent Project (NL, USA and Fr); the Princess Beatrix Fund (NL); the Muscular Dystrophy Association (USA); Action Duchenne (UK); and the Association Francaise contre les Myopathies.

that make reproductive decision making within DMD families easier (eg. den Dunnen and Beggs, 2006). These kinds of applications are directly translated to the clinic. But the most promising is the development of a potential exon skipping therapy (eg. van Deutekom et al., 2001). Muscle degeneration in DMD patients is caused by mutations or deletions of exons in the DMD gene leading to broken pre-mRNA, a disrupted reading frame, and henceforth dystrophin deficiency. The principle of the therapy is the inducement of a further deletion in pre-mRNA (AON-induced exon skipping) in such a way that the two ends of pre-mRNA can bind again. The result is that a transcript is generated that allows the synthesis of slightly shorter, but largely functional dystrophin as found in the mostly milder Becker muscular dystrophy. In 2008, phase I/II AON dose finding clinical trials are started in Belgium, Sweden and the Netherlands.

Science-industry collaborations

The notion of 'exon skipping' symbolizes the close links between scientific and clinical actors in the research very well. On the one hand exon skipping due to mutations in the DMD gene refers to the biological understanding of the disease. On the other hand it refers to the therapeutic possibility to skip more exons to restore the reading frame involved in dystrophin synthesis. But apart from the science-clinic link, exon skipping has also generated close science-industry links. The research proceeds in close collaboration with commercial partners. In the period we studied nine patents were filed, the first in 2000 (CMSB, 2008b; Van Ommen et al., 2000). These patents are exclusively licenced to Prosensa in return for patent costs, royalties and milestone payments (CMSB, 2008b). Prosensa is a biotechnology company with strong roots in the Leiden University Medical Center. The company's vice-president Drug Discovery has been involved in exon skipping research from the beginning. Since 2007, she collaborates in the research on behalf of her company and later patents are co-owned by Prosensa. In 2009, moreover, Prosensa and multinational pharmaceutical company GlaxoSmithKline (GSK) announced that they have entered into an exclusive worldwide

collaboration for the development and commercialization of RNA-based therapeutics for DMD, which resulted in a considerable growth of the company and a commercial success for the Leiden research group. Both industrial parties are currently involved in a phase III clinical trial (CMSB, 2009).

Science funding

Patient organizations and charities collect for DMD research. The Duchenne Parent Project and the Princess Beatrix Fund are major science sponsors. The European Neuromuscular Center (ENMC), a collaboration of patient organizations, played an active role in stimulating and focusing exon skipping research. It organized several workshops (2001, 2004, 2007) in which it brought together scientists, companies and patient organizations, discussing priorities and patient concerns. The Center also made resources available and supported plans for clinical trials (Boon, 2008). A number of funds for scientific and translational research are furthermore mentioned. The Center for Medical Systems Biology (CMSB), one of the centers of excellence funded by the Netherlands Genomics Initiative (NGI), is also mentioned four times as sponsor. This is striking because the DMD research projects that acknowledge CMSB are not mentioned in the program submitted to NGI. It is understandable, however, given that the scientific director of the CMSB happened to be one of the researchers involved in the Duchenne LUMC-Prosensa collaboration and asked NGI permission to use part of the CMSB budget to cover exon skipping patent costs (Timmerman, 2004). In a comment to a previous version of this article he explainded that researchers found it hard to get the money from their own institute at the time (Van Ommen, 2011).[9]

[9] This permission had the effect that the CMSB could strategically report the patents, the collaborations that this research spun off, and subsequent DMD valorization activities as valorization output in progress reports (e.g. CMSB, 2008b), despite the fact that research into rare diseases like DMD was no official part of the CMSB program.

Prosensa was initially financed by Biopartner and Medsciences Capital, a Dutch stimulation fund and a Dutch venture capital provider for starting life science entrepreneurs. Prosensa currently receives considerable support from GSK. The CMSB loan covering patent costs was paid back after the first milestone payment from Prosensa to the LUMC (ibid.).

Guiding principles

Genetic research into DMD is often justified in terms of its clinical potential and the steps that need to be taken to realize this potential. An example is the following agenda statement:

> "A relatively new therapeutic strategy is based on antisense oligonucleotides (AONs) that induce the specific skipping of a single exon, such that the reading frame is restored. We have previously successfully targeted 20 different DMD exons that would, theoretically, be beneficial for >75% of all patients. To further enlarge this proportion, we here studied the feasibility of double and multiexon skipping" (Aartsma-Rus et al., 2004, p. 83).

Similar examples can be found in articles reporting research relevant for diagnostic practices (eg. den Dunnen and Beggs, 2006). These guiding principles reflect a regime that is oriented towards external (clinical) goals and links with external actors. According to the finalization theory this orientation is typical for mature research fields characterized by a relatively stable scientific paradigm (Böhme et al., 1973, 1983).

Conclusions DMD case

Since the 1980s research into DMD has been conducted in the context of a clinical genetics regime. This regime has been characterized by a strong clinical orientation in terms of both patient involvement and clinical relevance of outcomes (Nelis, 1998; Boon, 2008). These features are still very visible in current DMD research although this research has been increasingly shaped by an industry-oriented innovation regime (Figure 4). The development of a therapeutic approach based on exon skipping appears to be commercially attractive and has

indeed given rise to increasingly strong links with companies. Exon skipping has therefore been mentioned as a best practice of knowledge valorization in the field of human genetics (eg. NWO, 2010; Thole et al., 2010)

<<Figure 4 about here>>

However, this new innovation regime cannot be understood as the immediate result of valorization policies at the landscape level. The research is not sponsored by the Netherlands Genomics Initiative or similar funding initiatives that prioritize knowledge valorization. It has rather been a profitable road that might have been taken anyway given that the first patent dates back to the year 2000, preceding the establishment of NGI. Researchers who make efforts to realize the potential of a therapeutic approach *repay* patient organizations for their long lasting support.

On the other hand, NGI's mission enabled DMD researchers to draw on CMSB resources to cover patent costs and Prosensa could start-up thanks to venture capital made available at the landscape level. Moreover, the alliance between LUMC and Prosensa came about after mediation by the Technology Transfer Office of the LUMC. Since the TTOs are manifestations of a changing social contract at the landscape level, landscape pressures did play some role. Thus, as one of the Duchenne researchers points out, commercialization might have happened anyway, but has been facilitated by developments on the landscape level:

> "There has been an element of chance. But there also was an atmosphere of founding small companies since about 1998. There was 'landscape pressure' to try to achieve something presentable, because you knew you would be judged on that. So I think that [without landscape pressure, the exon skipping therapy] would indeed have been developed anyway, but possibly not in the Netherlands. There were activities at different places."

Notwithstanding chance and landscape pressure, we maintain that the entrepreneurial spirit of the Leiden group had a history in clinical genetics. Bercovitz and Feldman (2008) have shown that localized social norms are conditional for adopting valorization policy goals. In the case of

DMD, this adoption process happened in a mature regime that had already been oriented towards external goals for a long time, an orientation that is also visible in other application-oriented activities than exon skipping therapy development.

Final conclusions

In the literature it has been suggested that the rise of genomics marks the emergence of a new kind of knowledge production, translation and application. Instead of direct links with the clinic, genomics researchers are supposed to be more strongly involved in collaborations with industrial partners that translate knowledge into commercially viable products. Moreover, these changes take place in a context that is itself changing. A new social contract is in the making, in which researchers are increasingly held accountable for doing research that is relevant beyond science. We indeed found that a new social contract manifests itself in the rise of a Dutch genomics landscape in which genomics is strongly stimulated as a strategic science. The Dutch government felt that the country could not afford losing its international position in the life science sector. In this context, valorization was introduced as a central policy goal. In two case studies, we further analysed to what extent changes at the regime level are driven by these new landscape pressures or by their own dynamics.

Implicated in the idea of a new social contract is the commitment of science to listen and act in response to society speaking to science (Gibbons, 1999, 2000). In the Dutch genomics program, society is speaking about valorization very explicitly. However, we have not found a clear response by scientists in our case. Genomics research regimes have emerged recently and deal with complex issues. Results beyond academic relevance cannot be assumed, but depend on dynamics that are regime-specific. In the case of DMD, researchers actively strive after commercialization of knowledge. This can even be observed in some genomics research regimes, for example in the field of Rheumatoid Arthritis (Verweij, 2011). However, researchers in the Alzheimer genomics regime (except a few geneticists) do not have strong links with clinical actors and there is no involvement from industry, despite large governmental

stimulation programs. This offers support for conclusions drawn in other contexts that stimulation of genomics research does not automatically benefit the clinic and economy (Hopkins et al., 2007; Nightingale and Martin, 2004).

This conclusion does not imply that regimes are static. We do observe the emergence of a new type of biomedical research system (Martin, 2001), but not one that is driven by a external pressures (cf. Hopkins, 2009). Another entrance to the issue of regime dynamics is to perceive new university-industry relations as a manifestation of technical complementarity (Bonaccorsi, 2008). According to this view, regime-specific drivers for change are more important than landscape pressures. Technological progress, for example, is mentioned several times as the single most important factor influencing the scale of data processing and approach to gene discovery in genomics regimes. Genomics research regimes were established in the 1980s and 1990s on the junction between epidemiology and genetics, the Alzheimer genomics research regime being a clear example. Within this regime, we observed a trend from candidate gene studies to genome wide association studies to whole genome sequencing, based on large population studies and the use of high-throughput technologies. A recent trend in Alzheimer research are assay-by-design technologies and commercial genotyping services. At the same time, it has become productive to separate data collection from specific research projects and use population data in biobanks as a generic resource for addressing a variety of research questions. This mainly occurs in international projects exploiting the power of aggregated data from several biobanks.

Whereas in genomics regimes technical complementarity is more important than landscape pressure, in the clinical genetics regime landscape pressures do seem to create response. We suggest that landscape pressures assert influence under the condition that a research regime has developed into a state where its theoretical program becomes attractive for external goals (cf. Böhme et al., 1973, 1983). In the case of Duchenne Muscular Dystrophy, the strong involvement of patient organizations in funding, priority setting and subject recruitment illustrates this focus on applications in the regime. Therapeutic possibilities had come within

reach after long-lasting research efforts. Researchers arrived at a stage in which they needed the help from private parties to realize the potential of their therapeutic approach. The regime was *ready for valorization* when a favorable atmosphere emerged, in which it was increasingly appreciated to collaborate with industry. The convergence of regime goals and landscape pressures thus resulted in an alliance between researchers and a start-up biotechnology company and commercial funding of therapy development. Still, it is interesting to note that policymakers and researchers alike do not hesitate to mention exon skipping as a successful fruit of knowledge valorization policies. We argue that the guiding principles of the regime were already aligned with the dominant values and objectives at the landscape level before they started to exert pressure.

What does this mean for the way genomics research (and perhaps also other emerging sciences and technologies) is managed, pushed and pressured? The Dutch government sees genomics as a strategic research area. Investments should be paid back with the creation of new jobs in companies that translate knowledge into medical applications. Granting subsidies happens under the condition that researchers put an effort in patenting and selling knowledge. This raises the question how compulsory these conditions should be. If the government sees valorization mainly as an instrument for economic policy, than these conditions should only apply to research fields that indeed have something to valorize. In fields like Duchenne genetic research starting points exist. But fields like Alzheimer genomics should then be spared. If the government wants to apply valorization targets to science policy in general, including these more difficult fields, then it is crucial that they adopt a broader conception of valorization. These fields can only be 'rewarded' if for example also indirect contributions to valorization in the future count. Our study implies that differences in capacities of medical research fields to economically valorize knowledge reveals a need for more differentiated targets. In general, science policy should take into account the characteristics of the field and its regime.

A final note concerns the juxtaposition of clinical genetics and medical genomics. For the sake of comparing we contrasted two kinds of regimes. This is justified by their distinct history,

disease areas, scientific approaches and external orientations. Juxtaposing the two regimes allowed us to show that genomics regimes have not displaced the older clinical genetics regime. Clinical genetics research continues to exist, but not within the large genomics programs. It also allowed us to distinguish different kinds of dynamics of regime change. However, a drawback of this approach is that another kind of dynamics remained underemphasized: the mutual influence of regimes. For example, even for monogenetic conditions like DMD, genomics research has generated insights and possibilities to base therapies on knowledge about where and how the gene is mutated. Conversely, therapies based on for example exon skipping also have potential for (understanding) multifactorial conditions, albeit that they only target single factors. We suggest that future research should pay more attention to mutual influences to understand these dynamics.

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Table 1. Operationalization of research regimes

Dimension	Variable	Indicator
Scientific collaborations	Co-author maps and disciplinary profiles of collaborators	Different or same Kinds of profiles Division of labor
Relations with clinic	Clinical input in research	Subject recruitment
	Clinical relevance of research	Statements about clinical implications/applications
Relations with industry	Technology platform	Purchased for in-house genotyping or outsourced
	Valorization	Industrial co-funding Patents filed (Spin-off) companies involved
Relations with public policy	Funding agencies/foundations foster PPP and valorization	NGI funding or other funding with high priority for PPP and valorization
Coordination rules	Agenda statements and guiding principles	Most general description of research objectives

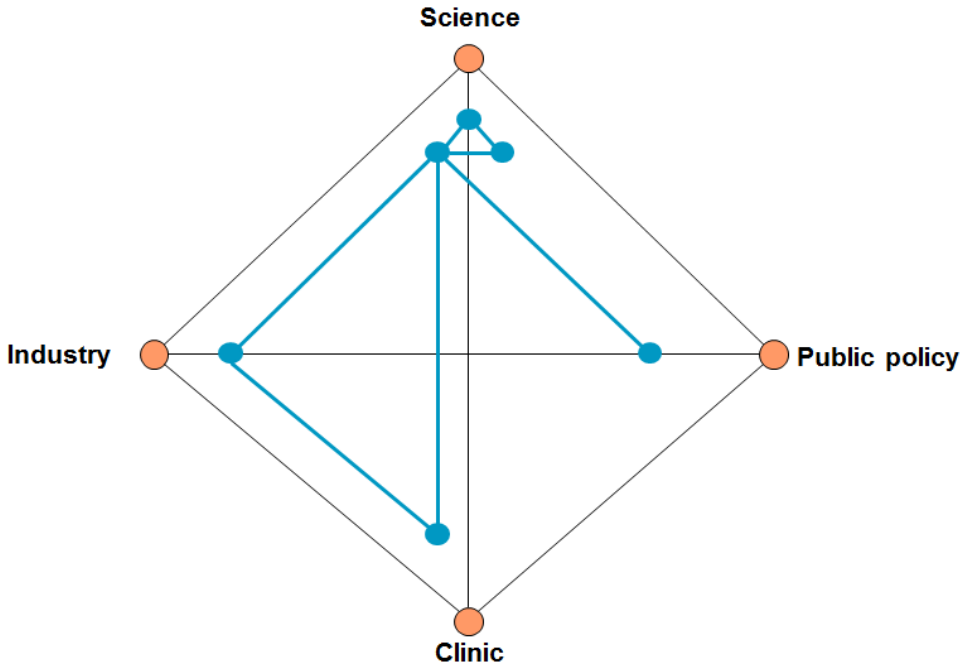

Figure 1. A multi-level approach of research and innovation

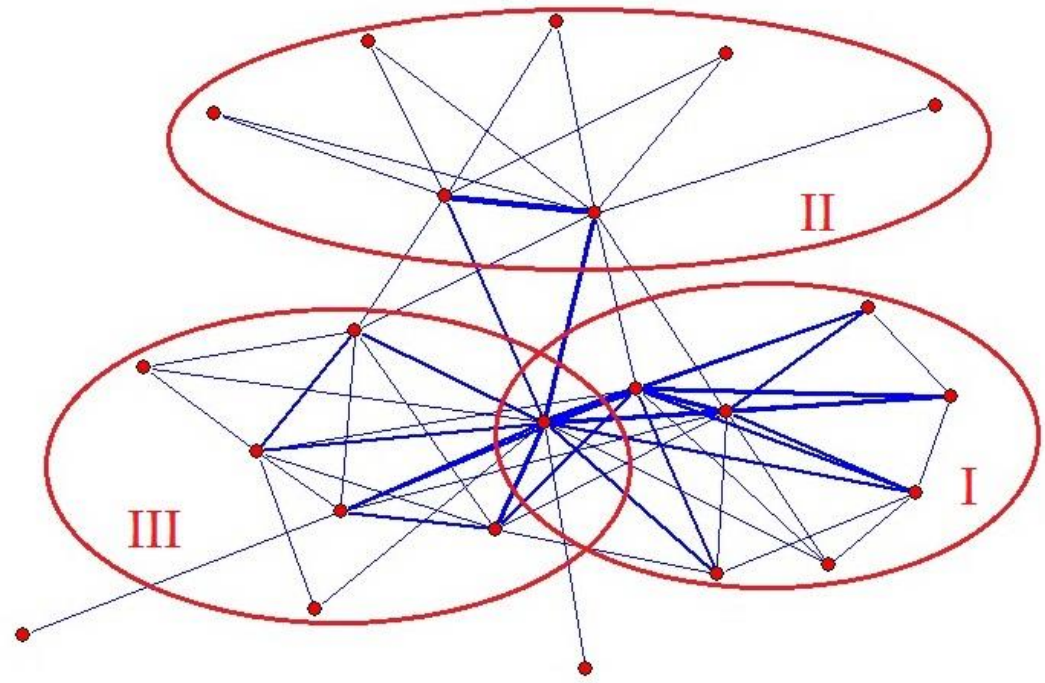

Figure 2. Co-author map of Rotterdam's Alzheimer genomics[10]

[10] The map is constructed with Pajek (available at: http://vlado.fmf.uni-lj.si/pub/networks/pajek/), using the algorithm of Kamada and Kawai (1989). Only five or more co-author relations are included.

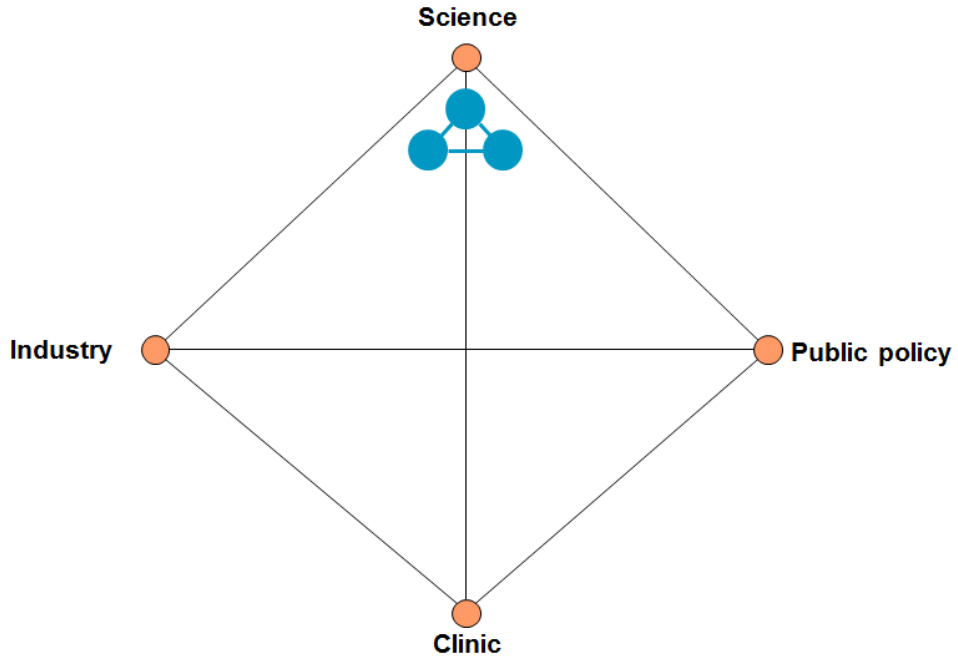

Figure 3. A schematic representation of the Alzheimer regime

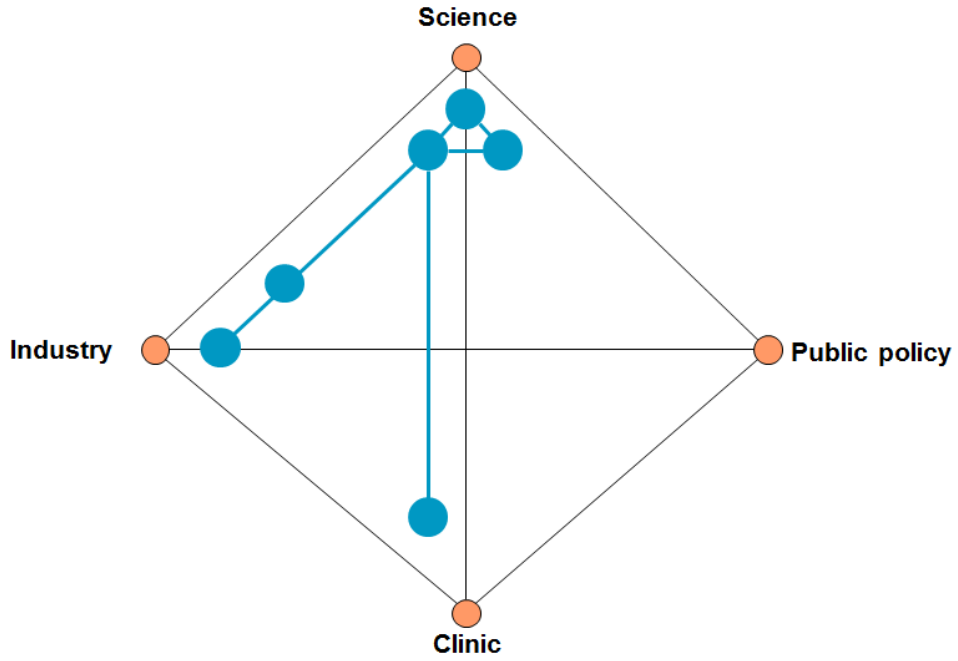

Figure 4. A schematic representation of the Duchenne regime