Spaces of Genomics

Exploring the Innovation Journey of Genomics in Research on Common Disease

Lise Bitsch

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EXPLORING THE INNOVATION JOURNEY OF GENOMICS IN RESEARCH ON COMMON DISEASE

DISSERTATION

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by

Lise Bitsch

Born on June 14th, 1982
in Aalborg, Denmark

This dissertation has been approved by the promotors:

Prof. dr. S. Kuhlmann
Prof. dr. H.F.M. Te Molder
Dr. Kornelia Konrad (assistant promotor)

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Til

Inger og Aksel

Ilse og Karl

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This thesis is the outcome of an almost seven year long journey. In my acknowledgements I want to celebrate the journey. It has been a journey that has taught me not only to be a researcher, but more importantly to be a researcher together with other researchers. No one writes a PhD alone. An important lesson for a PhD-in-training is learning to trust in order to share ideas that feel frail and "undone", to brainstorm, listen, collaborate and ask for help. My PhD is a celebration of such a process.

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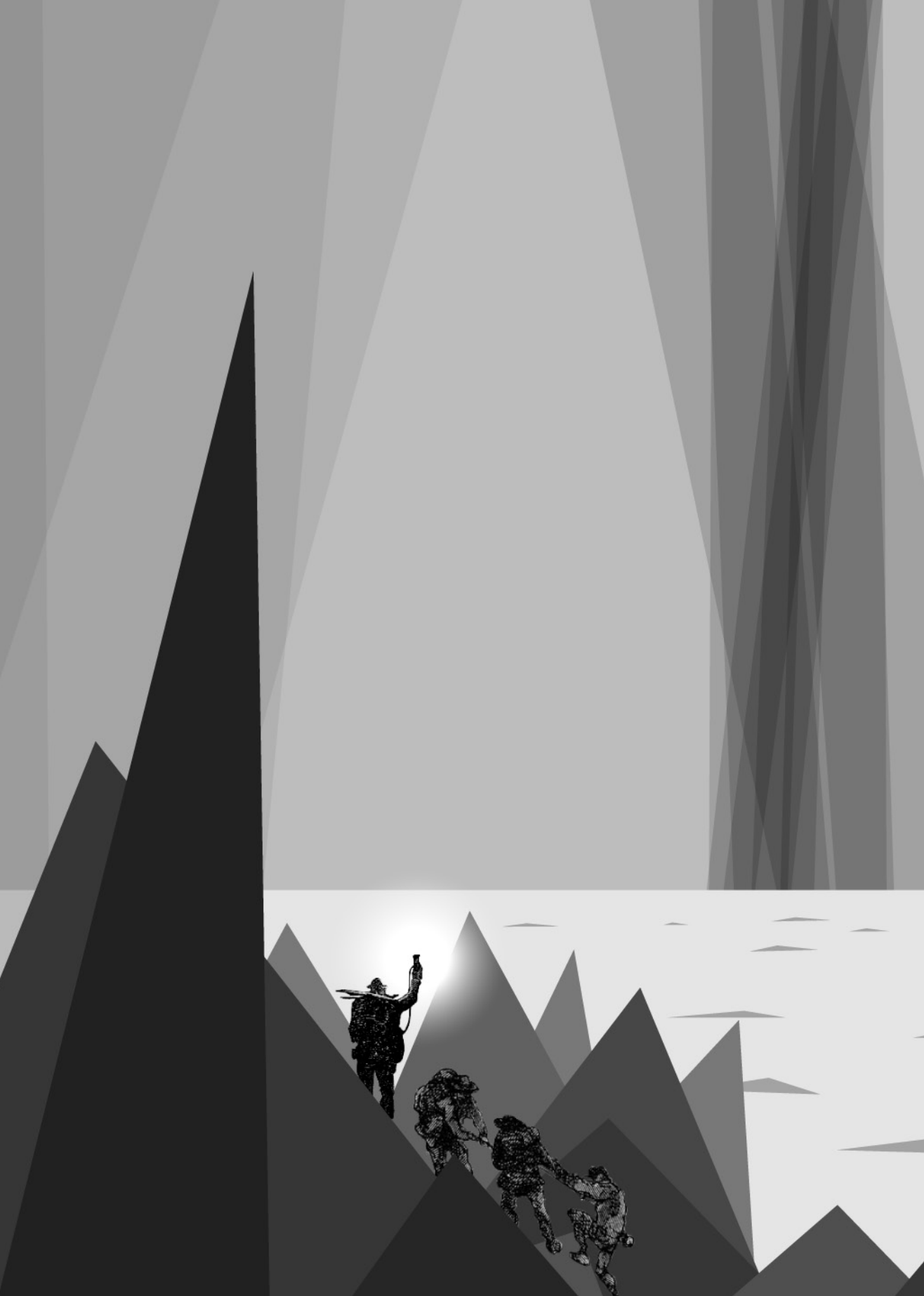
Rien, my love, my man, your love, patience, support and honesty is what keeps me. To the moon and back.

This book is dedicated to my grandparents, who, through their love and hard work, made this PhD a possibility for me.



1 Genomics and research on common disease

The study of the genome was introduced with promises of enabling a revolutionary shift from a care to a prevention-oriented health care system. The Human Genome Project (HGP) would lay the foundation for a revolution in personalised health care by providing the tools necessary for individuals to manage their health (National Institute of Health 2008; Collins 1999; Collins 2010).[1] Following the HGP, sequencing technologies like the genome-wide association study method (GWAS) and next generation sequencing were introduced as the follow-up methodologies to the HGP, and as the next step in taking genome-wide insights to the exploration of common disease (National Institute of Health 2008; National Institute of Health 2010).[2] The concepts 'personalised health care', 'personalised medicine', or 'genomics medicine' are associated with genomics and policy formulations of future health care goals (National Health Service 2003; Brand et al. 2006; Collins 1999). In these future visions, genomics medicine is crafted as part of personalised health care, allowing individuals increasing opportunities to manage and monitor their health. In this thesis, I analyse how the promises and expectations of genomics have been taken up and given shape in common disease research.[3] [4]

1 Following in the wake of the HGP several additional projects were initiated to follow up on the HGP and to facilitate the realization of the promised revolution. These projects include (not limited to): HapMap project, 1000 Genomes Project, Roadmap Epigenomics Project, Genographic study and ENCODE.

2 Please refer to Appendix A for a glossary of terms and concepts related to genomics.

3 While there is some contestation on the difference between genetics and genomics, I use the term genomics, as I am investigating the influences of the promises and expectations introduced with the mapping of the human genome. Genomics is often introduced with reference to the White House press conference on June 26 2000, where the first rough draft of the human genome was presented. It was in this presentation that grand claims were made of the future contributions, which would follow from the efforts of mapping the genome. I use the term genomics to refer to the promises and expectations introduced at this press conference; promises and expectations, which proponents repeat to this day. When I use the term genetics it is in keeping with practices that identify as genetics, or when I am describing the work of authors who use the term genetics. According to the WHO (2012) 'Genomics is the study of the structure and action of the genome, i.e. the sum total of genetic material present in an organism'. While genetics is the 'Genetics is the study of heredity and of the mechanisms by which genetic factors are transmitted from one generation to the next.' However in my material actors use genomics and genetics interchangeably and mix these definitions, which suggest that the two are not that easily separated.

4 With common disease I refer to diseases like cancer, cardiovascular disease, asthma, Alzheimer's, and mental diseases with a high population-wide impact. These diseases are ofen referred to as complex due to the current dominant idea that they result from an interaction between genetic and environmental factors. They are in other words multifactorial diseases.

The promise of mapping the whole human genome was perceived as a genuine game changer in genetics research because it promised to move the field of genetics from rare to common disease research (Collins 1999; Collins, Morgan and Patrinos 2003). For rare diseases, genetics is used for purposes of prevention, diagnosis, therapy and counselling. It was imagined that mapping the whole genome would likewise lead to options for prevention, improved diagnosis and therapies for widespread conditions, such as Alzheimer's, cardiovascular disease, cancer, respiratory conditions and mental illnesses. Doctors would be able to let individuals know of their risk of disease, so that they could take preventative action in terms of medications and changing lifestyles. In addition, doctors would be able to accurately predict the progression of a disease, as well as improve classification of diseases so that drugs would be tailored to these sub-classifications (The White House 2000).

An example, of how genomics will add to future health care practice, is given in a future scenario developed by Francis Collins in his 1999 Shattuck lecture. Francis Collins is the current head of the National Institute of Health (NIH), but he is perhaps better known as the leader of the Human Genome Project. His example featured the meeting between a 23-year-old college graduate with high cholesterol levels and his physician in 2010. The outcome of the meeting hinged on what the genetic information would cause the college graduate to do. In the scenario the confrontation with the genetic data is the key moment of change for the college graduate: 'confronted with the reality of his own genetic data, he arrives at that crucial teachable moment when a lifelong change in health-related behaviour, focused on reducing specific risks, is possible' (p. 35). The graduate already knew that his cholesterol was not at a normal level, but it is the genetic data, which makes a difference. With this data, and the guidance of his physician the graduate changes his behaviour and embarks on a lifelong journey of risk prevention. The scenario contains many expectations concerning scientific insights, technologies and social developments. By 2010, genomics will have led to insights on the role of genes in disease, which in turn have resulted in genetic tests for common disease. Parallel with these developments society has found ways of dealing with informed consent, the right not to know, and an infrastructure for collecting family histories. The scenario is a suggestion of what should happen with genetic data, and what people's response to such information should be. It draws together recognizable elements from established practice and reorders them to fit in a role for genetic information and genetic tests. The patient's behaviour is judged from how he responds to the 'teachable moment', suggesting that taking preventative action in terms of drugs for lowering cholesterol and quitting smoking is the right thing to do. It is the rational and responsible thing to do in the face of the 'sobering' (p. 35) evidence from the genetic tests. Not only that, but the college graduate is also able to follow though on these preventative actions. The storyline of genomics

and its future contribution is not just about genetic tests, but equally about changing social orders as a response to changing definitions of disease and risk.

The claims presented by Collins and other proponents of the HGP did not go unnoticed. Contestation and conflict are essential to emerging science and technology (Collins and Pinch 1979; Brown, Rappert and Webster 2000; Swierstra and Rip 2007). Opponents met these visions with doubt as to whether genetics would change the way common diseases are diagnosed and prevented. They argued that instead, the contribution of genomics would be the further elucidation of Mendelian disorders.[5] However, only a small portion of the general population is affected by these disorders, and thus calling genomics a revolution was not justified. (Holtzman and Marteau 2000) Furthermore, researchers pointed out uncertainties of genetic tests, and questioned if they would add predictive or diagnostic power (Janssens et al. 2006; Janssens and van Duijn 2008). In addition to contestation on the scientific and technological claims, the desirability of a future like the one described by Collins was also questioned. The geneticisation thesis is one of the more famous critiques of genetics.[6] Formulated by Abby Lippmann in a number of papers in the 90's (1990, 1991, 1998), geneticisation can be described as:

> *"The ever growing tendency to distinguish people one from another on the basis of genetics; to define most disorders, behaviours, and psychological variations as wholly or in part genetic in origin." (Lippman 1998:64)*

The thesis described a concern with a reductionist understanding of disease that would leave out economic, social and educational factors as part of understanding common disorders. Furthermore, the move towards genes as central explanatory factors was also thought to lead to an increased focus on, and demands to, the individual for taking responsibility for staying healthy (Shostak 2003). Lippman's thesis was criticized on a number of points. Scholars took objection to the broad claims of geneticisation as an intensifying process, and criticized it for not considering the historical context of genetics as based in debates on hereditariness (see for example Condit et al. 2001). More recently, Weiner and Martin (2008) have suggested that the term should be seen as a form of boundary work. Lippman and others would then be seen as more concerned

5 A Mendelian pattern of inheritance refers to that from each pair of genes, one is inherited from the mother and one from the father. That means that if a disease is inherited in dominant way, then one affected gene is enough to cause the disease in offspring. If the disease is recessive, then one must inherit an affected gene from both parents. Carrying a recessive disorder gives one a 50 percent chance of passing the mutation of to ones children.

6 The geneticisation thesis was developed as a critique of genetics. However, seeing the intimate relation between genetics and genomics, the thesis is worth considering in this connection as well.

with protecting their areas of expertise than with describing an on-going process. Hedgecoe (2001a, 2002, 2003, 2004) made a rigorous argument for the usefulness of geneticisation as an analytical tool. His aim was to introduce the consideration of empirical material into bioethical debates. According to him, the failure to do so meant that these debates did not engage with the reality of genetics.[7] For his purpose he adopted a stripped down version of geneticisation 'in medicine, geneticisation takes place when a disease is linked to a specific stretch of DNA' (Hedgecoe 2001a:876). Adopting this version of geneticisation avoids the part of Lippman's thesis criticised for its historical incorrectness. Furthermore, it avoids the position that geneticisation is necessarily a negative and undesirable process (Hedgecoe 2001a). Research on a genetic component to disease is on going. The post-genomic era is one of a continuous effort to further explore the human genome (and those of animals and plants) to understand the role and function of genes as part of a complex biological system where also proteins, RNA, metabolites and environmental factors seem to play a role, and to translate these insights into clinical practice.[8] The role of genes and how they should be included in our understanding of common disease are still on going.

In this thesis, I investigate what happened with genomics in research on common diseases like asthma, cancer, cardiovascular disease (CVD), mental disease and Alzheimer's. So far, very few applications have made their way into clinical practice. Where they have, the result has not been geneticisation. As Rabeharisoa and Bourret (2009) show for breast/ovarian, colon cancers and autism, information on mutations has become just one factor considered in diagnosis. The analysis of Rabeharisoa and Bourret suggests that clinical practice has changed in the post-genomic era, and that the separation between laboratory, clinic, diagnosis and research is increasingly blurred. On the other hand, scholars suggest that increased opportunities for molecular testing (genetic tests) have led to a strengthening of the professional eye and judgement of the clinician (Shaw et al 2003; Featherstone et al. 2005). While the reasons why and the questions if, genomic technologies will influence the use of genetic information in clinical practice remains unsolved, authors agree that the technologies developed with the HGP and the projects following from it, have had a significant impact on research practices (Cambrosio et al 2009; Rabeharisoa and Bourret 2009; Shaw et al. 2003). Not only research

7 Readers might be interested in the discussion on the need for an empirical grounding of geneticisation carried out between Adam Hedgecoe and Henk ten Have. For this see Hedgecoe (1998), Ten Have (2001) and Hedgecoe (2001b). In addition Adam Hedgecoe and Anne Kerr debated the merits of geneticisation as an analytical tool as well as specific points on the changing aetiological model of cystic fibrosis in Hedgecoe (2004) and Kerr (2004).

8 Post-genomics is here used to refer to the period after the Human Genome Project.

practices, but also the understanding of disease has been influenced by research on genes and their function. Hedgecoe (2001a, 2003) showed for diabetes and schizophrenia how explanations drawing on genes to explain disease enter into classifications of common disease even before the molecular link had been proven in practice. Still, as Weiner and Martin (2008) showed for coronary artery disease, other non-gene discourses co-exist with genetic ones. Authors have thus analysed the influence of genetics on clinical practice and on discourses of disease.[9] However, how the context of established research practices of common diseases is used by researchers in formulating the contributions of genomics to understanding disease and to clinical practice, is less explored. An exeption is Koch and Stemerding's (1994) study of screenig practices for CF. In their study, they showed how existing practices in Denmark enabled experimentation with screening for CF. Specific for Denmark were an elaborate organisation of prenatal care and a strong network of genetic researchers, clinicans and a CF patient organistion. In their conclusion Koch and Stemerding (1994) raised the question if a study of, for example, the Dutch practices of testing for CF would confirm the influence of established practice.[10]

I use a comparative approach to investigate how researchers of common disease respond to genomics and its associated expectations, and how they use elements of established practice in formulating the contribution of genomics to research and clinical practice. The point, that the situatedness of scientific practices matters is *'one of the most often cited results of the field of Science and Technology Studies'* (Cambrosio 2009:465). Practices are '[...] a sustained way of engaging in action and attributing meaning in an area of life [...]' (Hyysalo 2006:601). Thus research on common disease is characterised by established practice and ways of engaging in activities of researching and attributing meaning to a certain diseases. These practices might differ in different fields of common disease research. One the one hand, genomics presents itself as a novel opportunity for exploring a possible genetic component to common disease. On the other hand, research of common disease is embedded in established research practices. Researchers are therefore constrained —as well as enabled— by established practices in the way they can make connections with the expectations and promises of genomics. Collin's scenario is of a wholesale transformation of research as well as clinical practice. In his vision of future medical practice disease, diagnosis, prognosis, prevention and treatment is defined in relation to genes. While expectations like the ones Collins presents, are forceful in guiding actors, these actors also interpret and adopt general

9 I use the term genetics here as that is the term the authors of the implicated papers use.

10 The point of the influence of established practice is also made in Bourret, Koch and Stemerding (1998) and Stemerding and Nelis (2004).

expectations in light of their area of expertise (Van Lente 1993). For complex diseases, each research field has different practices of engaging with, or drawing on, genetic explanations of disease. This diversity allows the opportunity for differing interpretations and thereby different ways of shaping genomics. One might imagine that the scenario of risk prediction or prevention will look differently depending on the traditions already present within a research field. I therefore present, an investigation of how genomics has been taken up and given shape in two different areas of common disease research. The research question of my thesis is:

How do researchers of common disease respond to expectations of genomics and what role do elements of established practice play in their response, and how does that shape future options of prevention, therapy and diagnosis?

The aim of this thesis is to map and assess the dynamic negotiation and re-production of expectations to genomics by researchers exploring complex diseases. I conceptualise these researchers as travellers on an innovation journey. The concept of the 'innovation journey' is the key metaphor for developing my understanding as well as approach to researching the mutual shaping of established research practices and genomics. The question is what the development of genomics teaches us about the innovation journey, and what the innovation journey teaches us about the revolutionary potential of genomics.

1.1 The innovation journey

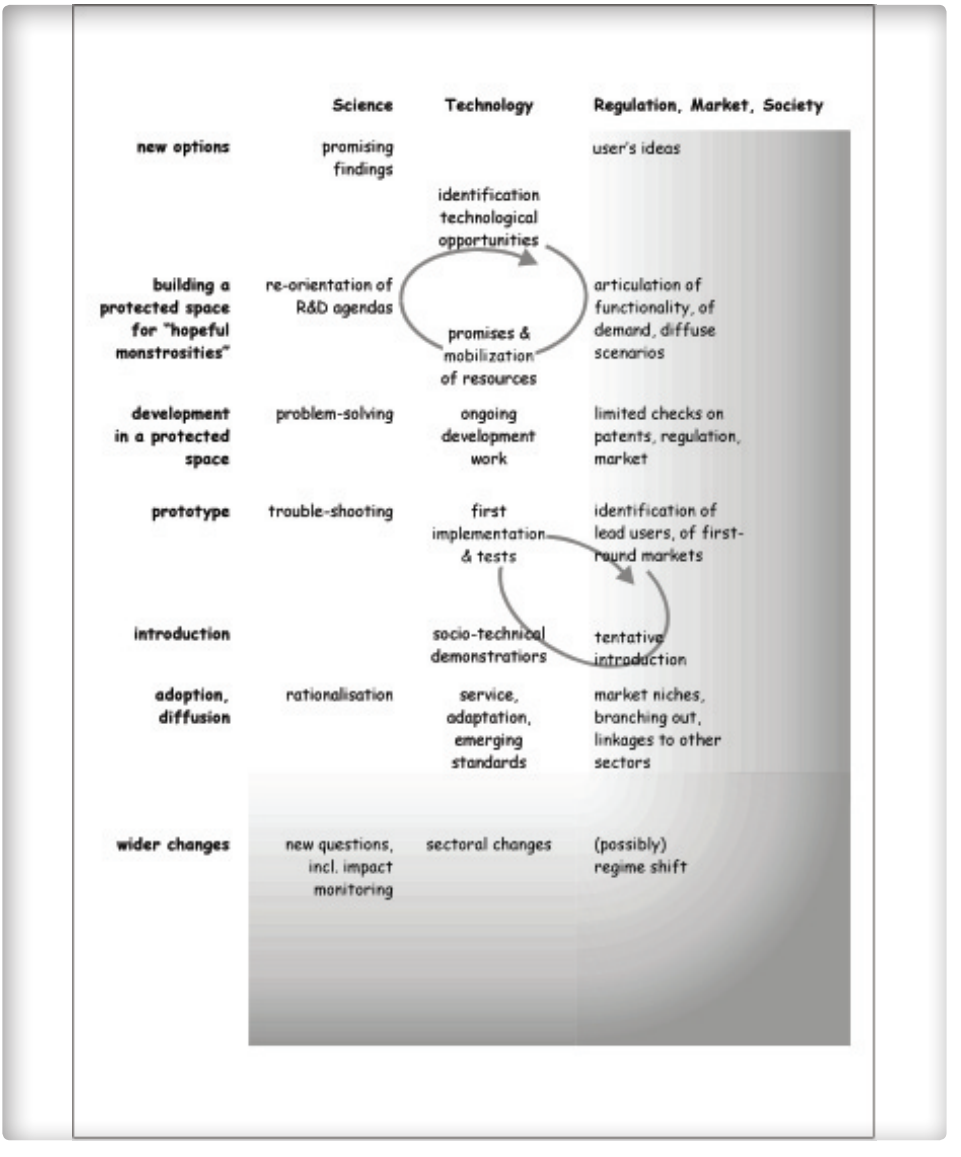
Van de Ven and colleagues (1999) first developed the concept of the innovation journey. On the basis of observing and analysing cases of product innovation, they came to the conclusion that innovation processes are non-linear and uncontrollable. Their key message to managers and engineers was therefore to give up on control and instead focus on steering innovation processes. In the terminology of Van de Ven et al., the innovation process is a journey into unknown waters, it is a like an 'uncharted river' (Van de Ven et al. 1999:212). The metaphor draws attention to the messy and complex conditions through which innovations emerge. However, the innovation journey is not completely unpredictable. A river runs through a riverbed, occasionally overflowing, but mostly keeping to its course. The innovation journey thus refers to patterns, and typical activities, like steering rapids and dangerous turns, which can be predicted.

Rip and Schot (2002) took up the insights on reoccurring patterns and the futility of trying to control innovation. Drawing on insights from evolutionary economics, they conceptualized the innovation journey as defining a general process of co-

evolution between technology and society. This conceptualization extends the context of the innovation journey from the immediate business environment of a firm, to broader societal developments and dependencies *'the innovation journey is a cross-section of the overall co-evolution, and one which is traveled following the enactors of innovation'* (Rip 2010:207). The innovation journey is the aggregated outcome of activities in many different spheres, like policy, industry, science, technology, markets and regulation, and many different actor groups contribute to the development and direction of the innovation journey. Co-evolution refers to the linkages between these spheres and their interdependencies (Sørensen and Williams 2002). Each sphere has its own dynamics, but development in the science sphere is interlinked with and dependent on developments in the society and technology sphere and the other way around. Rip and Schot (2002) created a mapping tool for the innovation journey across different contexts. With this tool, they sought to give an overview of the dynamics of the innovation journey

without losing sight of its complexity and non-linearity, shown in Figure 1.

Figure 1: Mapping the Innovation Journey in Context (from Rip and Schot 2002)



In their model, science is the sphere where promising findings emerge. Promising

findings can serve as inspiration for the start-up of innovation journeys as actors attempt to translate the promise into a prototype. New ideas, knowledge, and developments in science, can thus form the starting point for actor's imagination of possible future innovations. The other spheres through which the journey is shaped are technology, society, market and regulation. The journey is characterised by three phases: the build-up of a protected space, stepping out into the wider world, and sector-level changes (Rip and Schot 2002). The mapping tool creates an overview of the typical activities of innovation journeys. It pictures the build-up of a protected space as occurring through activities in all spheres. When a promising finding like genomics is the inspiration for the innovation journey, scientists play a key role in the initial phase of building up a protected space. In the emergence and development of a protected space, they articulate opportunities and future functions[11], since they do not only produce new knowledge, but also envisage a future world in which this knowledge may become part of novel societal practices (Wynne 2005). The eventual material shape and embedding of the emerging innovation is unknown, and much preparatory work is done through the construction of promises and expectations to the future (Van Lente 1993; Van Lente and Rip 1998a/b; Brown et al. 2000; Borup et al. 2006). As Koch (2006) elegantly puts it 'What we rarely think about is that our present is only one out of many outcomes that seemed possible or perhaps impossible in the past' (Koch 2006:329). Building expectations is thus a typical activity of innovation journeys. The protected space is not homogeneous, but heterogeneous, with different actor groups across the different spheres contributing to the space at the same time as working within the space. Eventually, a prototype of the protected space will be confronted with expectations and requirements of others. This happens during the initiation of the second phase, where a prototype emerges from the protected space, and is exposed to evaluation by actors outside the protected space. While a prototype might set the terms of imagination and discussion on future opportunities, it is important to remember that it is not the final version. The mapping tool describes the phases of the innovation journeys in general. It does not specify the dynamics of the different phases of the journey in each of the spheres.

For my research, the general description of the innovation journey functions as a heuristic for the imagination. In the next chapter, I will draw on it to develop a conceptual model for mapping the trajectory that scientists build during their on-going assessment of genomics and its potential. First however, I will describe the selection of my two case studies: asthma and cardiovascular disease. Following the

11 A dynamic, which Van Lente (1993) termed promise-requirement cycles, to emphasize how promises and expectations were translated into ideas about function and performance, leading to requirements that the future technology would also fulfill these functions and performances.

introduction to my case studies, I will provide an overview of the rest of the book.

1.2 Developing criteria for the case studies

The selection of my case studies is based on two criteria: the presence of a clinical genetic tradition, and the organisation of professional approaches to dealing with disease. Divergence in these two elements of established practice might lead to different responses to genomics. Consequently, the promises of genomics would also be shaped differently. If this is the case, the genomics' claim of a wholesale transformation of research and clinical practice start to acquire more nuance.

The general promise of genomics is a revolution in our understanding of common diseases, together with opportunities for prevention, diagnosis and treatment. When it comes to visions of applications for use in clinical practice, they are centred on genetic tests. Such tests would come in a variety of forms. They could be tests searching for a specific mutation, or tests searching for a wide number of mutations, tests with the purpose of deciding on treatment options or family planning, tests for ancestry or paternity tests, or tests for predispositions to disease.

In its current form, the entry point to the health care system is for most individuals, the general practitioner (GP).[12] GPs decide what complaints and worries are serious enough to warrant treatment, or need follow-up diagnosis by specialists. In addition GPs can advise individuals on lifestyle changes such as changing diet, to quit smoking or to deal with an alcohol addiction. GPs thus have an important function, not only as primary caregivers, but also in guarding and distributing access to the resources of the health care system. Accidents or sudden serious illness, such as a heart attack, are exceptions where the GP as an access point is usually left out.

Clinical genetics is a specialty within health care, and is not part of the primary care (Nelis 1998). Clinical geneticists are specialised in counselling families on monogenetic conditions and conditions with a strong genetic component (Vereniging Klinische Genetica Nederland 2013). Examples of monogenetic conditions are cystic fibrosis or Huntington's disease. Individuals inheriting the mutation associated with a monogenetic condition will eventually develop the disease. The degree and time of onset can differ though.(World Health Organisation 2012a) For conditions with a strong genetic component there is a high likelihood the affected individuals will eventually develop the condition. An example is breast

12 Since I am writing this thesis in a Dutch context, my description takes the Dutch health care system as a starting point.

cancer associated with the BRCA 1&2 genes. Affected women have a greater than 70 per cent chance of developing breast cancer. (World Health Organisation 2012b) Typically, it takes a death or a seriously ill family member to raise the suspicion of a genetic condition in a family. However, individuals may also contact their GP with the suspicion of a genetic condition in the family, and in this way be referred to a specialist. Such contact can be with the purpose of arranging for family planning or insight into carrier status (Stemerding and Nelis 2006). In comparison, most common conditions do not have a strong genetic component (WHO 2012b). Instead they are thought to be the result of interactions between genes and environmental factors. Genetic tests are primarily used for testing rare mutations. However, they are also used for paternity testing in cases where paternity is contested.

In addition to testing practices within the health care system, genetic tests are sold commercially (via companies like deCODEme or 23andMe). This practice really took off with the genome-wide association studies. These studies made possible the sequencing of large parts of the genome for association between mutations and common conditions. These test are typically for testing an individual's susceptibility to developing a common condition, or they can be tests for ancestry. The practice of selling genetic tests commercially has given rise to controversy. Mainly scientists object to the practice, on organisational and ethical/social grounds (European Society of Human Genetics 2010). Without delving further into these issues, it is clear that genetics is not part of the general practice of GPs, or of the management of common conditions.

GPs lack of knowledge of genetics, along with clinical utility[13] and validity[14] are often cited as the most important barriers for the uptake of genetic tests in clinical practice (Van Langen et al. 2002; Arnett et al. 2007; Teutsch et al. 2009). However, as Hedgecoe (2008) argued, there are other important factors to consider. These include a discrepancy between the interests of clinicians and scientists. From a scientific point of view, the classification of diseases and how genetics influences classification is useful in itself. However, for clinicians the usefulness of such information depends on how it affects the situation of the patient. Another difference is between numbers in scientific and clinical practice. While the idea that genetics could add certainty to clinical diagnosis seems appealing, it adds complications since the test also has implications for the family network of a person. The trade-off might not be worth the gain. Economic

13 Clinical utility: balance of benefits and harms when the test is used to influence patient management (Teutsch et al. 2009)

14 Clinical validity: balance of benefits and harms when the test is used to influence patient management (Teutsch et al. 2009)

incentives might also be at play. Take the example of a test for a rare defect that would influence the response to certain medication. When the costs of such a test would fall on the department of the medical specialist treating a patient, but the cost of treating the defect on another department, the specialist might be inclined to withhold the test. Finally there is culture. There is evidence that among clinicians, experience is in certain situations valued above scientific evidence. Thus, in situations where a test might contradict other diagnostic outcomes, the clinicians might disregard the results of a genetic test (Hedgecoe 2008).

When moving from the primary care context of GPs to specialist in academic hospitals, the division researcher and clinician becomes unclear. The practice of medicine and scientific explorations of disease overlap (Pickstone 2011). For example in academic hospitals, researchers perform the role of researcher as well as clinician. Still, depending on whether called upon as a clinician or a researcher, one person might evaluate genomics and genetic tests differently. The point here is the existing structures in which medical scientists work. In general, common conditions are thought of as the outcome of complex gene-environment interactions. However, for some common conditions there exist monogenetic sub-types, or sub-types with a strong genetic component. This is the case for breast cancer, where a strong hereditary component is involved in 5-10 percent of all cases (World Health Organisation 2012b). For cardiovascular diseases (CVD) as well, there are a group of genetic sub-types of diseases. For these sub-types clinical genetics practices are in place. The *presence of a clinical genetics tradition* might influence the response to genomics. It is therefore one criterion on which the choice of case studies is based.

In addition, approaches to managing different common conditions also differ. For heart diseases the way to the operating table might be shorter than for diabetes. Furthermore strategies and traditions for treatment, diagnosis and prevention differ. Heart associations often advertise recipes for low-fat meals, and smoking cessation courses (Nederlandse Hartstichting 2013). Associations for lung disease emphasise how patients can live a normally active life if they take their medications (LongFonds 2013). These differences in emphasis (prevention versus therapy) are a sign of *different existing socio-cultural configurations* for dealing with common disease. Depending on the existing emphasis in a disease field, the response to genomics might also differ. The second criterion for choosing my case studies is therefore based on how clinical practice is organised. In the next two sections, I describe my cases and how they live up to the two criteria.

1.2.1 Characteristics of asthma research and clinical practice

For asthma there is no monogenetic sub-type, and no straightforward definition of the condition.[15] The Global Initiative for Asthma (GINA) provides the definition as:

> *"Asthma is a disorder defined by its clinical, physiological, and pathological characteristics. The predominant feature of the clinical history is episodic shortness of breath, particularly at night, often accompanied by cough." GINA 2011:2)*

The common way of introducing asthma is by referring to its status as a chronic condition affecting 300 million people on a global level. Often mentioned in this connection are the costs associated with asthma, both in terms of caring for this chronically ill population, and in terms of lost work and school days. Western lifestyle is often mentioned as a collective term for factors thought to influence the development of asthma. There are two well-known hypotheses related to lifestyle on the cause and development of asthma. The allergen hypothesis proposes that allergen exposure triggers a response in a susceptible immune system, which then in turn induces bronchial hyperresponsiveness (difficulty breathing). The hygiene hypothesis, suggests that heightened standards of hygiene result in an under stimulated immune system, which then in turn over-reacts to environmental influences (Kaufmann et al. 2004). There is even a 'Dutch hypothesis', that all airway diseases should be considered as one disease with similar genetic origins. The thesis was strongly opposed by UK and US researchers. Recently however, and argument has been made for its validity in limited cases (Barnes 2006).

Diagnosis and treatment are at the centre of the management strategy for asthma. The goal of diagnosis and treatment is to attain control of asthma symptoms. Asthma patients are thus divided into groups depending on the degree to which their symptoms are under control. Control is achieved through medication, which the asthma patient must continuously take. (GINA 2011; Nederlands Huisartsen Genootschap 2007) Not all cases of asthma are easy to control and these cases often end up in the hospital and can even have fatal outcomes.

Prevention in terms of making changes to the living environment of the asthma patient is also emphasised. Treating physicians are encouraged to advice patients

15 When I asked about the definition of asthma in my first interview with an asthma researcher, I got the intriguing answer: "Asthma is like love: we all know what it is, but no one can define it" (Interview 1, S3 2009)

and their families on changes they can make to their surroundings; like removing a cat or dog from the home, avoiding second hand smoke, and reduction of house dust mites. Depending on the individual situation lifestyle advice in relation to smoking and exercise is encouraged. Prevention efforts are made to prevent asthma from worsening after the disease has manifested. Specialists in asthma become involved in cases where there is uncertainty of the correct diagnosis, when medication does not help, where the patients suffers from additional chronic conditions, or where the patient is normal functioning is impaired. (Nederlands Huisartsen Genootschap 2007) Genetics is mentioned as a component that plays a role in individual susceptibility to developing asthma. However, genetic information is described as uncertain, and as a factor that does not need to be considered for clinical practice. (GINA 2011; Nederlands Huisartsen Genootschap 2007)

1.2.2 Characteristics of cardiovascular disease research and clinical practice

Cardiovascular disease (CVD) is a collective term for a large number of conditions related to the heart and circulatory system. The spectrum of CVD thus ranges from the rare monogenetic conditions, conditions with a strong genetic component, to common CVD like coronary artery disease, hypertension and myocardial infarction (heart attack).

> *"Heart disease – also called cardiovascular disease and coronary heart disease – is a simple term used to describe several problems related to plaque build-up in the walls of the arteries, or atherosclerosis. As the plaque builds up, the arteries narrow, making it more difficult for blood to flow and creating a risk for heart attack or stroke. Other types of heart disease include heart failure, an irregular heartbeat – or arrhythmia – and heart valve problems." (American Heart Association 2012:NA)*

Often introductions to the most common CVDs emphasise risk factors. Modifiable risk factors include: smoking, diet, exercise, blood pressure and type 2 diabetes, while sex and age are often mentioned as non-modifiable risk factors that are also important. In addition, the costs of treating cardiovascular diseases as well as costs associated with disability, rehabilitation and mortality are used to situate cardiovascular disease as a serious problem. (Reiner et al. 2011; Perk et al. 2012)

When it comes to managing cardiovascular disease, prevention, risk prediction and recognition of symptoms and risk factors are of central concern (Nederlands Huisartsen Genootschap 2012). Treating physicians are encouraged to develop

risk profiles for patients above a certain age, and with a family history of CVD or a medical history including diabetes, kidney damage of earlier cardiovascular events. Furthermore, when family history indicates risk, GPs are encouraged to refer patients to clinical genetic specialists. (Nederlands Huisartsen Genootschap 2012)

For the hereditary cardiovascular conditions, not only the individual, but also the family is the unit of concern. Once an affected individual is identified (proband), the clinical genetics specialist will ask the individual to talk to family member about their possible risk, and encourage them to consider DNA diagnostics. When the family structure is considered to convey enough of a risk, individuals can take part in surveillance programs, where their health is monitored. The management of familial hypercholesteromia (FH) is an example. In the Netherlands the STOEH (the association for the early tracing of hypercholesteromia), keeps track of affected families and actively approaches individuals and families thought to be at risk of FH.

Contrary to asthma, cardiovascular disease is characterised by the presence of monogenetic sub-types of disease, as well as sub-types with a strong genetic component. These conditions are managed through screening programs of different organisational structure. However, common to them all, is the focus on risk prediction and prevention before the manifestation of disease.

Table 1 shows how the two case studies differ in relation to the criteria: presence of a monogenetic sub-type of disease and a tradition for clinical genetics, and the approach to managing disease.

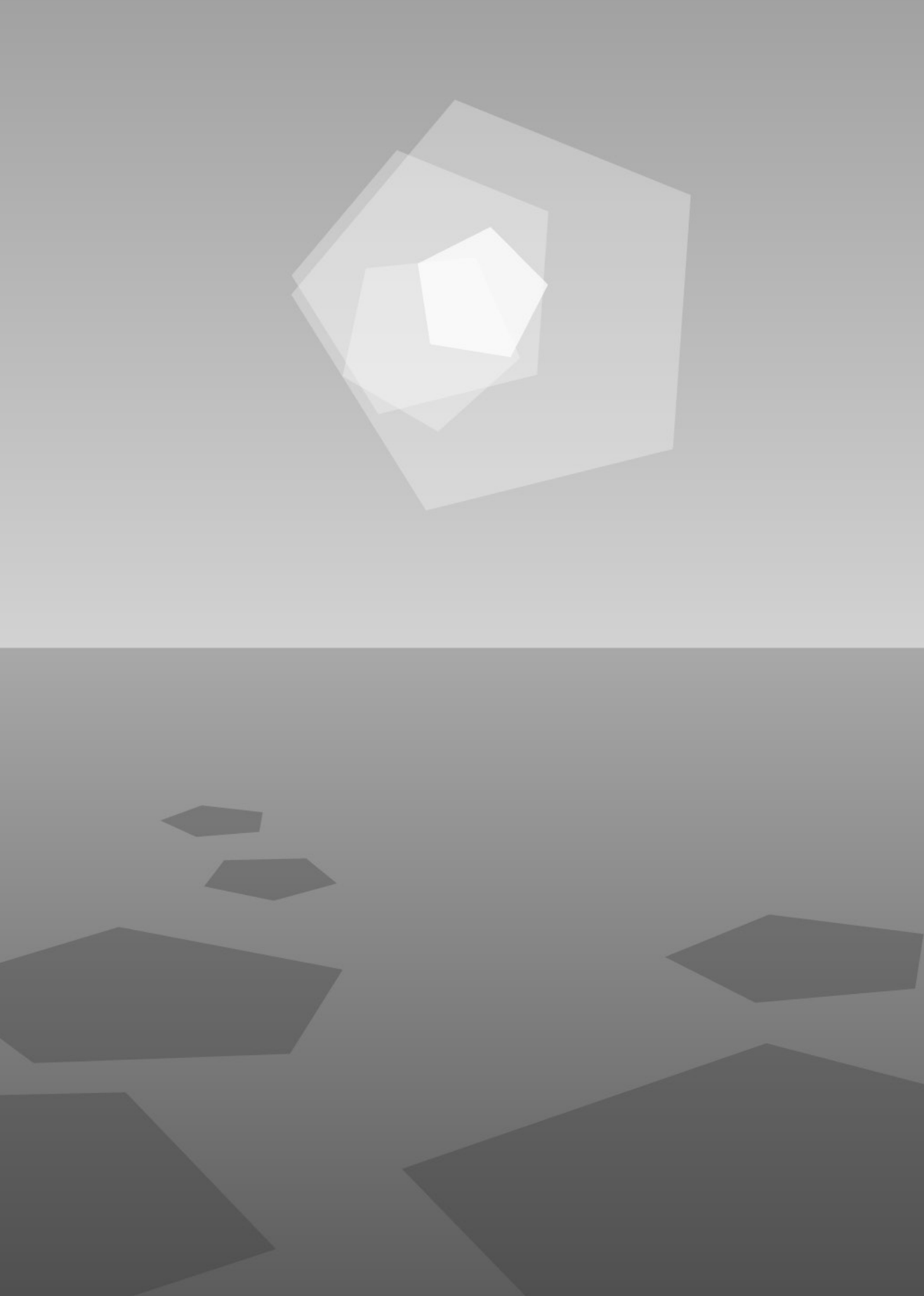
Table 1: Criteria for the case studies

	Asthma	Cardiovascular diseases
Screening		✔
Prevention		✔
Diagnosis	✔	
Treatment	✔	
Mono-genetic sub-types and tradition of clinical genetics		✔

1.3 Structure of the thesis

This thesis is divided in three parts. Chapter 2, part 1, develops a conceptualisation of the meeting between genomics and research on common disease. Chapter 3 presents the research design and methods, which inform the empirical investigation. Part 2, consist of three chapters where I analyse how a space for genomics was created in asthma and cardiovascular disease research, and how this space was structured. The question is approached from three different access points: review papers, workshops and interviews. Through an analysis of scientific review papers in chapter 4, I discuss how asthma and cardiovascular disease researchers developed a space for genomics. The chapter shows the influence of established practice on how the researchers configured the potential of genomics and opportunities of new understandings of disease, prevention, diagnosis and therapy. Chapter 5 presents an analysis the interaction in two workshops that were held with asthma and cardiovascular disease researchers. I explore how they configured the potential contributions of genomics in interaction, and discuss what additional elements of established practice emerged to play a role in shaping genomic. In the workshops, the participants created critical descriptions of genomics' potential for changing clinical practice towards a more personalised and preventive approach. Patient's behaviour and their ability to take action in response to information on risk, was perceived as a key obstacle. In chapter 6, I further explore this point. Drawing on interviews with researchers, I ask what the researchers achieved by creating problematic descriptions of the future potential of genomics for clinical practice. In particular, I explore the interpersonal achievements of using these descriptions, and I discuss what it reveals about the boundaries and structure of the space. In part 3, chapter 7, I come back to my research question and discuss my findings. I draw on my conclusions to develop a forward look and an evaluation of the shaping of the innovation journey of genomics in asthma and cardiovascular disease research.

Part 1



2 Configuring the innovation journey through spaces of assessment

In this chapter, I develop a conceptual tool for addressing the aim of this thesis: to map and to understand the configuration of innovation journeys in science. I focus on the typical pattern of the first phase of the innovation journey as it was presented in chapter 1: the build-up of a protected space, and develop an understanding of this space as a social space defined by discursive action. In this space, storylines for developing a novelty take shape through actors on-going evaluation of the potential of the new option (section 2.1). In section 2.2, I develop an understanding of the general dynamics of sociotechnical change in which innovation journeys are embedded. Actors as modifiers of on-going processes of variation and selection are essential to understanding the opportunities for shaping novelty. Actors are embedded in established practices, which influences their response to an emerging novelty. Established practices are social orders supported by dominant storylines. Storylines order practice, and provide the context for actors to go about their work (section 2.3). In section 2.4, I move from general lessons to a specification of the configuration of innovation journeys in science. The context of science is characterised by cultures of knowledge production. I outline the position of scientific cultures in society to understand the storylines of established practice specific to science. Finally, in section 2.5, I collect the insights from the literature review into a conceptual understanding under the heading 'spaces of assessment'. Spaces of assessment are a description of the social spaces in science, where actors assess and re-produce storylines on the position and role of a novelty in their practice.

2.1 Spaces and novelty

A novelty begins life as a hopeful monstrosity (Mokyr 1990; Schot and Rip 2002): hopeful because actors recognise it as an opportunity for change, and monstrous as its eventual function and impacts are highly uncertain. Emerging science and technology, like genomics, thus introduces new opportunities, but is accompanied by concerns about the extent of, and the consequences of the eventual changes that it will afford. When actors recognise an opening for change, they can actively pursue its materialisation by mobilizing resources to gain legitimacy including symbolic and moral ones (Borup et al. 2006). Spaces, as conceived in this thesis, are the openings that emerge in established order as a response to a novelty.

Actor's mobilisation of resources leads to the creation of a 'rhetoric space' (Van Lente and Rip 1998a:222). The aim of Van Lente and Rip (1998a) was to show the parallel construction of promises and expectations of membrane technology as a worthwhile strategic research area, and the configuration of a social reality of membrane technology. According to Van Lente and Rip, as more actors create connections with the rhetoric space, they mutually position each other in relation to the future of membrane technology, and by that membrane technology is configured and developed. They defined a rhetoric space as *'a locus for particular kinds of events, an opportunity for particular actions, and a gradient for, and thus a constraint on, the range of actions'* (Van Lente and Rip 1998a:222-223). This space is not geographically located, but is rather conceived of as a discursive space. The effect of a discursive space is in how it enables or constrains actors in positioning themselves in relation to the gradient of the space. A space thus has a topic: the potentiality of the novelty, and a structure: the positioning of actors, institutions and organisation in relation to the topic.

Rip and Joly (2005, 2012) further developed the dynamics of spaces by pointing to deliberation, negotiation and aggregation as the key activities. Actors do not just mutually position themselves and others, but deliberate and negotiate their position as well as the promises and expectations of a space. This is how rules of interaction develop together with a mutual understanding of the kind of work the space affords. As the space evolves, aggregation of assessments and positions form a structure for the space. The structure of a space is therefore not a given, but it develops with the space. The concept of space underlines the gradual emergence of a structure for engaging with a novelty. It highlights how the novelty itself is already given shape through actor's articulations of its potential, their own role, and the role of others in relation to developing it. With positioning and the emergence of a structure also comes an implication of boundaries and 'insiders' and 'outsiders' of the space.

Spaces have material and geographical features. The discursive space creates the affordance for actors to engage in evaluations concerning the potential inherent in the topic of the space. These evaluations take place in concrete spaces where interactions occur. Concrete spaces can be journals, workshops and conferences. Abstract spaces lend legitimacy to the creation of concrete spaces and the other way around (Rip and Joly 2012). A novelty, like genomics, thus represents an opening for actors to create social spaces for exploring its potential.

2.2 Actor's response to novelty

The first point to realize is that an innovation journey implies a breaking

up of existing social order and the subsequent reestablishment of a new one (Abernathy and Clark 1985; Rip 2010). The innovation journey is the outcome of the reconstruction of social order. Evolutionary economics offer a fruitful starting point for conceptualising this process; it describes technological development as an evolutionary process of variation, selection and retention (Nelson and Winter 1977). Society forms the selection environment for innovation, and variation in the form of novelties must be nurtured and protected from this harsh selection environment (Nelson and Winter 1977). Nelson and Winter were primarily interested in firms, but as Van den Belt and Rip (1987) showed in their sociological interpretation of the theory, it can be expanded to a general theory of innovation and the emergence of novelty. Reading variation, selection and retention from a sociological perspective also means paying attention to the social dynamics of these processes. Variation in the form of novelty does not just emerge at random. Rather, actors follow heuristics that promise but do not guarantee the development of successful solutions (Van den Belt and Rip 1987). An example, of how actors attempt to influence the selection environment is advertising. Likewise, processes in the selection environment are guided by heuristics for evaluation and decision. An example here could be consumer groups that have developed tests for evaluating new products. In short: variation is not blind, and selection is not independent. One can therefore better speak of a quasi-evolutionary process (Van den Belt and Rip 1987). The key point is that actors anticipate the reception as well as function of a novelty. This anticipation does not only refer to the technical properties and function but equally to societal functions and contexts (Van Lente and Rip 1998a; Wynne 2005).

Garud and Ahlstrom (1997) developed a conceptualisation of patterns through which technologies are assessed. In their description, the shape of a technology and its field is influenced by the pattern of assessment between 'insiders' and 'outsiders', which emerges due to a difference in perspectives. Insiders are *'researchers directly associated with the development of technologies'* (p. 28), while outsiders are *'actors who sponsor, evaluate and regulate technologies, without directly engaging in their development'* (p. 28). These two positions draw on differently structured perspectives to assess the potential of technology. Insiders create scenarios centred on the technology, and they identify obstacles to its development. Outsiders, on the other hand, develop a perspective that is comparative in form. They abstract from the details of a specific technology, so that it can be compared with others. When insiders and outsider meet in a 'bridging event' their interactions are shaped by the difference in the form of their perspectives. Perceptions of the problem to be solved, as well as the appropriate criteria by which the technological option should be judged, differentiate between the insiders and the outsiders. Rip (2006) coined the terms 'enactor' and 'comparative selector', to emphasise the structural difference of the perspectives, and to avoid an emphasis on boundaries between insiders and

outsiders. Enactors and comparative selectors will experience communication problems due to the structural differences in their perspectives, and the divergence in problem definitions and criteria, which they bring to 'bridging events' (Garud and Ahlstrom 1997; Rip 2006). The two perspectives are connected with variation and selection dynamics. Due to historically developed patterns in co-evolution between science and society, scientists and engineers employ enactor type perspectives in promoting a technology or promising finding (variation) while actors from the society sphere draw on selector type perspective (Rip 2011; Shelley-Egan 2011).

The enactor and selector perspective thus refer to the form that anticipation by scientists or engineers will take. However, when it comes to the content of the enactor perspective, actors may choose between contextual elements. Mulkay, Potter and Yearley (1983) argued for attention to the way discourse functions as an interpretive resource for scientists in explaining their worlds. Gilbert and Mulkay (1984) illustrated the point through the identification of the empiricist and contingent repertoires. While the two repertoires refer to the same range of activities, they draw on contradicting contextual elements for explaining beliefs about the natural world. Scientists drawing on the empiricist repertoire construct beliefs and theory as following seamlessly from empirical data. In contrast, scientists drawing on the contingent repertoire problematise this assumption, and draw on contextual elements like interest and other person bound-characteristics to explain beliefs and theories (most often the ones they do not agree with). The empiricist and contingent repertoires open up for understanding how actors can fill in the enactor perspective by choosing between contextual elements.

The notion of a (technological)[16] regime has been developed to describe the situated character of innovation (Nelson and Winter 1977; Dosi 1982; Van den Belt and Rip 1987; Kemp 1994; Rip and Kemp 1998; Van den Ende and Kemp 1999). Scientists as well as engineers working within a regime are guided in their search processes by their beliefs of which directions to follow, what problem to solve, and what knowledge to use. Regimes are characterised by shared normative and cognitive rules and a functional structure, however these rules do not form a perfectly coherent framework, and some parts might be more widely shared than others (Van den Ende and Kemp 1999). For my purpose, the characteristics of a (technological) regime serve as a general understanding of the situatedness of change.

16 In developing the notion of a regime, the authors focus on engineers and technological innovation. However, following the constructivist point of view, the description 'technological' could just as well be technoscientific or techno-social regime. When scientists as well as engineers routinely draw on technical as well as scientific elements, their innovation processes are technoscientific (Latour and Woolgar 1979; Latour 1987). Furthermore, change processes are always socio-technical following the insights of co-evolution between technology (science) and society (elaborated further in section 2.4).

Van den Belt and Rip (1987) described the influence of regimes in how actor's anticipation of variation and selection is shaped by (promising) heuristics. Heuristics are for example ideas of a successful design, the knowledge relevant for developing an innovation and the relevant actors to involve in the process. The reliance on heuristics in developing new science and technology provides directedness to innovation processes. In this sense the actors who respond to a novelty and work to create a discursive space, are enabled or constrained by their embedding in established practice. In addition to established practice as a resource, actors can also draw on more general heuristics for anticipating on the potential of a novelty. General heuristics are not specific to a regime, and include automation and electrification, as broader expectations of the development of a sector or society (Van den Belt and Rip 1987; Rip 2010). The possibility to combine specific and general heuristic opens up for innovation and the possibility for developments to shift in new directions.

The special case is thus innovation proceeding within a technological regime or a stabilised discursive space. The case of the DC-3 aircraft design was used by Nelson and Winter (1982) to illustrate it. The specific design choices of this model of aircraft outlined design directions for engineers for more than two decades. The design of aircrafts was guided by a set of heuristics that engineers expected had the potential for even more successful designs. In the case of innovation within a regime focused on an exemplary design like the DC-3 airplane, there is thus a certain degree of directedness to the innovation process. However, heuristics are not enough. In addition actors must share expectations that continuing work using these heuristics will keep leading to successful designs, and these expectations must be shared within the community of practitioners. Van den Belt and Rip (1987) conceptualised such embedded expectations as a 'cultural matrix of expectations' (p. 155) in which innovation is embedded.

Hyysalo (2006) elaborated on how the anticipatory activities of professional communities are embodied in and recreated through practice. Anticipation or expectations to future technological options are not free-floating, like imagination, but 'practice bound imaginaries' (Hyysalo 2006:600-04). An imaginary is that through which a practice makes sense to actors. Specifically this imaginary, like the cultural matrix of expectations, is bound to *'sets of tools, ways of doing and imagining, desires, expectations, models, procedures and norms are* **bound together** *to form a coherent whole'* (Hyysalo 2006:601, bold font is in italics in the original). The practice-bound-imaginary is, like expectations, also about the desirable future state of the practice, but unlike expectations, it is reproduced through material practice. In the case of emerging science and technology, actors are therefore configured in their responses and in their work of creating a space, by the established practice

in which they are embedded. Discursive spaces include actors from different practices, and so actors have different starting point for exploring the novelty. For genomics, spaces are created in different fields of research on common disease. As I described in chapter 1, asthma and cardiovascular disease differ in their explanations and descriptions of the disease (presence of monogenetic sub-forms, acute, chronic, surgical, lifestyle-related), and the organisation of clinical practice (the presence of screening programs, diagnostic and treatment traditions). The researchers therefore have differing resources and starting points when it comes to responding to the expectations and promises of genomics. In the next section I describe how spaces for exploring novelty are created and become structured.

2.3 Storylines and the structuring of spaces

In this section I draw on insights from the sociology of expectations literature to describe how actors create spaces for exploring novelty. Not only are expectations key to the reproduction of practice, they are also essential for actor's creation of spaces and thereby for organising work on the development of a novelty. When a novelty like genomics is recognised as promising, actors organise their work by constructing and referencing expectations to the future (Van Lente 1993; Van Lente and Rip 1998a/b; Brown et al. 2000; Borup et al. 2006). The sociology of expectations, can be seen as a further development of the general point made by Van den Belt and Rip (1987) of a 'cultural matrix of expectations' as an essential feature of variation and selection processes.

A working definition of expectations is as *'real-time representations of future technological situations and capabilities'* (Borup et al. 2006:286). Expectations, to what the Human Genome Project and the projects following from it will produce, are widespread among many actors. These actors might differ in their interpretations of what the medical, social and academic and business value of genomics will be. Common for all of these groups is the strategic role that expectations play in creating spaces and building agendas within these spaces. Expectations guide actors and act as sources for legitimating choices and help secure funding and interest. In this sense expectations are generative as they facilitate a certain social order implied in the expectations. Expectations are performative, as they do not only serve as reference points for specific futures, but also actually help bring into being structures aimed at their realisation. (Borup et al. 2006)

Actors may voice expectations spontaneously, or as part of deliberative strategies to persuade others, and to enrol them to support their projects. Strategic or not, such anticipatory work can become institutionalised as collective futures to

which large and diverse groups of actors subscribe (Konrad 2006, 2012). Future visions of genomics as contributing to new and improved understandings of disease, along with improved diagnostic methods, therapies and prevention are collective expectations. As are expectations of genomics medicine as personalised, individual and preventative. In the Dutch context, these expectations to genomics are institutionalised in initiatives like the Netherlands Genomics Initiative (NGI), or in the US context the National Human Genome Research Institute (NHGRI). These visions are not only about technological change, but also about changes in understanding and practices as well. Collective expectations form a backdrop for the actors creating a space, and can also be drawn on as resources. There are thus diverse kinds of expectations spread across spheres as well as between actors, groups of actors and expectations embedded in the practice of fields.

In creating a space for exploring novelty, expectations are a resource for actors to draw on. The space that is created is an outcome of actors work to align collective and practice specific expectations into a working structure for exploring novelty. Van Lente and Rip (1998b) described the combination of expectation into a structure of a space as 'prospective structure' (p. 203). Prospective structure is the combination of the collective expectations of a novelty, and the practice specific expectations of actors. Prospective structure facilitates the mutual positioning of actors in relation to the future fulfilment of the collective expectations of the novelty. Key to the mechanism of coordination is the content of expectations and how actors position themselves and others in relation to fulfilling them. Positioning invites others to position themselves in relations to the ever-evolving storyline. Possibilities for action are implied in these prospective structures, and storylines develop to define them and strategies for action.

Through this on-going process of assessment, a structure will emerge for coordinating interactions in the space. This structure includes concepts and ways of understanding, but practical arrangements like research clusters, funding schemes, and journals are also changes related to the discursive structure that emerge. The prospective structure, with which the space was created thus becomes bound into the emerging structure of the space, and so can change storylines of established practice as well as collective storylines of expectations and promises of the novelty.

In introducing storyline as a concept for addressing the development of a structure in a space, I draw on the work of Hajer (1995). Hajer developed the concept of a storyline to explain actor's role in constituting their reality, and to show how discourse becomes hegemonic. Following Hajer:

> *"Storylines are narratives on social reality through which elements from*

many different domains are combined, and that provide actors with a set of symbolic references that suggest a common understanding." (Hajer 1995:62)

A storyline brings order to reality. The emergence of novelty challenges existing order, and in creating a space to explore novelty, actors are faced with the task of reconstructing a reality, and thereby a social order wherein the novelty will fit. To create the storyline of the space they can draw on elements from other storylines. Following the descriptions above, the resources available to actors include practice specific expectations, collective expectations as well as elements from the 'cultural matrix' in which they are embedded. Expectations are just one resource. Other resources used to position and justify the space are metaphors, concepts and ideas (Hajer 1995). Creating and developing a space, is a process of developing a storyline for positioning the novelty in a social reality, and for organising the work of actors.

Hajer's description of storylines can be used to elaborate on Van Lente and Rip's description of the space as having a 'gradient', and thus on how structure emerges through discursive interactions. The strength of a storyline lies in its ability to reduce complexity and to impose order. A dominant storyline will structure interactions, since most actors accept its description of reality. Drawing on the dominant storyline provides an actor with credibility. Storylines rationalise an approach to understanding reality, and they position actors as 'front runners', '(ir) responsible', 'insiders' and 'outsiders' (Hajer 1995). A dominant storyline makes it difficult to construct opposing positions and understandings of reality, since they will not be seen as credible or judged as misunderstood. When a space for exploring a novelty becomes structured, its dominant storyline affect the positioning and interaction of actors. Initially the effect is limited to the space, but if the space gains a stronghold and grows into, or spills over into, the next phase of the innovation journey, the storyline might gain wider acclaim. Going back to the basic dynamic of variation and selection, the question is of course how receptive the selection environment will be. A dominant storyline will thus consist of concepts, models and ways of explaining, which it is difficult for actors not to take on board in developing their storylines. The potential for diverging storylines implying different future directions is still there. However, they are likely to draw on many of the same concept, models and ways of explaining for their ordering of reality.

Hajer (1995) conceptualised the structuring effect of discourse as 'discourse structuration': when the credibility of an actor depends on the use of terms and concept of a certain storyline, that storyline can be said to structure interactions. In other words it enables and constrains the actors possibilities for arguing on the role of genomics. The translation of a storyline into organisational and institutional arrangements is the next step, and referred to by Hajer as 'discourse

institutionalisation'. The storyline is hegemonic and dominates all attempts at engaging with a certain subject matter. In my analysis a structuring effect of terms and concepts of the storyline of genomics points to the influence of the gradient of the space of assessment on the possibilities of other actors to formulate alternative storylines (not using concept and terms from the dominant storyline).

The creation of a space, and the emergence of structure, can now be understood as a process of assessment. In this process, deliberation, negotiation and aggregation are the key activities. I subsume these activities under the term assessment. Assessment covers the evaluative nature of the process. Furthermore, evaluation is always evaluation in relation to 'something else'. Assessment helps to bring out how actors assess expectations, concepts, ideas and metaphors in relation to their place and role in a storyline of the social reality in which novelty will fit. Assessment describes an evaluative process of deliberation, negotiation and the eventual aggregation of concepts, models and understanding into a structure for actors to construct their storylines.

My investigation of spaces of genomics in research on common disease is an exploration of the storylines with which a discursive space for exploring genomics is created, what elements emerge for structuring actor's storylines, and what opportunities for future directions for genomics emerge. The creation of discursive space for genomics has the potential to introduce new concepts, models and understandings of disease, which in turn will affect storylines and future directions of a field of research.

2.4 Creating spaces for exploring novelty in science

In this section I bring the general insights on the dynamics of opening and developing a space back into the context of science. My understanding of science, as a social activity, where data, fact, theories and knowledge is actively constructed is based in insight created in what can be broadly referred to as STS. The work of Robert Merton and Thomas Kuhn are the key inspirations for what is now known as the sociology of scientific knowledge, and which later developed into science and technology studies (STS). Merton's functionalist view of science is an early sociological attempt at understanding what science is. He famously described four norms that guide scientific research: universalism, communism, disinterestedness and organised scepticism (Merton 1942, cited in Sismondo 2004). Science thus progresses because it rewards the people who act according to certain norms promoting knowledge growth and punishing the

ones who hamper it. In contrast, Kuhn suggested that science is organised on ideas and practices, which he conceptualised as making up incommensurable successive paradigms (Kuhn 1962, cited in Sismondo 2004). Kuhn opened the door for a different understanding of science as local both in time and space and of scientists as conducting their work within these local spaces.

Merton and Kuhn kept silent on the content of science and the status of scientific beliefs. Their work however, opened the way for a group of sociologists that made it their mission to understand how scientific knowledge is produced, and how this knowledge becomes accepted as rational and true. The 'strong programme' marked the beginning of this turn. David Bloor (1976) outlined the program that took as its basic tenets the approach that sociologists wishing to investigate science should be impartial to the truth or falsity of these beliefs. In other words, they must treat these beliefs symmetrically. The key argument behind this approach was that scientific beliefs are socially constructed, and thus the mission of sociologists must be to explain why some beliefs gain the status of objective truths about the world, while others are rejected. (Sismondo 2004; Pinch and Bijker 1984; Knorr-Cetina 1983)

A constructivist understanding of the world implies three assumptions: one, reality is socially constructed, two, the construction of social reality demands active participation from social actors, and three, science and technology are not natural (Sismondo 2004). The first claim amount to saying that if people believe something to be real they act as if it was real, thereby reinforcing a specific social reality (Berger and Luckmann 1966, cited in Sismondo 2004). In science, reality is made up of disciplinary boundaries, epistemologies and methods (Sismondo 2004). The second claim is about the contingent nature of the social divisions of reality. Scientists and other agents (be they human or non-human) perform work in order to establish facts and boundaries. The third claim is about the unnaturalness of the objects that scientists work with. Natural objects in the laboratory setting are changed in three important aspects: the object 'as it is', the object 'where it is' and the object 'when it happens' (Knorr-Cetina 1999).[17] The concept of co-evolution emphasise, that although technologies and science social activities and as such shaped by dynamics in the society sphere, societal dynamics are also shaped by and dependent on dynamics in the science and technology spheres (Sørensen and Williams 2002).

Fujimura (1997) described the construction of 'proto-oncogene' research as the

17 That scientists construct facts about nature instead of simply discovering and reporting on natural facts, is a related point from the famous laboratory studies in SSK/STS (see for examples. Latour and Woolgar 1979; Lynch 1979; Knorr Cetina 1981; Zenzen and Restivo 1982; Law and Williams 1982; Traweek 1988).

solution to the question of what cancer is and where it originates. The creation of a new realm in science was an accomplishment of the collective work of scientists across the spectrum of research traditions and disciplines, but also including actors beyond science. Congress, industry and shareholders also had to be aligned to contribute to the positioning of proto-oncogenes as a promising solution to cancer. To achieve such all encompassing alignment the scientist were assisted by protocols, standard storylines and standard technologies, like the OncoMouse™, to present proto-oncogenes as a 'doable' problem.

> *"Proto-oncogene research problems became doable through the transformation of the world inside and outside the laboratory. By 1983 proto-oncogenes and many different research worlds had been co-constructed." (Fujimura 1997:11)*

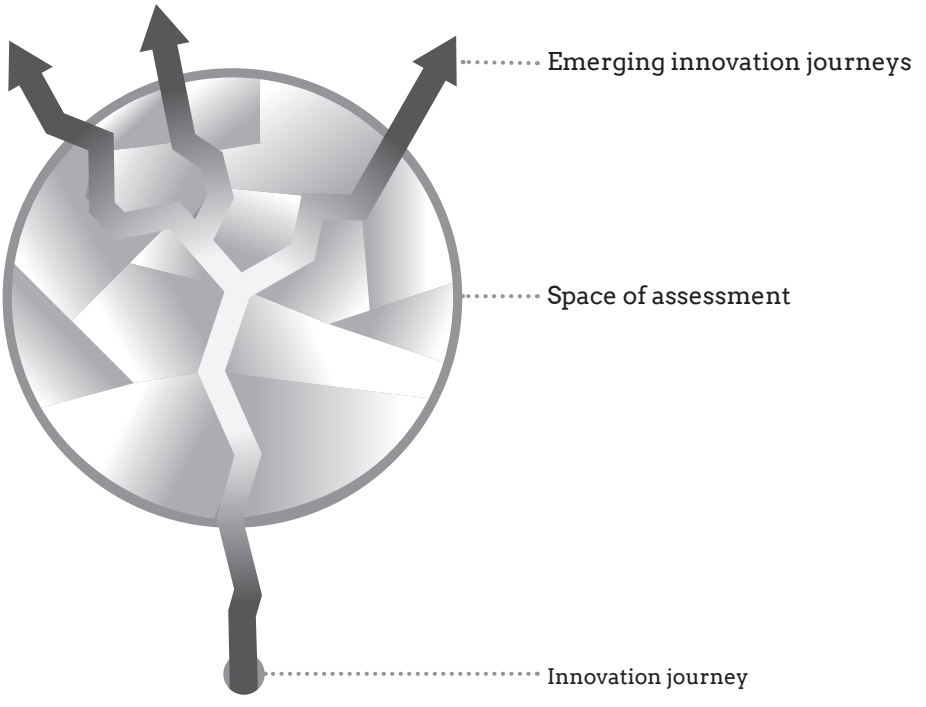
The example of proto-oncogene research shows, how the creation and development of a space in science is achieved through collective efforts among actors from different disciplinary backgrounds. Furthermore, the space is not completely isolated from the surrounding world, but dependent on aligning with actors in the world outside science. The nature of the alignment between the space in science and the surrounding world can be pictured as a 'contract' (Hessels, Van Lente and Smits 2009). A division of work emerges, with scientists trading promises of future benefits for funding and the mandate to work in a relatively protected space with few checks and questions from the outside world (Shelley-Egan 2011). The space in science is thus structured by the development of a storyline about how it will solve an on-going scientific as well as social problems. Fujimura showed how proto-oncogenes became a central concept which actors from many different disciplines could draw on to develop storylines of how to solve problems in their research as well as clinical practices. In the last section of this chapter I collect the insights from the above literature review, and propose 'spaces of assessment' as an integrative concept for describing the process of creating a space to explore novelty.

2.5 Spaces of assessment

I suggest conceptualising the shaping of genomics within different areas of disease research as taking place in 'spaces of assessment'. Spaces of assessment refer to discursive spaces wherein actors mutually position themselves and others in relation to a promising opportunity (in this case genomics). Spaces of assessment are initially spanned by: the promises and expectations of a novelty, and the storylines of the established practice of the actors who are creating the space. As the assessment activities unfold, a dominant storyline emerges

which align the promises and expectations of the novelty with storylines of established practice into a dominant storyline on the future potential and function of the novelty. The development of the dominant storyline has the potential to influence actor's storylines of established practice, as well as the promises and expectations to the novelty. This change is part of an alignment process where actors continuously assess the potential of the novelty to contribute to established practice. They will try out different positioning of the novelty in terms of its contribution to solving on-going problems of practice as well as societal problems. In the process of positioning the novelty in a storyline, its potential and the form of scientific and societal problems are "fitted" together.

Figure 2: Spaces of assessment



A key characteristic of spaces of assessment is that they emerge in relation to novelty. Spaces emerge when actors recognise an opportunity for doing something differently. The space for genomics of disease x is created by researchers with expectations that genomics will contribute to research on common diseases. However, the actor's definition of the kind of contribution might differ. To make it

concrete; with genomics and the Human Genome Project emerged a space for doing genetics differently. This space is felt by researchers as a novel opportunity to explore a possible genetic component to common disease. As researchers on common disease act on the emerging opportunity of genomics, they create spaces for genomics in their area of research. With the creation of this space, they also re-define common disease as having a potentially relevant genetic component. A space thus emerges in relation to promises and expectations (both utopian and dystopian ones) about future outcomes of an emerging science and technology (in this case genomics). As actors from different fields take up and assess expectations and promises of genomics, they create specific spaces for genomics. The spaces might become structured on diverging or similar storylines on the potential of genomics for solving research and societal problems. As interactions develop, a structure aggregates as key concepts, models and ideas of describing and understanding the potential of genomics stabilise. This dominant storyline will structure interactions among actors. A reverse of roles occurs. From creators of a storyline on the potential and contribution of a novelty, the actors become entangled with their storyline and the roles and positioning which it suggests. In the case of genomics, the researchers first have to convince other researchers that genomics is the solution to problems of understanding and researching the disease as well as problems in clinical practice. However, once their storyline stabilises and becomes collectively shared, they are bound to their storyline and a possible genetic component becomes a certain genetic component.

The first event in the creation of a space of assessment is thus the recognition by actors of a promising novelty. The novelty will be cast in terms of expectations of how it will help to solve on-going problems. Genomics was originally cast as a solution to the limited power and labour intensive methods of genetics, as well as a solution to problems with understanding preventing and treating common conditions. Researchers within a field of common disease research link up with such expectations but modify them to what they see as the relevance of genomics in relation to the ‘issue at hand’ for their research area.

3 Research design

In this chapter I outline my research design for investigating and analysing the shaping of established practice and expectations of emerging science and technology and the outcome in terms of a storyline on the potential and contribution of genomics to common disease research and clinical practice. I conceptualise the process of developing a storyline as an effort of opening up and developing a space of assessment. The spaces of assessment afford a space for researchers to explore genomics and to experiment with the shape of its contribution. As the space develops a storyline emerges that structures a new social order in where the position and role of genomics is defined. If successful, a storyline will structure interaction in the space and function as a reference point for the researchers in understanding the role and contribution of genomics.

My approach to studying spaces of assessment is and the influence of established practice in configuring storylines is first of all a qualitative approach. Since the goal is to compare the opening up and structuring of a space of assessment, the basic design is a multiple case study based on qualitative methods. In general qualitative studies are thought to be better suited to explore the intricate interweaving of the phenomena under study and its context, and to be suited for answering "why" of "how" question (Yin 2003). Qualitative case studies provide the opportunity to draw on a variety of data sources to explore the phenomena of interest from different access points, and so form a nuanced description of a phenomena (Yin 2003; Silverman 2006).

The choice for a multiple case study is made to test the theoretically informed assumption that established practice will influence the creation and development of the storylines of spaces of assessment. In my design, I therefore want to explore two case studies, which differ in terms of the established practices from which the researchers can choose elements to combine with the promises and expectations of genomics. The results of the two case studies are thus expected to differ but for predictable reasons. In chapter 1, I described the context for genetics in the current health care system. I argued for the absence or presence or a tradition for clinical genetics, together with a practice orientation with differing emphasis on the elements screening, prevention, therapy and diagnosis, to be the key element that would influence the construction of storylines on genomics. In this chapter I present and discuss my methods for data collection, and elaborate on the principles of analysis for each data source.

3.1 Methods of data collection and analysis

The data collection in this thesis is based on three sources of data: documents, interviews and participant-observation in workshops. The research strategy is built as a three-step approach, where each step builds upon information from the previous step. The first step in the research design is the analysis of scientific review papers. Analysing review papers provides access to how, and with what discursive resources researchers open up a space of assessment for genomics in asthma and cardiovascular disease research. The reviews reflect the efforts of dedicated actors, and is a way of tracing in relation to what elements of established practice and expectations the storyline of the space is created, and if and how the storyline changes over time. Review papers, thus gives an overview of the creation and development of a space of assessment and a storyline for genomics in asthma and cardiovascular disease research. The second and third step consists of interviews and workshops. The interviews and the workshops provide to additional access point to the spaces of assessment and the storylines that structure them. The workshops probe interactions at the level of storylines and how they structure interaction among researchers. The interviews shift the focus to how certain elements from storylines are mobilised in interpersonal interaction. Each of the three methods opens a window onto on-going dynamics, and together contributes to answering how researchers construct a space of assessment for exploring genomics. In the following section, I argue in more detail for the use of each method, explain the procedure I followed for using and analysing the data.

3.1.1 Scientific review papers

The first step of the research strategy consists of an analysis of scientific review papers. The aim of the analysis is to trace the creation and development of spaces of assessment for genomics. I trace this process through an analysis of how researchers create the linkage between genomics and asthma or cardiovascular disease at three separate points in time. The analysis will show in relation to what elements of established practice and with what expectations to future contributions in research and clinical practice the storylines of the space is created.

Review papers are a highly accessible area of science. They belong to a particular group of academic papers, since they represent an interpretive effort on the part of the author(s) to create an overview of the past, present and future of a scientific field (Myers 1990, 1991). Review papers are meant to be useful, not only for researchers within a field, but also convincing to researchers outside or on the

fringes of a field. Their originality lies in the discrimination and interpretation of on-going work. Myers (1991) argues that review papers shape the literature of a field into a story, to enlist the support of other researchers in continuing that story. Reviews encourage speculation on the future work that will give shape to this story. The persuasive power of reviews arises from their ability to enlist readers, and to make them see their own work as part of the on-going story. *'Taken together, they can make or reflect changes in the discourse of a field'* (Myers 1991:61). Generalisation and discussion of terms is a sign of a process of stabilisation/generalisation (Myers 1991). In review papers, actors thus highlight what they see as the history, i.e. the past, present and future of their field; review papers are therefore particularly helpful in providing insight into how actors create links between specific expectations and existing structures. Tracing the evaluative process through which genomics is linked with certain areas of disease research, therefore gives insight into how the space of assessment is created, develops and how its structure (begins to) influences the assessments of the medical scientists.

The reviews for each case study were found through a bibliographical search in the ISI Web of Knowledge. Table 2 illustrates the strategy.

Table 2: The iterative process of selecting reviews for analysis

	Asthma	Cardiovascular disease
Keywords used searching the ISI Web of Knowledge	"asthma OR bronchial hyperresponsiveness" AND "genome OR genomics"	"cardiovascular disease" AND "genome OR genomics"
Reviews found (total/final selection)	130/13	214/15
Date of search	May 1 2009	May 21 2010

The initial sets of reviews contained 130, and 214 review papers for asthma and cardiovascular disease research, respectively. I narrowed down the sample by focusing on reviews at three points in time. Furthermore the main criteria were that the review appeared in a high-ranking journal, had a general title and belonged to one of the ISI categories dominant in the set. To reach the final selection, recognized experts in asthma genetics research and cardiovascular genetics research were consulted. The possible bias, introduced by such a consultation, was minimized by the simultaneous application of my own selection criteria. The first data point of interest was the creation of a link between genomics and

the two areas of research. The third data point was picked as close to the time of search as possible, and for the second data point, a time in between points one and three was picked, in order to look for changes or shifts in assessments. Eventually I ended up with a relatively small sample of reviews. The sample size is a consequence of the selection criteria. An overview of the reviews is found in appendix E. The iterative procedure of selecting the reviews is documented in logbooks, which can be acquired by contacting the author of this thesis.

The reviews were analysed in several rounds. I coded pieces of text describing expectations to what genomics would do for the research practice in question, pieces on how the authors described the definition and explanatory models of disease. Then the selected text pieces were compared, first within the sample of reviews and then between the reviews in the two cases. For example, comparing the different ways in which the explanatory model of asthma was described in the reviews from 1999 with the description in reviews from 2008, and then again with how cardiovascular disease was described in the reviews of that case. I compared descriptions of how the outcome in terms of additions to clinical practice was described and how it did or did not change over the years. Finally I went through several rounds of writing and checks and comparison with the text in order to arrive at my analysis.

3.1.2 Interviews

In addition to the analysis of scientific review papers, open-ended interviews with asthma, cardiovascular and genome researchers were held. The interviews provide access to the experience of individual researchers. As a research tool, interviews are a highly targeted method in that the topic of the case study can be directly addressed in interaction with people who are part of, and have access to unique information on the topic under study. The interviews thus provide data on the perspectives of the actors, and what parts of the storylines of the space of assessment they draw on, and how they assess it in relation to what elements of established practice.

Interviews are collaborative social encounters where versions of reality are co-constructed. These versions of reality are at once the production of the specific interaction in the interview, and a re-production of broader social context and norms. (Rapley 2004) The window that the interviews open to the space of assessment is thus not to the space as it exists ‘out there’. Rather, it is a window that is constructed in interaction in the conversation between the interviewer and the interviewee. In the process of the specific interview, the

interviewee draws on broader contextual elements. These broader contextual elements are elements of the storyline of the space of assessment that are felt and made useful by the interviewee. Storylines are explanatory resources for positioning the interviewee as well as the relevance of genomics in the interview and in local and global contexts. The elements of the storyline of genomics that the interviewees use, give insight into how the structure of the space afford the interviewee specific options for engaging with genomics.

I conducted 20 one-hour interviews with medical scientists in the Netherlands and the US. Three of the interviewees are primarily genome researchers (two of them the US researchers) with an interest in research on common disease, of the remaining, seven work within asthma research, and use genomic methods, and ten work within cardiovascular disease research and use genomics methods. The US interviewees are based within the National Institute of Health (NIH). The Dutch interviewees work within a range of Dutch academic hospitals, research clinics or/and larger pharmaceutical companies. In the process of locating interviewees I used two strategies. For both research fields, contact with a knowledgeable informant was established as part of writing the proposal for the research project. I contacted and interviewed these informants, to get information on the structure of their field and persons to interview. In each of my interviews I solicited the interviewee for other persons to interview. I also searched in the Dutch database NARCIS, in which the large majority of persons conducting research in the Netherlands are registered. I looked for persons reporting asthma or cardiovascular disease together with genomics as their field of interest. I subsequently read through their research and bibliographic description, and on that basis decided if they were candidates for an interview.

I used the outcome of the analysis of the review papers as background knowledge in the interviews. Four main topics were used to structure the interviews; important developments in research in the last 10-15 years, current challenges for research, perspectives on future developments and thoughts on future contribution of research to clinical practice. These categories remained stable during the whole interview process. However, in each interview the questions were specified to fit the context of the interviewee. I used a digital recorder during each interview. The interviews were transcribed to word-level accuracy. Most of the interviews were conducted in English, but 2 were in Dutch. A standardized interview protocol is attached in appendix D.

In analysing the interviews I wanted explore the interpersonal effect of drawing on certain elements of the storyline of genomics. I therefore draw on analytical principles from discourse analysis. Discourse analysis encompasses

a range of approaches to understanding as well as analysing talk. Common for social scientific approaches to discourse analysis is the move away from seeing language as a neutral tool through which you can learn about the real world and what people really think. Instead language is part of the tools with which we construct our world and ourselves. Accounts of reality are necessarily selective and therefore they should be understood in relation to their situated use and effect (Potter 1996; Sacks 1992). Key differences between these approaches are how context and people are understood (Te Molder 2009).

I draw on discourse analytical principles, which see people as active sense-making agents, who in order to make sense of and construct their world use context reflexively. Context is understood as the storylines and elements thereof, which are available to people. Context is thus both a resource as well as a constraint. Discourse analytical principles, makes it possible to show how actors use (elements of) storylines to mutually position themselves and others as well as the relevance of genomics.

The analytical principles of discursive psychology are used for analysis. Discursive psychology shares with other discourse analytical approaches an understanding of language as an actively constructed tool. Accounts of reality are necessarily selective and therefore they should be understood in relation to their situated use and effect (Potter 1996; Sacks 1992). The crux of discursive psychology is to understand how descriptions are made available in talk for particular interactional purposes, such as blaming, shifting responsibility or building specific forms of expertise. Analysis focuses on discursive actions in sequence, and draw on the turn-by-turn development of a conversation to make sense of the social actions achieved by participants. The way conversational partners treat and understand each other's talk is therefore an important focus points for the analyst. In addition to the turn-by-turn development of a conversation discursive psychologists use the rhetorical principle (Potter and Hepburn 2005; Woffitt 1992). The analyst considers why a specific version of reality is produced at certain moments in the conversation. A claim to a certain version of reality functions to undermine alternative versions, and alerts the analyst to the interactive purpose of a specific construction. It is important to notice that we do not make any claims with regards to the truth-value of accounts, nor report on what people really think or feel. Instead the aim is to analyse the interactional achievements of participants' talk by the active deployment of particular interpretive repertoires.

3.1.3 Workshops

As the third step in the research design two workshops were held: One for asthma researchers and one for the cardiovascular disease researchers. The asthma workshop was held on February 4 2011, while the cardio workshop was held on June 1 2012. The aim of the workshops was to explore the storyline of genomics in asthma and cardiovascular disease research and thereby the structure of the spaces of assessment. Specifically, to probe how researchers deliberate and evaluate storylines on genomics and asthma or cardiovascular disease research. The use of workshops to explore storylines of stakeholder groups is an established research methodology in constructive technology assessment (CTA).[18] In CTA research, workshops in combination with scenarios have been used for experimenting with broadening the discourse of stakeholders to facilitate learning (Van Merkerk 2007; Robinson 2010; Te Kulve 2011; Parandian 2012). Workshops provide insight into the macro cosmos of the researchers and the storylines on disease, which are used (Te Kulve 2011; Parandian 2012). The workshops are a way of situating the space of assessment at a physical location to explore what storylines structure and order the spaces of assessment and the interaction of the researchers. Key conditions in relation to the expected outcome of the workshop are how interactions are initiated, the composition of participants, moderation and setting of the workshop.

In setting up the workshops, it was assumed that the participants were aware of the storylines of the space of assessment in the review papers.[19] The question for the workshops was, how the space of assessment is re-created in each case, and what storylines the participants drew on to align genomics with their area of research. However, it was also assumed that the alignment of genomics with asthma or cardiovascular disease research presented a dilemma for the participants. To facilitate the researchers in addressing dilemmas, the analysis must identify these dilemmas and use them to initiate interactions (Parandian 2012). The first task of the analyst is therefore to analyse how researchers themselves address or discuss the place of genomics in order to identify contradictions and contestation among accounts. For this I analysed policy documents and scientific articles as well as opinion pieces on arguments for or

18 My aim with the workshops is to 'broaden and enrich' the discourses of the participants. Therefore I also do not introduce scenarios of possible future developments as this type of CTA workshop is known to do. Instead I use the workshops to get at the macro cosmos of the researchers, and the storylines of genomics that are part of their world.

19 That is that the asthma researchers are aware of the story-line of genomics as a whole-sale transformation, and the cardiovascular disease researcher aware of how genomics is positioned as a broadening the success of genetic research of monogenetic conditions to the common complex cardiovascular diseases.

against genomics. Likewise, I drew on the data from my interviews and from reading the review papers. Each workshop was thus initiated with a 10-minute presentation of an outsider's perspective on dilemmas facing the research area in the positioning of genomics (Presentation images can be found in appendix F).

As a researcher and an organiser of a workshop designed to probe into the dynamics of a field of on-going research, one faces the challenge of linking up with the concerns and perspectives of the participants, while still retaining a design and theme suited to answering ones research questions. In order to link up with participants concerns the themes were formulated on the basis of the how expectations to genomics were formulated in the reviews and the interviews. The general themes were then formulated as 'provocations' to 'taken-for-granted' expectations. This stance is possible since the analyst is an outside agent anyhow, and might as well play on this role in order to draw out actor's justifications for specific expectations. It also opens up for interpretations of participants with less positive/alternative interpretations of general expectations.

The two themes of the workshops were open-ended as to stimulate actor's own articulations and attempts at formulating alignments. The participants received an invitation, where I briefly diagnosed current developments and challenges for genomics and asthma or cardiovascular disease research. In it I asked questions about priorities in research as well as eventual benefits. The document hinted at tensions in the field as to how expectations to genomics should be interpreted for their area of research (Appendix B). In addition to the invitation the participants received a program (Appendix C). The decision, to only provide participants with a rather limited 'work-package' beforehand was based on a concern with influencing the discourse of the participants as little as possible. I wanted to probe into their justificatory discourses, and not have it 'tainted' by any terminology or representations, which I might bring into the workshop The workshops were set up to initiate discussion on two major themes: the future potential of genome-based methods for asthma or cardiovascular disease research, and challenges of translating findings into clinical practice. These two themes echo broad and general expectations to genomics.

For a fruitful discussion, it is important to pay attention to the composition of the workshop participants. For a productive discussion one should aim for optimal heterogeneity (Robinson 2010), which is somewhere between homogeneity and extreme heterogeneity. In my case the basic rule for selecting participants was that they were involved with asthma or cardiovascular disease research and that they were senior researchers. The aim was to get together groups that would represent the disciplinary mix of researchers that perform research the

diseases, including both researchers involved with genomics and researchers not directly involved genomics. In this way I aimed to cover as much of the macro space as possible, thereby capturing a diversity of storylines on genomics. The participants were found by searching through the Dutch database NARCIS, in which the large majority of persons conducting research in the Netherlands are registered. I identified persons listing asthma or CVD as their research interest. I cross-referenced the selection with recommendations from my key informants.[20] For the comparative research design, it is important that the selection of participants represent the same groups of disciplinary backgrounds. Each workshop had participation from the disciplines: pulmonology/cardiology, epidemiology and genetics/genomics. However, there are also differences in the composition and disciplinary backgrounds of the participants. The different disciplinary background provides an insight into the complexity that makes up asthma or cardiovascular disease research. My data set is however too limited to conclude on general structural differences in the disciplinary background of the researchers exploring these conditions. In each workshop I also invited an outside expert. These experts were not involved with asthma or CVD particularly, but are researchers on the application of genomics for researching common diseases. In order to facilitate the researchers in mobilising diverse storylines on genomics, the two experts were invited to prepare a commentary as a reaction to the discussion of the other workshop participants. In practice, the two experts mixed into the discussion during the workshop as well.

As part of the recruitment process, I discovered that some researchers had a strong reaction to the topic 'genomics'. I attempted to frame the workshops rather neutral. The titles were 'Future visions of prevention, diagnosis and therapy for xx research: priorities in xx research'. Still, some invites declined stating a lack of expertise or lack of desire to discuss genomics. This finding indicates a bias in the workshops towards participants interested in/ engaging with/taking part in developing genomics. It also indicates that there might exist a stronger division on the storylines that researchers use to position genomics than what comes out in the workshops.

An experienced moderator from the Dutch Centre of Society and Life Sciences (CSG) led the discussion in the workshop. The moderator has no direct relation to the research project or the themes under discussion. The task of the moderator was to intervene in case participants strayed of course, in case discussion would

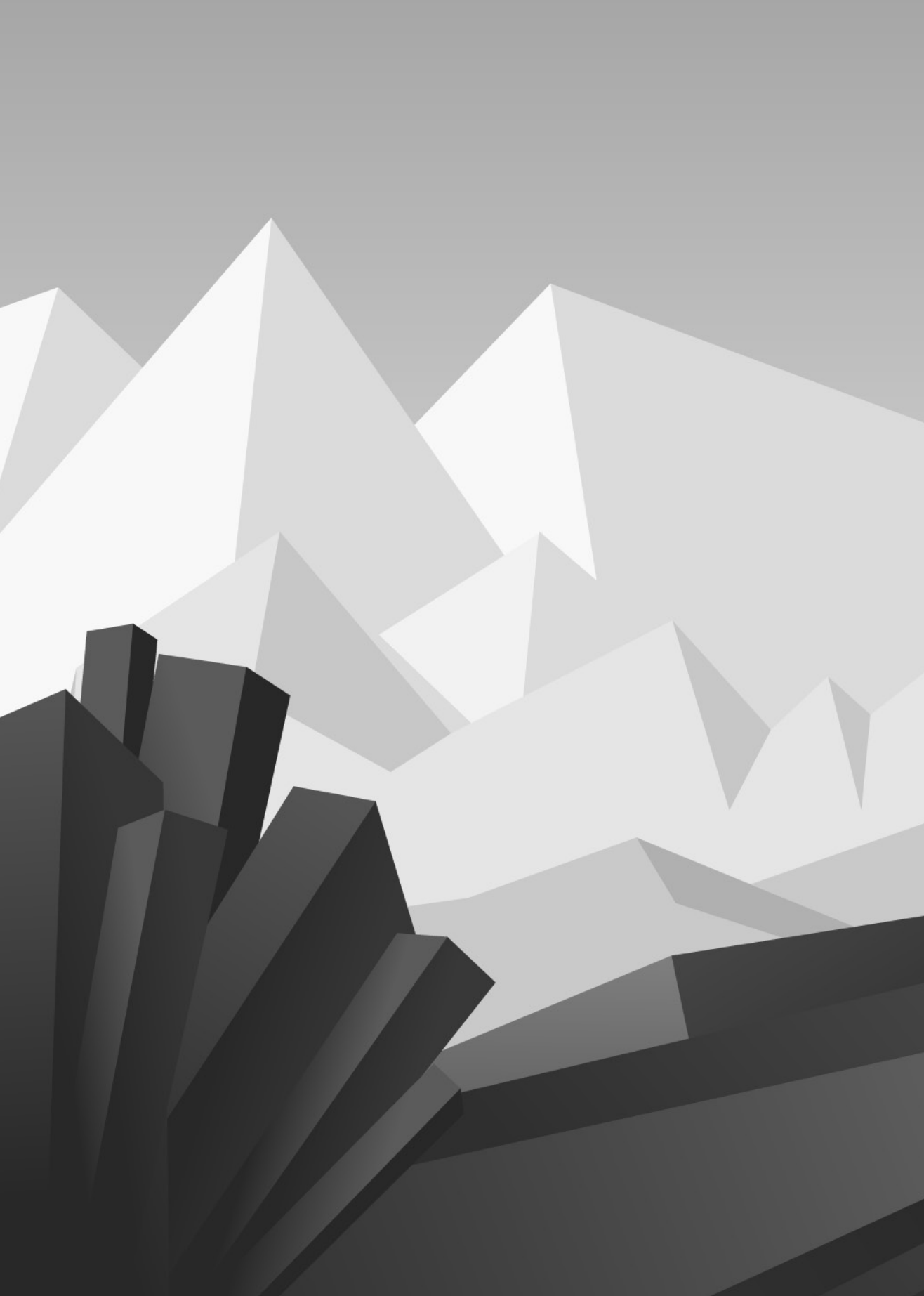
20 As explained in the previous section (3.2.1), during the upstart of the project collaboration was sought with a key informant in each research area. These key informants provided information on the developments within their research field, and gave advice on people to contact.

stall, to get a hearing for all participants, and to manage time. Discussion in the workshop was so intense that the moderator only had to intervene very minimally. Two additional observers were present to monitor the workshop, and take pictures. My role in the workshop was limited to an introduction to the workshop and recording the discussion. The workshops, except for my introduction, were carried out in Dutch. Both workshops were digitally -and audio recorded and transcribed to word-level accuracy. The audio recordings were mainly used to assist in matching statements on the digital recordings with participants in the workshop. Recordings and transcriptions are in the possession of the author of this thesis. The PowerPoint presentations, which supported the 10-minute introductions to the workshops, can be found in appendix F.

The workshops were analysed using the software tool ATLAS.ti, which is developed for qualitative data analysis. Sections of text where contestations emerged on the contribution of genomics to research and clinical practice were coded. Summaries of the interaction throughout the whole workshop were written and analysed in relation to the context of the whole conversation. This was done to get an understanding of the responses of the participants, if they were just referring to statements in the immediate interaction or also to statements given at other points during the talk. The general narrative of the two workshops was compared, to discover differences and similarities in the construction and in contestations on genomics. The process was repeated several times, simultaneously writing up the analysis of the two workshops. The interaction in the workshop show, what storylines are shared and which ones are contested.

In part 2 of this thesis I present the results of my empirical investigations. I begin with the analysis of the opening of spaces of genomics in review papers.

Part 2



4 New destinations: Creating spaces for genomics

The Human Genome Project (HGP) enabled an opportunity to do things differently in research on common disease. Until that point, tools for exploring genes to disease were suitable for finding highly penetrant genes.[21] The data and tools from the HGP allowed new search strategies for less penetrant genes assumed to be involved in common disease. Information on single-nucleotide polymorphisms (SNPs)[22] allowed researchers to look for associations between a polymorphism and the expression of disease in the whole of a population (as opposed to a family). The advent of DNA chips (also called microarrays) made it possible to analyse the expression of multiple genes simultaneously. Thus, the HGP opened a space to move from genetics and its focus on single genes to genomics and a focus on multiple genes (Collins 1999). In this chapter, I analyse how researchers took up this opportunity for doing things differently in asthma and cardiovascular disease research. In each case the researchers created a space of assessment, and through it an innovation journey of genomics took shape. An overview of the procedure for selecting reviews is given in Table 3.

Table 3: The iterative process of selecting reviews for analysis

	Asthma	Cardiovascular disease
Keywords used searching the ISI Web of Knowledge	"asthma OR bronchial hyperresponsiveness" AND "genome OR genomics"	"cardiovascular disease" AND "Genome OR Genomics"
Reviews found (total/ final selection)	130/13	214/15
Date of search	May 1 2009	May 21 2010

21 Penetrance is expressed in the percentile with a mutation that will lead to the expression of the disease (phenotype). When the penetrance of a gene is 95%, 95% of the individuals with that mutation will go on to develop the disease, while the remaining 5% will not develop the disease.

22 SNPs are single base-pair changes in stretches of DNA that differ between individuals of a biological species. SNPs can affect an individual's risk of developing a disease; stretches with mutations are therefore compared in order to discover associations between SNPs and disease outcome in populations.

The initial sets of reviews contained 130, and 214 review papers for asthma and cardiovascular disease research, respectively. A first step towards narrowing down the sample was to focus on reviews at three points in time. Furthermore the main criteria were that the review appeared in a high-ranking journal, had a general title and belonged to one of the ISI categories dominant in the set. In reaching the final selection, recognized experts in asthma genetics research and cardiovascular genetics research were consulted. The possible bias, introduced by such a consultation, was minimized by the simultaneous application of my own selection criteria. The first data point of interest was the initial creation of a link between genomics and the two areas of research. The third data point would be as close to the time of search as possible, and the second data point at a time in between, in order to look for changes or shifts in assessments. The resulting sample size was relatively small. The sample size is a consequence of the selection criteria.

In order to create a space of assessment for genomics, researchers must enrol other researchers by convincing them that it is a worthwhile approach. In the review papers, literature on the two research practices and the promises and expectations of the contribution of genomics are shaped into a storyline. One aim is to encourage others to speculate on the future work that will give shape to the storyline. The persuasive power of the reviews thus derives from their ability to enlist readers, and to make them see their own work as part of the on-going storyline. In telling the story, the authors connect the past, present and future of the research practices with genomics to create a promising storyline. They align genomics with established research and clinical practice. In this process of alignment, the purpose and problem definitions of genomics and established practice are brought together. The eventual storylines of the spaces of assessment reflect the influence of this 'fitting' process. For example, the space that emerged for genomics in asthma research was characterised by a storyline that positioned genomics and related 'omics' approaches as *the* solution to figuring out the cause and development of asthma, as well as to improvements in clinical practice. Conversely, the space emerging in cardiovascular disease research characterises genomics and related approaches as comprising *part of* an on-going effort of investigating a genetic component and it function in cardiovascular disease, which begun with the monogenetic cardiovascular diseases. Most importantly however is how genomics might *add to* established practise of prevention. In this chapter, I first analyse the creation of a space of assessment for genomics in asthma research. The space is initially characterised by a storyline attempting to connect genome-based expectations and findings with already established knowledge in the field. However over time, the story takes the shape of an effort to frame the exploration of a genetic component to asthma through genome-based methods as a true reconstitution of the field. In section 4.3, I analyse the process

for cardiovascular disease research. In contrast to asthma research, the space created for genomics is framed throughout as an addition to existing practices.

4.1 Aligning asthma and genomics[23]

4.1.1 Rising expectations (1999)

In 1999, on-going efforts taking place under the heading of the HGP constitute the common reference point for collectively shared expectations that genes for asthma can actually be found (Anderson and Cookson 1999; Los, Koppelman and Postma 1999; Moffatt and Cookson 1999; Wiesch, Meyers and Bleecker 1999):

> *"The Human Genome Project is working hard to sequence the human genome and will probably detect new candidate genes implicated in the pathogenesis and severity of asthma. The identification of asthma susceptibility genes will probably provide more insight into the identification of individuals at risk of asthma in the near future and open the way for early prevention." (Los et al. 1999:1222)*

Results from the HGP project are expected to greatly aid asthma researchers in their efforts to unravel and understand the genes possibly part of asthma. While there is a long-established agreement among asthma researchers that genes must play a role in the aetiology of asthma, it is the flow of information from the HGP, which raises expectations that genes for asthma can actually be found. Simultaneously, the authors of the reviews conceive of a future health care structure in which more specific knowledge about genes plays an important role. Within this future structure, the focus is on the identification of susceptible individuals and the optimisation of diagnosis and treatment (Anderson and Cookson 1999; Los et al. 1999; Moffatt and Cookson 1999; Wiesch et al. 1999). The model that is conceived for the future thus contains a novel element in terms of prevention, but it also adds to established health care practices of diagnosis and treatment:

> *"Genetic studies of asthma continue to provide insight into the pathophysiological mechanisms of the disease. This should ultimately lead to new and more effective therapeutic interventions, new diagnostic tools for presymptomatic diagnosis, the development*

23 Substantial sections of the analysis of asthma have been published in Bitsch, L. and Stemerding D. (2013). The innovation journey of genomics and asthma research, *Sociology of Health and Illness* 35(8)

of strategies for disease prevention in susceptible individuals, and delineation of the interaction between genotype and the response to specific treatments (pharmacogenetics)." (Wiesch et al. 1999:900)

In the above extract, genetic studies of asthma are linked to continuous efforts to understand the pathophysiological mechanisms of the disease. By framing genetic studies as an activity that has already contributed to the knowledge base of asthma, these studies take the form of *'perceived established structures'* (Konrad 2006), which create a sense of stability and continual progress. In turn, this move justifies collective expectations of the way in which growing insights in the role and function of genes will lead to the ultimate aim of disease prevention and the optimisation of diagnosis and treatment.

The link to on-going efforts is laid down by presenting genetic factors as the key to solving principal and vexing questions in current asthma research. In particular, asthma researchers are struggling to understand the environmental factors that may explain the development of asthma, as well as the question as to why only some develop asthma in response to the presence of these factors (Anderson and Cookson 1999; Los et al. 1999; Moffatt and Cookson 1999; Wiesch et al. 1999). In this context, genetics is presented in the reviews as an essential element contributing to the established understanding of the importance of environmental factors:

"The widely accepted paradigm is that environmental factors are important to the development of asthma, but one must be genetically predisposed to respond to environmental differences." (Los et al. 1999:1210)

Accordingly, the reviews not only present and discuss a list of the most relevant environmental factors that contribute to the aetiology of asthma, but also contribute evidence for its hereditariness, and thus a role for genes on the basis of observations made as long ago as 1650. Asthma, however, does not seem to be transferable from parent to child in a straightforward Mendelian manner (Anderson and Cookson 1999; Los et al. 1999; Moffatt and Cookson 1999; Wiesch et al. 1999). The search for a genetic component to asthma is thus presented both as a new challenge and as part of established research efforts in asthma research. In taking up this challenge, two different agendas are sketched in the reviews. One suggestion by Los et al. (1999) is that already established methods for studying the genes will be appropriate:

"The latter (twin studies) will be particularly helpful in studying the relation of the genetic and environmental variances contributing to a trait. The classical twin study, the parental twin design and the cotwinn

control study are suitable for this purpose." (Los et al. 1999:1223)

On a second agenda is the claim that a new direction has to be taken with regard to the basis of emerging technology, although it might prove a more uncertain pathway:

> *"Chip and array technology already allows the expression of thousands of genes to be measured simultaneously. [...] Genome-wide association studies by the typing of multiple SNPs [single-nucleotide-polymorphisms] have been proposed as a more powerful method of detecting genetic effects than linkage mapping. The number of SNPs to be typed in such an exercise may exceed 500,000. This is just feasible with current technology but might be prohibitively expensive." (Moffatt and Cookson 1999:608)*

As genomics and asthma are linked together for the first time, collective expectations of improved understanding, prevention, diagnosis and treatment of asthma are introduced with reference to the HGP. Care is taken to connect these expectations to the established structures of received knowledge on the importance of environmental factors and on continuous efforts of understanding the pathophysiological mechanisms of asthma. However, a storyline is also introduced, with a focus on the identification of susceptible individuals with the aim of preventing the disease and optimising its diagnosis and treatment. Two items for the further exploration of a genes of asthma are also suggested, and thus filling in the storyline on genomics. One is to follow known methods, while the other is to break with traditional methods in order to apply new, more risky technologies. The latter proposal implies the formation of a new branch on the innovation journey of asthma research. It suggests a move away from characterising phenotypes on the basis of observational features like bronchial hyper-responsiveness and towards identifying phenotypes on the basis of genomic information. In the next section, I show how this branch continued to be shaped as asthma researchers framed the connection of genomics and asthma as an opportunity to discover novel pathways of the disease.

4.1.2 A promise is reinforced (2002–2004)

In the reviews from the period 2002–2004, the exploration of genes for asthma is formulated for the first time as contributing towards a profound change in received understandings of asthma. This way of framing the exploration of genes asthma is connected to the data from the HGP as well as the successful identification of genes for asthma. In addition, the explicit attention paid to environmental factors in

the 1999 reviews disappears during this period. Instead, ongoing efforts in asthma research are framed in terms of discovering novel pathways of disease, understood as regulated through the model of gene–gene and gene-environment interactions.

As data from the HGP arrives, it appears that there are far fewer genes than originally expected (Vercelli 2002). This challenges ideas of a linear relationship between genes and the expression of a trait like asthma. For asthma, this 'unprecedented flood of data' (Vercelli, 2002:15) sees the introduction of the hypothesis that genes have a subtler and complex influence on the development of asthma. It thus introduces the model of gene–gene and gene–environment interactions. Contrary to previous reviews, environmental factors are no longer explicitly presented or discussed. Instead they are now factored into sentences such as:

> *"More sophisticated analytical approaches that identify gene–gene and gene–environment interactions on a genome-wide level are required to fully elucidate the genetic risk factors for asthma and atopy, and to understand the pathogenesis of these common conditions." (Hoffjan and Ober 2002:714)*

Or:

> *"In conclusion, we envision a scenario in which a constellation of small quantitative variants in critical genes fine-tunes innate and adaptive immune responses and the way in which they interface with the environment, resulting in a wide spectrum of phenotypes." (Vercelli 2002: 19)*

The hypothesis of subtle and complex gene–gene and gene–environment interactions signify a shift away from a research agenda primarily concerned with adding to existing knowledge on the importance of environmental factors. Rather than describing environmental factors in their own right, they are reduced to factors that can be understood through the study of genes (Kauffmann 2004; Vercelli 2002; Wills-Karp and Ewart 2004). The inclusion of traditional environmental factors in the models of gene–environment interaction creates a perceived established structure for the exploration of this model as it adds a sense of contributing to past research. However, the implications of interpreting the findings of the HGP and the identification of genes in terms of interactive models leads to an increased emphasis on the space between the genotype and the phenotype and hypothesis-free research strategies (genome-wide scans). The identification and interpretation of the first genes for asthma therefore represent a decisive moment for genomics in asthma research. Finding actual genes is interpreted as proof that a genes for asthma exists, but is also clashes with the understanding of the linear

relationship between genes and the environment implied by earlier research. The outcome of this tension is to frame this finding as introducing a new era in asthma genetics research, leading to radically changed understandings of the disease:

> *"Although great strides have been made in the past decade, the next decade will almost certainly yield pronounced changes in our understanding of asthma susceptibility that, it is hoped, will translate into improved diagnosis, prevention and therapeutic strategies for this ever-increasing disease. With the recent successes, we might predict a time in the not too distant future when these strategies will be tailored to the individual on the basis of their genotype at a few key loci and their unique environmental exposure history." (Wills-Karp and Ewart 2004:386)*

The interpretation of the identification of asthma genes as the first step towards 'pronounced changes in our understanding of asthma susceptibility' (quote above) opens the way for so-called hypothesis-free research methodologies. Because the genes are seen as pointing to novel insights, researchers scramble to find a research methodology with which this novelty can be explored and understood. Available methodologies suffer from two critical shortcomings: they are either problematic in terms of producing statistically significant results or they are not suitable for discovering novel pathways and genes (Hoffjan and Ober 2002; Kauffmann et al. 2004; Vercelli 2002; Wills-Karp and Ewart 2004).

On the one hand then, the identification of asthma genes allows for an enormous boost of confidence and a strengthening of the storyline promising future clinical improvements of better therapy, diagnosis and prevention. On the other hand, this way of framing the contribution of genetics to asthma implies the opening up of the space between the genotype and the phenotype. It also focuses on gene-centred explanations of asthma. Instead of environmental factors acting as central touchstones in explaining asthma cause and development, genes are the central explanatory unit in terms of which environmental factors are considered. The resulting challenge now lies in connecting these two levels with each other.

4.1.3 A new research agenda (2006–2008)

The 2008 reviews see the emergence of a new research agenda for pursuing the prospective health care structure of improved understanding, diagnosis, treatment and options for preventing asthma. Framing the genes as a matter of gene–gene and gene–environment interactions leads to a demand for improved means of exploring the connections between the genotype and

then phenotype. The genome-wide association study (GWAS) methodology is introduced as a solution to this challenge. However, it has become increasingly clear that the effect of genes on asthma is minor and that no single gene or set of genes is strongly predictive of asthma. This prompts a reframing of the role of genes in interactive models, which opens the way for additional approaches like proteomics, metabolomics, systems biology and epigenetics.

Following the identification of the first genes for asthma, many regions thought to harbour asthma genes are identified, but, as the list of susceptibility genes expands, new challenges emerge. The challenge for the asthma researchers involves elucidating the role of the suspected genes and their interaction with each other and the environment. Researchers find it difficult to replicate and validate their findings of susceptibility genes, and none of the susceptibility genes can be said to be strongly predictive for asthma (Ober and Hoffjan 2006). This challenges the expectation of being able to predict who is susceptible to developing asthma in order to improve its prevention and treatment. Instead, the hypothesis of more genes with small effects is strengthened:

> *"On the basis of this review we suggest that the total number of genes that contribute to risk may exceed 100 and that the individual effect of any of these genes on disease effect is quite small." (Ober and Hoffjan 2006:98)*

So far, the search for genes of asthma is driven by the expectation that the HGP will facilitate the discovery of genes, and once genes had been found, improved understanding, diagnosis, treatment and the possibility of prevention through the identification of susceptible individuals would follow. Seeing that the effect of the genes suspected to be involved in asthma is likely to be 'quite small' (quote above), asthma researchers have to figure out how to interpret these findings. They could signal an end to the expectations of future applications for predicting asthma. Instead, a new cycle of collective expectations is introduced with the emergence of the new research methodology of genome-wide association studies (GWAS). One example, is an introduction in the review articles:

> *"The year 2007 has witnessed a quantum leap in genotype and phenotype association analyses with the publication of the first GWA study for an asthma trait (childhood asthma)." (Vercelli 2008:178, parenthesis in the original)*

A heading in a work by Moffatt (2008) introduces GWAS thus: 'New approaches and the future for disease gene identification' (Moffatt 2008:414). This method is moulded as the solution to a specific problem: the exploration of an association between the genotype (the genetic

make-up of an organism) and the phenotype (its physical expression). Furthermore, the method introduces a specific collaborative structure:

> *"This is an exciting time to be studying the genetics of asthma, with large-scale, collaborative, whole-genome association studies under way in the United States and Europe. These are expected to yield results within the next year, and epidemiologists may quickly be able to translate genetic associations into a better classification of the disease. In addition to this, further advances are already occurring with the application of genome-wide expression to understand complex disease. Add to this developing areas of proteomics, metagenomics and metabolomics and the so called 'systems biology' approach, rzesearchers in the field of complex disease genetics will find themselves deluged with an abundance of relevant data. This ultimately will result in a deep understanding of the aetiology of previously mysterious diseases such as asthma, leading to the real potential of prevention and cures." (Moffatt 2008:416)*

The GWAS method does not stand alone: proteomics, metagenomics, metabolomics and systems biology are lined up to complement it. All these approaches are directed at bringing interacting systems and their products in the body into view. Vercelli (2008) adds epigenetics as a promising new agenda in addition to GWAS. Characteristic of all these approaches is the turning of attention away from genes as a determining factor in these systems.

The above approaches are introduced as 'quantum leaps' (p. 416) that will finally allow a 'deep understanding' (p. 416) of the 'previously mysterious' (p. 416) condition of asthma and lead to 'the real potential of prevention and cures' (p. 416) (Moffatt 2008). Thus, the connection between asthma and genomics is made through a discourse implying a break with previous understandings and approaches to asthma. The storyline of genomics and asthma research is thus characterised by: a growing confidence about asthma genetics as a mature field, with a history of past achievements pointing to a promising future, GWAS as a method marking a new era in which links between asthma and genetics may be established in more elaborate and concrete ways, and the introduction of other so called "omics" methodologies and epigenetics to complement the approach to finding and understanding the role of genes for asthma. The shape of the claims of transformation of this storyline – improved treatment, diagnosis and prevention – remains a moving target throughout the development of the storyline. As the prospective structure of the innovation journey is maintained by the introduction of GWAS, accompanying methods and epigenetics, asthma is reframed as a mysterious condition in which knowledge of genes and other complex internal mechanisms are an essential aspect.

4.2 Transforming the field of asthma research

Genomics is given shape in asthma research through the development of a storyline characterised by unspecified expectations to improved understanding, prevention, diagnosis and treatment. Specific expectations of the possibility of finding genes related to asthma were fulfilled in the period 2002–2004. Some aspects, however, did not develop as expected. Instead of a few major genes involved in the development of asthma, a yet-to-be-determined number of genes involved in gene–gene and gene–environment interactions emerged as explanatory factors (Anderson 2008; Koppelman, te Meerman and Postma 2008; Moffatt 2008; Vercelli 2008). Asthma genome researchers went from shaping their research agenda in terms of contributing to existing knowledge to that of creating new knowledge. This implied hypothesis-free investigations and an opening for the GWAS method, together with epigenetics, metabolomics, proteomics and systems biology. In the preceding sections I followed the development of this storyline by tracing the dynamic process in which links were created between asthma and genomics. How does this storyline relate to established knowledge and practices in asthma research? My analysis does not necessarily imply that gene-centred research is transforming asthma research in general, or that clinical practice is changing through the incorporation of genetic information. What I show in the above sections is how expectations of future changes in clinical practice play a role in the creation of a storyline for genomics in asthma research. The authors of the reviews, shape the storyline of genomics as a potentially major contribution to reconstituting the general field of asthma research by a redefinition of the aetiological model of asthma.

4.2.1 Asthma redefined

In the 1999 reviews asthma is mainly described in terms of clinical manifestations. It is defined by the obstruction of the airway and chronic inflammation, and subdivided into early-onset and late-onset asthma, allergic asthma, asthma without evidence of allergy, occupational and exercise-induced asthma. Patient questionnaires and clinical observations are usually used to establish the diagnosis of the disease. Asthma is directly observed via the obstructed airway and the causal explanation referred to the clinical phenomenon of airway inflammation (Anderson and Cookson 1999; Los et al. 1999; Moffatt and Cookson 1999; Wiesch et al. 1999).

However, for researchers interested in finding genes this definition is problematic. A common complaint centres on the difficulty of defining the asthmatic

phenotype. The definition, with its focus on the obstructed airway and the role of inflammation, is criticised for being too general; it mixes together different clinical entities. The diagnostic methods are too subjective, as they are left to the assessment of individual doctors and patients' own judgment. Intermediate markers (also called intermediate phenotypes) are introduced as more objective units for measurement (Anderson and Cookson 1999; Los et al. 1999; Moffatt and Cookson 1999; Wiesch et al. 1999). These intermediate markers are imagined in closer, and even direct causal connection with the genes searched for.

In reviews from 2008 asthma is redefined as a condition resulting not from inflammation and an obstructed airway, but from unknown mechanisms of gene–gene and gene–environment interactions (Anderson 2008; Koppelman et al. 2008; Moffatt 2008; Vercelli 2008). Clinical characteristics are still used to describe the condition but no longer featured as the cause of asthma. The subtle change in the definition of asthma implies a major shift in research attention. While the obstructed airway and inflammation are key to understanding asthma according to the 1999 definition, gene–gene and gene–environment interactions are at the centre of such understanding in 2008.

4.2.2 Towards a new aetiological model of asthma

In addition to these attempts at a redefinition of asthma, the storyline of the reviews also challenges the aetiological model of asthma. In the 1999 reviews, researchers refer to two environmentally based hypotheses of the aetiology of asthma: the allergen and the hygiene hypothesis. A western lifestyle is generally argued to account for the rise in the observed incidence of asthma. According to the allergen hypothesis, exposure to allergens such as house dust mites, smoke and diet is responsible for sensitising individuals to an extent that asthma results (Anderson and Cookson 1999; Los et al. 1999: Moffatt and Cookson 1999; Wiesch et al. 1999). Similarly, the hygiene hypothesis suggests that, due to heightened hygiene standards, the adaptive immune response does not receive adequate stimulus to develop properly. As a consequence it overreacts when exposed to allergens, and asthma results (Wiesch et al. 1999). An explanation is, however, lacking as to why only some people develop asthma. Thus, in the 1999 reviews, genetic susceptibility is highlighted as a determining factor in triggering responses to these environmental factors. Genetic susceptibility is double-faced, as it can both increase and decrease the sensitivity of the individual (Anderson and Cookson 1999; Los et al. 1999; Moffatt and Cookson 1999; Wiesch et al. 1999).

As more and more susceptibility genes for asthma are found, a so-called

endophenotype model develops. This model is based on an understanding of a non-linear pathway from genotype to phenotype. Groups of susceptibility genes, found in various physiological systems in the body, are imagined to lead to a broad range of asthma's (Anderson 2008; Vercelli 2008). These different endophenotypes each represents a subset of the disease, with a discrete pathogenic pathway connected to a group of genes. This model is more complex than the clear-cut model of the gene–environment interaction, with differentiated internal pathways interacting amongst themselves and the environment. In this construction, attention is also drawn to the role of epigenetics (Vercelli 2008). In the reviews, a shift has taken place from talking about asthma to talking about asthmas. As in other cases, the identification of genes (mutations in genes) has led to a fragmentation of the definition of asthma (Rabeharisoa and Bourret 2009). The proposal of an aetiological model of asthma based on complex non-linear relations has also fragmented asthma into asthmas, and hence seemingly endless opportunities for sub-characterisations of the disease. The reframing of the aetiological model of asthma is central to understanding the necessity of shaping the link between asthma and (gen)omics as activities aimed at unraveling novel disease pathways and creating novel knowledge about asthma, now framed as a mysterious disease. It is an aetiological model essentially different from models such as the hygiene or allergen hypothesis because it takes molecular biological mechanisms as its reference for explaining phenotypic expressions. In the storyline on the exploration of a genetic component to asthma, it represents a turning point, as aetiological models (like the hygiene hypothesis) and methods of classification (like questionnaires) are framed as both dogmatic and imprecise.

4.3 Aligning genomics and cardiovascular disease

4.3.1 Genomics as a continuous effort (2000-2004)

The main aim of research into a genetic component of cardiovascular disease (CVD) is presented as a contribution to improved diagnosis, strategies for therapy and the development of more specific drugs (Ferrari and Bianchi 2000). The HGP is presented as a future development supporting these expectations. Genes involved in monogenetic forms of cardiovascular conditions are already known. These genes are expected to also play a role in multifactorial cardiovascular diseases (also referred to as complex cardiovascular diseases), as *'Genes responsible for monogenetic diseases may also play a role in more common forms of cardiovascular disease'* (Gibbons et al. 2004:IV-53). Genomics is aligned with research on

multifactorial CVD through a storyline that creates a genetic connection with monogenetic CVDs. Genomic approaches are expected to enable therapeutic trajectories better suited to the individual patients, in addition to contributing to an increased understanding of the pathophysiology of multifactorial CVD.

> *"We may hypothesise that a better understanding of their genetic mechanisms will not only encourage the development of new pharmacological approaches to the discovery of novel drugs, but also will furnish a powerful tool for a better and more appropriate use of the available ones." (Ferrari and Bianchi 2000:1038)*

As with asthma, genes are presented in relation to environmental factors. However, differentiations are made in the reviews with regard to monogenetic and multifactorial cardiovascular conditions. The key difference separating these two groups of CVDs is the influence of environmental factors on the eventual manifestation of disease.

> *"As stressed in section 4, in complex, multifactorial diseases like hypertension, the pathogenic role of an individual polymorphism must be evaluated in the context of its overall genetic and environmental background." (Ferrari and Bianchi 2000:1038)*

In furnishing the space for genomics in cardiovascular disease research, concrete examples of possible innovation journeys are given. One example relates to expectations of pharmacogenomics. Pharmacogenomics is positioned as a promising, and much needed future, since many patients cannot tolerate current drugs very well. A specific polymorphism (PLA2), is positioned as potentially enabling the circumventing of an excess of recurrent coronary events in patients who have already suffered a heart attack. These patients could then preventatively be treated with aspirin, clopidogrel and statins. (Mukherjee and Topol 2002)

> *"A potential pharmacogenomics application of the PLA2 polymorphism would be to treat these individuals with aspirin and clopidogrel for primary and secondary prevention of CAD and also with statins." (Mukherjee and Topol 2002:486)*

Another example of a possible innovation journey is the suggestion that information on gene-environment interaction could be incorporated into

the Framingham risk score[24] already in use in clinical practice (Stephen and Humphries 2003; Gibbons et al. 2004). The idea is that cardiovascular events only occur when individuals with high-risk genes enter a high-risk environment. Ideally, information on gene-environment interactions would then be incorporated into a risk score like the Framingham risk score, and used to enable genotype-specific lifestyle advice, or tailor clinical and therapeutic decisions to an individual's genotype (Stephen and Humphries 2003).

The clinical implications of expanding research on genetics in the direction of genomics thus take a central place. Authors emphasise this point by arguing that the most important question is not about finding mutations associated with disease, but the clinical implications of these associations (Mukherjee and Topol 2002; Stephen and Humphries 2003; Gibbons et al. 2004). Still, the authors devote space to discussing existing approaches of exploring genetics.[25] These approaches are not seen as suitable for exploring possible genes of multifactorial CVD. The expectation is that new high-throughput genotyping technologies will make genome-wide association studies (GWAS) possible. The GWAS are expected to be better suited to multifactorial CVD, since they offer better coverage of the entire genome than existing approaches (Ferrari and Bianchi 2000; Stephen and Humphries 2003; Gibbons et al. 2004). GWAS pick up on common variants, which influence, but do not determine, susceptibility and development of complex CVD. However genomics is just one approach, which the review present as important for discovering and understanding the genes of multifactorial CVDs. Proteomics and bioinformatics are positioned as equally important to future developments and together the approaches are described as comprising a systems biology approach to CVD. The systems approach is not seen as replacing, but rather complementing methods such as linkage analysis. (Ferrari and Bianchi 2000; Gibbons et al. 2004)

> *"The integration of high-throughput systems biology has the potential to translate insights gained from DNA microarrays and proteomic analysis to new diagnostic tools relevant to cardiovascular medicine in the 21st century. We predict that within the next decade, biomarkers identifying high-risk cardiovascular patients will be discovered in clinical and epidemiological studies that make use of these new genomics and proteomic platforms." (Gibbons et al. 2004:IV-55)*

24 The Framingham risk score is the outcome of a longitudinal epidemiology study following a group of residents and their offspring in Framingham Massachusetts in the US. The study was initiated in 1948 and is still on-going. Significant results include the relation between cardiovascular disease and age, gender, blood pressure, blood triglyceride, cholesterol and psychosocial issues.

25 Existing approaches are linkage analysis and candidate gene association studies.

As with the space of assessment created for genomics in asthma research, the HGP is referenced as the development that allows for expectations of a future with improved understanding of disease and new therapeutic options. However, in opening this space researchers are already providing examples of concrete innovation journeys. The main concern is the patients who do not tolerate certain kinds of medication well, and are at risk of recurring cardiovascular events are the primary concern. The importance of gene-environment interaction is established as the model for thinking about genetic insight stemming from genomic investigations. As with asthma, genomics approaches are presented as supplementing existing insight into the pathophysiology of CVD. However, contrary to genomics, mutations and genes involved in monogenetic CVD are already known. The transition to the exploration of genes for multifactorial CVD is shaped as an extension of genetic discoveries in monogenetic CVD. Furthermore, the translation of these findings and comparisons with clinical practice takes central place in assessing the relevance of genomics.

4.3.2 Genomic medicine (2005-2007)

Four key themes dominate the reviews in this period: emerging 'omic' technologies and their contribution to understanding disease pathology; the integration of various kinds of information into a comprehensive 'systems' view for prognostic and diagnostic purposes; possibilities for pharmacogenomics; and finally preparatory activities needed to realise a vision of genomics medicine. The storylines attached to each of these four key themes are still characterised by attempts to make concrete the clinical contribution of genomes, and to provide examples and recommendations for laying the path to the realisation of the potential of genomics.

There is a general storyline taking shape in the reviews in this period. GWAS technology represents a game changer for the genetic exploration of multifactorial CVD, as it will allow unbiased searches for mutations associated with disease (Ginsburg, Donahue and Newby 2005; Podgoreanu and Schwinn 2005; Arnett et al. 2007; Cambien and Tiret 2007; Seo and Goldschmidt-Clermont 2007). However, a developing hypothesis is that complex cardiovascular conditions are influenced by common, as well as rare, mutations. Therefore, so called resequencing approaches —which *'[...] may provide fully "personalized" characterisation of an individual's genome once costs are no longer prohibitively high'* (p. 2889-2890)— are necessary (Arnett et al. 2007). One suggestion is that GWAS might be combined with existing approaches such as linkage analysis (based on families) in order to capitalise on the strength and weaknesses of each approach (Seo and Goldschmidt-Clermont 2007).

Expectations regarding the outcome of GWAS and resequencing studies are limited to a contribution towards better understanding the pathophysiology of multifactorial and monogenetic CVD (Cambien and Tiret 2007). Instead, RNA expression profiling, proteomics, metabolomics and pharmacogenomics are shaped as approaches that are more likely to contribute to changes in clinical practice (Ginsburg et al. 2005; Podgoreanu and Schwinn 2005; Arnett et al. 2007; Cambien and Tiret 2007; Seo and Goldschmidt-Clermont 2007).

While the storyline of pharmacogenomics is continued from the reviews in the period 2000-2004, RNA expression profiling, proteomics and metabolomics are included in a storyline concerning their contribution to prognosis and diagnosis in clinical settings. 'Genomic medicine' (Ginsburg et al. 2005:1615) is a vision of a paradigm shift from acute intervention to prospective and personalized cardiovascular health care (Ginsburg et al. 2005).

> *"A paradigm shift is taking place in cardiovascular care, driven by the capability to perform routine genomic analysis of individuals. In principle, this will include susceptibility screening, comprehensive expression analysis, proteomic and/or metabolomic testing, and probabilistic relation of those results to discrete clinical end points. Ideally genomics medicine will be preventive and seamlessly integrated into patient care. In the coming years, we expect that the addition of genome-level testing and sophisticated analysis of genomic and environmental risk will further refine individualized approaches to care in CVD patients. Genomics will become increasingly pervasive in cardiovascular medicine. It is imperative that the cardiology community be comfortable with and embraces it so that patients can realize its full potential." (Ginsburg, Donahue and Newby 2005: 1624)*

The vision of 'genomic medicine' (see quote above) encompasses the integration of various types of information, from susceptibility testing of genes, expression analysis of RNA, proteomics in exploring the use of proteins as biomarkers, to metabolomics as the final step in the integration of this information to a complete picture of disease (Ginsburg et al. 2005, Arnett et al. 2007; Seo and Goldschmidt-Clermont 2007). The vision is that many genes with smaller effects will be analysed together to yield quantitative risk assessments, which would be used to sub-categorize patients in order to provide increasingly precise diagnosis and prognosis and to initiate more effective therapeutic trajectories (Ginsburg et al. 2005, Arnett et al. 2007).

The exploration of gene-environment interactions is developed as a crucial research direction in two of the reviews, since 'The importance of these

interactions [gene-environment interactions] considerably mitigates the concept of genetic determinism' (Cambien and Tiret 2007:1717). Such studies are viewed as crucial for the development of a preventative genomics medicine aimed at lifestyle interventions (Arnett et al. 2007; Cambien and Tiret 2007).

Pharmacogenomics is emphasized as the area in which near term clinical applications can be expected. (Ginsburg, Donahue and Newby 2005; Cambien and Tiret 2007; Arnett et al. 2007; Seo and Goldschimdt-Clermont 2007). However the effort is frustrated by a dearth of studies demonstrating the cost effectiveness of developing differentiated therapeutic trajectories for sub-groups of patients. One specific example is that of Warfarin.[26]

> *"With 11 studies in hand the association is now unquestioned, but the information is still not used in clinical practice. We have not yet established whether genotyping for these variants will substantially improve patient care in a cost-effective manner." (Seo and Goldschimdt-Clermont 2007:49)*

Next to the lack of studies on the effectiveness of screening for polymorphisms for the prescription of drugs, the reviews establish a number of other barriers. These include the limited availability of genetic testing services, a lack of interest in restricting the group of patients for which a drug might be used, and finally a lack of knowledge of genetics among clinicians (Arnett et al. 2007).

In addition to examples of pharmacogenomics applications, the potential of genomics is also made concrete through specific suggestions of how to prepare for 'genomic medicine' in clinical practice. Specific suggestions for how to pave the way for genomics medicine is collected in a number of guidelines issued by the American Heart Association. These guidelines include prioritisation of research agendas, as well as the establishment of criteria for screening programs in at risk populations, and initiatives to raise awareness of genetics amongst clinicians, the general public and researchers. (Arnettt et al. 2007) This storyline is supported with reference to on-going screening efforts for FH (familial hypercholesterolemia).[27] Families, who are known to be carriers of the mutation for FH are registered, offered genetic counselling and enter into treatment trajectories for the condition (Arnett et al. 2007).

26 Warfarin is a commonly used drug used to treat and prevent blood clots. Some patients run a higher risk of 'bleeding' depending on a polymorphism in cytochrome P450 (CYP)2C9.

27 FH is a genetic condition which is inherited in families. It causes a build-up of LDL ("bad cholesterol") levels in the blood, which subsequently increases the risk of narrow arteries and eventual heart attacks.

The space of assessment is thus broadened to include a storyline of genomic medicine as prognostic and preventative. Cardiovascular conditions, like FH, that are already part of screening efforts serve as examples guiding future visions of the development of prognostic and preventative aspects.

4.3.3 From bench to bedside (2009-2010)

In the 2009-2010 reviews, the results emerging from GWAS are evaluated as successful in terms of confirming a genetic component to complex CVD, and in pointing to novel loci (Arking and Chakravati 2009; Bos et al. 2009; Lamberts and Uitterlinden 2009; Pereira and Weinshilboum 2009; Chico, Milo and Crossman 2010). In evaluating the success of genomics, Chico et al. (2010) present two research goals: the identification of genes modifying/causing disease and a genetic test that accurately can identify persons at risk. In their interpretation, research has been more successful in reaching the first goal. (Chico et al. 2010). The evaluation resonates with positions put forward in the remaining reviews. Even if GWAS are interpreted as successful, the step from identifying new loci to translating those findings into new understandings of disease is fraught with difficulties. The loci found to be associated with complex CVDs only account for a small part of hereditariness. As a result, the hypothesis that rare mutations, which cannot be accessed with GWAS, must play a role in disease mechanisms is again advanced in the reviews. A new approach called 'next generation sequencing' is introduced as a solution to this problem.[28] (Arking and Chakravati 2009; Lamberts and Uitterlinden 2009; Pereira and Weinshilboum 2009; Chico et al. 2010) However, even if researchers manage to identify these rare mutations, the translation into biological mechanisms remains a second challenge. The 'systems-level' approach is again promoted, but this time with the aim of exploring particular biological hypothesis. (Arking and Chakravati 2009)

The link between increased understanding of disease mechanisms and practical applications continues to be precariously laid out in the reviews. If the aim is risk prediction, GWAS are not the right tool.

> *"For nearly two decades genetic research has attempted to determine the genes responsible for this risk [of coronary artery disease and myocardial infarction], and it is worth considering why one might still embark on such studies." (Chico et al. 2010:186)*

28 Next generation sequencing or deep sequencing is promoted by the 1000 genomes project. The aim of the project is to fully sequence the genomes of 1000 persons using next generation technology.

However, as with challenges to the next step in understanding disease mechanisms, it is the emerging approach of next generation sequencing, which is interpreted as sufficient reason to continue:

> *"We conclude with the prediction that, within 5 years, next-generation DNA sequencing will be widespread in research and clinical practice, genomic information will be incorporated into routine clinical practice for diagnosis and risk prediction of common polygenic cardiovascular disorders [...]." (Chico et al. 2010: 194)*

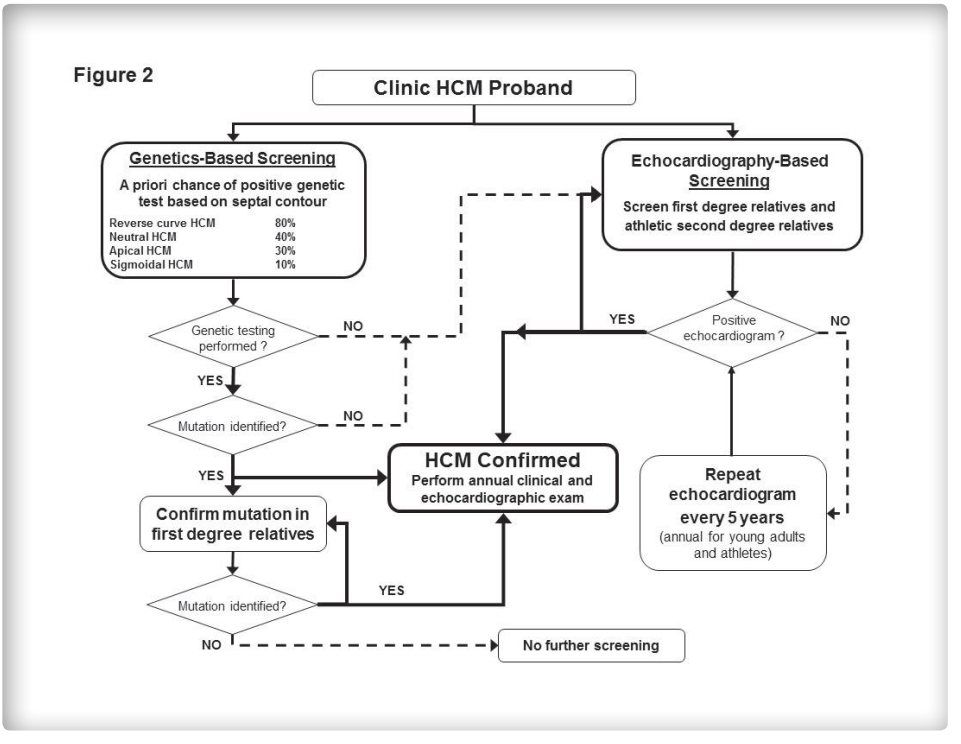
When it comes to the actual storylines on the development of clinical applications, different storylines are developed for therapy, diagnosis and risk prediction. When it comes to risk prediction, two storylines are developed. One expectation concerns the development of diagnostic testing for susceptibility genes for HCM (hypertrophic cardiomyopathy) (Bos et al. 2009).[29] Another expectation concerns next generation sequencing as a reason for renewed hope of discovering susceptibility genes for complex CVD (Chico et al. 2010).

In developing the storyline on HCM, the authors emphasise that the genetic tests, which are clinically available, are for diagnostic purposes. However, they still draw up possible therapeutic and prognostic implications of the tests. HCM is not a monogenetic condition, but falls somewhere in between the monogenetic and complex cardiovascular conditions. The genetic tests for HCM are imagined as tools in counselling trajectories. In these counselling trajectories, a patient suspected of HCM presents the starting point for initiating a counselling trajectory. Subsequently, family members are contacted and also offered counselling. The

29 HCM is a prevalent hereditary heart condition that results in a "thickened " heart muscle. There is significant variation in genotype and phenotype. The disease is most commonly known as the cause of sudden cardiac arrest in young athletes.

genetic test would be part of a counselling trajectory as sketched out in Figure 3.

Figure 3: The figure shows how genetic tests are imagined to be part of screening programs for HCM. (from Bos et al. 2009)



The genetic test is introduced as offering patients 'psychological freedom' (p. 209), since it is considered the only means of being "safely" excluded from regular screenings (see the figure) (Bos et al. 2009). Diagnostic genetic tests are also available for FH, where they are presented as part of similar counselling trajectories. However, these genetic tests are not recommended on a population level, or as the only tool in counselling trajectories, since there is such a large variation in the expression of disease, meaning that diagnosis needs to be supplemented with additional information. (Lamberts and Uitterlinden 2009)

For the complex cardiovascular conditions, expectations of future risk prediction are —as shown above— justified by expectations regarding so-called next generation sequencing (Arking and Chakravati 2009; Lamberts and Uitterlinden 2009; Pereira and Weinshilboum 2009; Chico et al. 2010).

Therefore while the paradigm shift towards 'genomic medicine' as prognostic and preventative is not abandoned, it is toned down in these reviews. Instead, the

storyline of pharmacogenomics is emphasised once more. The examples of drugs are the same as in the previous reviews. However, pharmacogenetic testing kits are now actually available for clinical practice. In addition, the FDA (US Food and Drug Administration) approves the changing of the label on Warfarin to include information on the possible relevance of genetics into decisions on use. (Lamberts and Uitterlinden 2009) These developments are interpreted in the reviews as the first steps towards 'personalised health care', as expected with genomics.

The introduction of genomics is evaluated as relevant in relation to knowledge on genes obtained with non-(gen)omic methods. The transition to genomics in exploring a genes for complex CVD can therefore be positioned as an addition to and continuation of these studies. This has the consequence that the lack of strong association between genes and complex CVD does not lead to calls for radical new understandings of complex cardiovascular disease, since this was in a sense expected. Instead the authors see their contribution as relevant for a reconstitution of clinical practice in which testing for mutations will have a more prominent place.

4.4 Transforming clinical practice of cardiovascular disease

The configuration of genomics in cardiovascular practice is characterised by evaluation of its relevance in relation to clinical practice. As the first attempts are made to bring the storyline of genomics and cardiovascular disease research together, the implication of mutations for clinical practice comprise the main priority (Mukherjee and Topol 2002; Stephen and Humphries 2003; Gibbons et al. 2004). Pharmacogenomics and genomics medicine as prognostic and preventative medicine are the two key threads running through the storyline of genomics and cardiovascular disease research. The continuation of this storyline is motivated by expectations of the results that will come from GWAS, in addition to next generation sequencing and other 'omic' technologies. Strikingly however, these emerging technologies are not configured as replacing or revolutionising traditional ways of exploring genomics. Instead, they are configured as being complimentary to these approaches.

The way in which expectations of genomics are configured in relation to the story of the success of genetics/genomics for monogenetic CVD is key to understanding this configuration of genomics. Furthermore, the Framingham risk score is influential in thinking about the possibilities of a genomics medicine as prognostic and preventative.

Contrary to asthma, common CVD are already defined in terms of gene-environment interaction. However, as in asthma research, data from the HGP and GWAS studies do generate suggestions for changes to disease classifications. In both cases, classification based on outcomes of clinical or pathological characteristics is criticised as being imprecise and faulty (Ashrafian and Watkins 2007). A fragmentation in the classification of disease seems to be a general consequence of genetic and genomic approaches to studying disease. For clinical practice on certain types of cancer (breast, ovarian and colon) and autism, this has already affected practices of diagnosis in the clinic. A 'clinic of mutations' (Rabeharisoa and Bourret 2009:699) has developed in which researchers and clinicians from different disciplines negotiate the status of mutations in diagnosis alongside other disease traits.

The key question here, as with asthma, is how the creation of a space of assessment for genomics relates to other approaches for studying cardiovascular disease. My analysis shows that expectations of future changes in clinical practice play a central role in the development of a storyline for genomics. In this storyline, pharmacogenomics and prognosis and prevention play a key role in configuring genomics for clinical practice. The implementation of new guidelines for Warfarin and the screening programs for FH function in the space of assessment as reference points for how this configuration might play out in practice.

4.5 In Conclusion

My analysis followed the emergence of storylines for spaces of assessment of genomics in asthma and cardiovascular disease research. In both cases, genomics is configured through the development of a storyline of its promises for research and clinical practice. However, these storylines differ in the specific ways in which alignment between genomics and established research and clinical practice is achieved.

In asthma research, a genomic agenda for studying asthma emerges. Initially genomics is positioned as an approach to find major genes and contribute to existing knowledge. Eventually genomics is configured as an approach that will discover the many genes with small effects that are part of the asthma aetiology and as contributing to the creation of novel knowledge. An explanatory model of asthma belongs to this storyline, which places gene–gene and gene–environment interactions at the centre. The storyline also contains expectations that genomics will contribute to clinical practice, but no examples are given on how these expectations may play out. Instead genomics is positioned in a rather general way

as expected to contribute to diagnosis, and therapy and ultimately to prevention or even a cure for asthma. As the storyline develops, it is characterised by a growing confidence in genomics. The discovery of genes for asthma enhances confidence in the value of a genomics approach. Furthermore the emergence of new genome-wide methods is also taken as a sign of progress and strengthening expectations to the potential of genomics. At the same time, genomics is no longer positioned as the only approach to fulfilling these expectations. In addition, epigenetics, metabolomics, proteomics and systems biology are included in this storyline as necessary for exploring the gene-environment interaction model. These approaches do not have genes as their central focus, but are essential for understanding the function of genes and the influence of polymorphisms.

The storyline is an attempt to align genomics with established practice. This is illustrated through efforts to, on the one hand, incorporate existing definitions and aetiological models of asthma into the search for a genes, and on the other hand, to change the definition and aetiological models. The emerging definition emphasises gene–gene and gene–environment interactions as causal factors. This change could be interpreted as demonstrating a shift towards prioritising genetic explanations, since it draws attention away from environment and the organ level. However, the accompanying emerging aetiological model focuses on non-linear discrete pathways leading to a diversity of asthmas and the necessity of understanding cellular as well as molecular processes. Furthermore these pathways are conceived as being intimately connected to environmental stimuli.

The construction of genomics as a relevant contribution to asthma is characterised by the challenge of positioning genes in relation to environmental factors. Contrary to CVD, there are no monogenetic sub-types of asthma and no genes already found to draw on for an argument of the relevance of genomics. In the review papers from 1999, this challenge is visible in how the authors recognise the importance of environmental factors by devoting sections to describing established knowledge on their influence. However, their explanations of why and how asthma develops subtly prioritise genetic factors. Asthma is positioned as a condition that develops only when individuals are genetically susceptible, and studies of hereditariness are presented as proof of a genetic component to disease.[30] The explanations, while seemingly acknowledge the importance of environmental

30 Such studies, like for example twin studies, can also be seen as proof of an environmental component to disease.

factors, place understanding of genes as central to understanding asthma.[31] Following the arrival of data from the HGP and the discovery of the first genes for asthma, the storyline changes dramatically. The storyline of the importance of genomics for understanding asthma is strengthened, and environmental influences are only cited as part of gene-environment interactions. The strong influence of the established practice of understanding asthma as a disease with a substantial environmental component crucially affects the configuration of genomics as contributing to a profound new understanding of asthma.

For CVD, a storyline on the contribution of genomics is developing as well. The storyline explains the way in which genomics will lead to an increased understanding of disease. Already from the beginning the gene-environment interaction model is the central explanatory model for thinking about complex CVD. The review authors emphasize that it is the contributions to clinical practice, which are the most important reason for a genomic approach to CVD. Furthermore, the way in which knowledge of genetics is applied in clinical practice for monogenetic conditions is part of the storyline of genomics for complex CVD. Contrary to asthma, concrete examples are given. One of the key examples of therapy is a pharmacogenomics approach to figuring out whether Warfarin is the best therapeutic option. For prognosis and prevention, it is the established screening programs like the one for FH, which give structure to the storyline of genomic medicine.

For CVD, the configuration of genomics is characterised by efforts to align its contribution with how genes and risk information are used in clinical practice. Three examples comprise central elements for developing a storyline that aligns genomics with clinical practice: the way in which genes have contributed to understanding monogenetic CVD; the practice of using the Framingham risk score to provide a prognosis; and the example of pharmacogenomics. Monogenetic sub-types are argued to be rare forms of the more common CVD, and therefore increased knowledge of these conditions is inherently valuable for the more common forms. The configuration of the contribution of genomics in relation to the Framingham risk score provides direction to the form and use of risk information. It shows readers how risk information is already used and successful, and thus makes it easier to argue for the usefulness of risk information based on susceptibility genes. Finally, the argument of pharmacogenomics is constructed in relation to its relevance for the recurrent problem of finding

31 Hedgecoe (2001) referred to this way of presenting research on genes as *'enlightened geneticization'* (Hedgecoe 2001: 875). The trick is that such accounts seem less biased towards genetic explanations and thus avoid accusations of being deterministic or reductionist.

the right therapeutic approach for cardiovascular patients. The relevance of genomics is established as the approach, which will make it possible to test patients and match them with an appropriate therapeutic option. In addition to the construction of the knowledge of genes for monogenetic conditions, the clinical practice of screening is also drawn on as a structure for other CVDs. The example of HCM show how the possibility of genetic tests inspires future imagination of screening programs like the ones known for FH. In sum, established knowledge and practices also influence the configuration of genomics for CVD. The storylines emerging in the review papers are summed up in Table 4.

Table 4: Storylines on genomics emerging in the review papers

	Research	Clinical practice
Asthma	Genomics is the solution to understanding asthma	Genomics will lead to a radically changed practice with opportunities for prevention, cure and improved diagnosis and therapies
Cardiovascular disease	Genomics is a relevant approach for complex CVD since they share a genetic component with monogenetic CVD	Genomics will improve risk prediction of complex CVD by adding to the Framingham risk score; Pharmacogenomics will change practices of prescribing medicine, making them safer and more effective by being tailored to the individual; Genomics will strengthen current screening practices and open up opportunities for using genetic tests more extensively for CVD with a strong genetic component

Returning to the question of the transformative power of genomics for research on common disease, it is clear that genomics has led to the formation storylines on the importance of genomics. Another question concerns whether the different storylines imply options for different future practices. For example, for CVD, genomics is envisioned as contributing to existing risk assessment procedures. The current tool, the Framingham risk score, is based on information on the influence of environmental, social and personal factors that play a role in the development of disease. These factors are accepted as valid on a population level, meaning that they are less predictive at the individual level. Nonetheless, they are accepted guidelines for risk prediction. For asthma, this is different; environmental, social and personal

factors are implicated as playing a role in the development of disease. However, there is much interpersonal variation and there are no standard "hard" guidelines for clinical practice.[32] Using information on the genome for risk assessment thus links up more easily with cardiovascular practice than with asthma clinical practice. However, one could speculate that there is greater room for introducing genomic information as relevant to asthma practice, given the weak position of environmental factors. However, the way in which this will develop remains to be seen. Furthermore, my analysis only shows that storylines of spaces of assessment for genomics are created in asthma and cardiovascular disease research in review papers; my research does not demonstrate how they affect (if at all) other storylines of the two conditions. Therefore, in the following chapter, I turn to the way in which the storyline of these two spaces of assessment developed in two workshops.

32 Asthma researchers experience general frustration that they are not able to provide concrete advice regarding the environmental factors that play a role in the development of disease. In 2009, I attended an international conference (Bronchitis 8: Obstructive Lung Disease from Conception to Old Age, June 15-17, Groningen, The Netherlands) in which leading researchers participated. In one session, the question of guidelines on which environmental factors to avoid came up. Both the presenter and the audience were looking for, but unable to point to, any valid recommendations. The session ended in with a feeling of collective frustration.

5 Configuring potentialities: storylines of genomics in research and clinical practice

Chapter 4 showed how two spaces of assessment emerged in asthma and cardiovascular disease research. These spaces were structured by storylines in which genomics was given a place in explaining the two diseases as well as in contributing to future clinical practice. As I argued in chapter 4, the storylines are the outcome of an on-going process of assessing genomics and its contribution in relation to established research and clinical practice. The storylines align the purpose and problem definitions of genomics with the purpose and problem definitions of research and clinical practice resulting in a re-shaping of established practice as well as of genomics. The process of constructing alignment resulted in two different storylines. Genomics was configured, either as a wholesale transformation (asthma), or as a contribution to established practices (cardiovascular). Differences in the storylines also emerged in the assessment of the contribution of genomics to clinical practice. For asthma, the contribution to clinical practice was not elaborated more than the general argument that genomics would lead to improved prevention, diagnosis and treatment. For CVD, the general argument was immediately made concrete through examples and suggestions of ways to facilitate genomics in clinical practice. These differences are the outcome of starting conditions in terms of the established research and clinical practice with which genomics was aligned.

The 10-year anniversary of the Human Genome Project

In between my analysis of the review papers and organising the workshops, the Human Genome Project (HGP) celebrated its 10-year anniversary. Anniversaries often call for a reflection on past achievements, and with the HGP it was no different. In the face of the 3 billion dollar investment, the question on everyone's lips was: has the HGP delivered on its promises? In short the commentaries of a select group of scientists in the anniversary additions of *Science* and *Nature* can be summarised as: yes and no. On the one side Francis Collins, the director of the NIH, looked back at past development to note the breath-taking acceleration in technological developments and sequencing abilities. Making a brief remark on the modest impacts of genomic knowledge on clinical practice, he emphasised pharmacogenomics as the most promising application to come out of the HGP (Collins 2010). Other proponents remarked on the how the HGP had facilitated a tremendous increase in knowledge on the molecular mechanisms of common disease, and made it only a matter of time and dedicated efforts before such discoveries would be translated into clinical practice (Green and Guyer 2011). However, other commentaries raised question on the achievements, approach and costs of genomics. Weinberg (2010) argued that the so called hypothesis free approach of GWAS is just bigger but not better, and has so far nothing to shows that justified the enormous investments required to carry out the experiments. While Hudson (2011) wished for the wisdom of hindsight, and argued that the choices made for collecting data, has made the integration of genomics with clinical practice a very difficult. Genomics simply does not answer the kind of question that clinicians desire answers to (Hudson 2011). While this brief description is just a very small portion of the commentaries released in connection with the anniversary of the HGP, they give insight into the controversy surrounding the scientific as well as clinical success of genomics: in the present as well as the future. In the workshop discussion the researchers assessed the potential of genomics in terms of negotiating accusations that genomics had been a disappointment. While they connect this discussion to their own fields, the discussion can also be understood as a reference to broader development. The 10-year anniversary of the HGP is thus an important background story to understand the discussion in the workshops.

In chapter 1, I argued how genomics implies a re-ordering of several elements of established research and clinical practice. In research, the promise of a genome-based revolution in understanding as well as researching disease implies a shift to gene-centred explanations of disease. This consequently implies introduction and dominance of new research methodologies and technologies. As I showed in chapter 4, the spaces of assessment include storylines where disease is explained with reference to genes, and with genomics technologies as the means to explore this model of disease. The storylines do not explicitly, but rather implicitly prioritise not genetic, but 'omic' and system-level explanations of disease as well as the research methodologies and technologies of (gen)omics. The gene-environment interaction model is the key reference for understanding disease, but it is the gene side of the equation, which the storylines prioritise for future work. When it comes to clinical practice, genomics implies a shift from the roles and responsibilities of the established doctor-patient relationship (Ch. 1). Patients are imagined as proactive

health-conscious consumers motivated to take action to reduce future risk by engaging in prevention in the present. The storylines of the spaces of assessment seemingly embrace these expectations to genomics. At least, opportunities for risk prediction and prevention are presented as the ultimate promise of genomics. The storylines from chapter 4 position genomics and the shifts in understandings and research methodologies as natural and uncontroversial progression of the scientific exploration of asthma and cardiovascular disease. The review papers thus raise the question if these storylines are indeed more broadly accepted among researchers.

The storylines emerging in the review papers only tell one part of the emergence of spaces of assessment for genomics. One purpose of review papers is to persuade other researchers of the potential of genomics, and to enrol them into contributing to the fulfilment of the prospective structure. The task of the authors is to align genomics with established research and clinical practice. The more the authors succeed in their task, the more compelling and convincing their reviews will be. Review papers are argumentative efforts to convince. They therefore do not provide (much) information on concerns and contestations surrounding their storyline, or alternative interpretations of the place of genomics in storylines of in research and clinical practice. The static accounts in the review papers, with their universal claims of relevance, can be seen the outcome of a social translation process. In this process, claims of a number of articles are collected and brought together in a new formation to create a story that the authors of the reviews would like to tell. Reviews are selective stories told from the point of view of authors. Even further, the articles on which the reviews build are themselves the outcome of intricate social processes of translation. The authors of each article have had to perform work on their data to separate it from its local circumstances in order to be able to present the data as scientific fact (Latour and Woolgar 1979; Latour 1987). The process of writing the review papers therefore erases many a trace of the origin and context of the claims made.

In this chapter, we therefore move to a different work floor where such concerns and contestations have the opportunity to emerge: workshops. The workshops are another point of access to the spaces of assessment and the configuration of the storyline on genomics. The workshops provide the opportunity for exploring the structuring effect of the storylines in the review papers, as well as allows for adding nuance to its ordering of genomics and elements of established research and clinical practice. Discussions during the workshops also involves persuasion, but of a different kind than the reviews. It is a discussion among colleagues. In this type of discussion, the researchers will not be held accountable by funding agencies or other scientific peers. In that sense, the workshop is a "free" space for the researchers to discuss and assess. For the analyst, discussion

during the workshop provides insights into what type of storylines structure the space of assessment, and if they enable or constrain interactions and argumentation of the researchers. To what extent are the participants dependent on certain concept and storylines for credibility? That is, are the participants dependent on the storyline of the review papers to make their argument, or can they introduce alternative storylines and orderings of elements?

5.1 Design of two workshops

The aim of the workshops was to explore the storyline of genomics in asthma and cardiovascular disease research and thereby the structure of the spaces of assessment. Specifically, to probe how researchers deliberate and evaluate storylines on genomics and asthma or cardiovascular disease research. The use of workshops to explore storylines of stakeholder groups is an established research methodology in constructive technology assessment (CTA).[33] In CTA research, workshops in combination with scenarios have been used for experimenting with broadening the discourse of stakeholders to facilitate learning (Van Merkerk 2007; Robinson 2010; Te Kulve 2011; Parandian 2012). Workshops provide insight into the macro cosmos of the researchers and the storylines on disease, which are used (Te Kulve 2011; Parandian 2012). The workshops are a way of situating the space of assessment at a physical location to explore what storylines structure and order the spaces of assessment and the activities of the researchers. Key conditions in relation to the expected outcome of the workshop are how interactions are initiated, the composition of participants, moderation and setting of the workshop.

In setting up the workshops, I assumed that the participants were aware of the storyline of the space of assessment in the review papers.[34] The question for the workshops is, how the space of assessment is re-created in each case, and what storylines the participants draw on to align genomics with their area of research. However, I also assume that the alignment of genomics with asthma or cardiovascular disease research presents a dilemma for the participants. To facilitate the researchers in addressing dilemmas, the analysis must identify

33 My aim with the workshops is not to 'broaden and enrich' the discourses of the participants. Therefore I also do not introduce scenarios of possible future developments as this type of CTA workshop is known to do. Instead I use the workshops to get at the macro cosmos of the researchers, and the storylines of genomics that are part of their world.

34 That is that the asthma researchers are aware of the storyline of genomics as a wholesale transformation, and the cardiovascular disease researcher aware of how genomics is positioned as a broadening the success of genetic research of monogenetic conditions to the common complex cardiovascular diseases.

these dilemmas and use them to initiate interactions (Parandian 2012). The first task of the analyst is therefore to analyse how researchers themselves address or discuss the place of genomics in order to identify contradictions and contestation among accounts. For this I analysed policy documents and scientific articles as well as opinion pieces on arguments for or against genomics. Likewise, I drew on the data from my interviews and from reading the review papers. Each workshop was thus initiated with the presentation of an outsider's perspective on dilemmas facing the research area in the positioning of genomics (PowerPoint presentations can be found in appendix F).

For a fruitful discussion, it is important to pay attention to the composition of the workshop participants. For a productive discussion one should aim for optimal heterogeneity (Robinson 2010), which is somewhere between homogeneity and extreme heterogeneity. In my case the basic rule for selecting participants was that they were involved with asthma or cardiovascular disease research and that they were senior researchers. The aim was to get together groups that would represent the disciplinary mix of researchers that perform research on asthma and CVD, including both researchers involved with genomics and researchers not directly involved genomics. In this way I aimed to cover as much of the macro space as possible, thereby capturing a diversity of storylines on genomics. The participants were found by searching through the Dutch database NARCIS, in which the large majority of persons conducting research in the Netherlands are registered. I identified persons listing asthma or CVD as their research interest. I cross-referenced the selection with recommendations from my key informants.[35] For the comparative research design, it is important that the selection of participants represent the same groups of disciplinary backgrounds. Each workshop had participation from the disciplines: pulmonology/cardiology, epidemiology and genetics/genomics. However, there are also differences in the composition and disciplinary backgrounds of the participants. The different disciplinary background provides an insight into the complexity that makes up asthma or cardiovascular disease research. My data set is however too limited to conclude on general structural differences in the disciplinary background of the researchers exploring these conditions. In each workshop I also invited an outside expert. In the asthma workshop that is W1_P11, and in the cardiovascular workshop that is W2_P9. These experts were not involved with asthma or CVD particularly, but are researchers on the application of genomics for researching common diseases. In order to facilitate the researchers in mobilising diverse

35 As explained in chapter 3, during the upstart of the project collaboration was sought with a key informant in each research area. These key informants provided information on the developments within their research field, and gave advice on people to contact.

storylines on genomics, the two experts were invited to prepare a commentary as a reaction to the discussion of the other workshop participants. In practice, the two experts mixed into the discussion during the workshop as well. Table 5 and Table 6 provide an overview of the composition of the two workshops.[36]

Table 5: Composition of the asthma workshop (W1)

Characteristics workshop design	Asthma workshop
Composition of workshop participants	11 researchers (W1_P1-11) 1 moderator (W1_P12) 3 analysts (W1_P13-15)
Disciplinary background of participants	4 professors in pulmonology (W1_P1, W1_P2, W1_P3, W1_P4) 1 professor in paediatric pulmonology (W1_P5) 1 professor in environmental epidemiology (W1_P6) 1 professor in pathology (W1_P7), 1 professor genetic epidemiology (W1_P8) 1 professor in pharmacology (W1_P9) 1 professor in pharmaceutical technology assessment/head of EU research for a large international pharmaceutical (W1_P10) 1 professor in human genetics/ founder of a large centre for medical systems biology (W1_P11)

36 In terms of coding, the asthma workshop is W1 and the cardiovascular disease workshop W2. The coding of the participants first makes clear what workshop, so W1 for asthma or W2 for cardiovascular, P refers to participants and the numbers are assigned at random to cover the total amount of participants in each workshop

Table 6: Composition of the cardiovascular disease workshop (W2)

Characteristics workshop design	Cardiovascular workshop
Composition of workshop participants	9 researchers (W2_P1-9) 1 moderator (W2_P10) 2 analysts (W2_P11-12)
Background of participants	1 professor in cardiology (W2_P1) 1 cardiologist (W2_P2) 1 professor clinical genetics (W2_P3) 1 professor in molecular genetics (W2_P4) 1 professor in nutritional epidemiology (W2_P5) 1 professor in genetic epidemiology (W2_P6) 1 researcher vascular medicine science (W2_P7) 1 general practitioner/clinical geneticist (W2_P8) 1 professor in translational epidemiology (W2_P9) *

* This participant is chiefly known as an expert on genome testing and is highly visible in the debate on the usefulness of such tests in clinical practice.

In CTA workshops, it has been found productive to share the division of labour between the moderator and the analyst (Robinson 2010; Te Kulve 2011; Parandian 2012). The moderator is responsible for the flow of the discussion. The analyst is the one with knowledge of the macro cosmos and might therefore intervene strategically to push perspectives of an issue, which

the participants do not address. Overall, the discussion should be allowed to flow freely and the participants to bring up their own topics for discussion. The role of moderator is therefore important, and the same experienced moderator chaired both workshops (programs can be found in appendix C).

The presentations of an outsider's perspective on the positioning of genomics in each research field summed up in two questions/statements. The formulations were meant as icebreakers to get the discussion in the workshop going. Since the aim of the workshop was to investigate how the researchers would re-create the space of assessment and with what storylines, the question/statement was formulated as a reference to the storyline of the space of assessment found in the review papers. Chapter 4 showed how genomics was positioned as the solution to problems in asthma research. The first question in the asthma workshop therefore referred to that part of the storyline.

> *Are genome-based approaches unlikely to improve our understanding of the aetiology of asthma or lead to improved prevention, diagnosis and therapy?*[37]

As noted in the introduction, future opportunities for changing clinical practice played an important role in motivating the relevance of genomics in the storylines on genomics in chapter 4. However, for asthma the storyline on clinical improvements and changes remained unspecified. Seemingly, a shift towards more prevention oriented clinical practices was embraced. However, at no place did the reviews address how such changes would be facilitated in clinical practice. Since a shift towards prevention implies a change in the role of the clinician as well as the patient and an extension of their responsibilities. The second statement therefore refers to shifts and increased responsibility of patients to be proactive and engaged with their future health in the present. The statement was aimed at facilitating the participants in filling in the part of the storyline on clinical practice and to provide alternative storylines as well.

> *The assumption that genomic information will make a crucial difference in prevention and treatment of asthma rests on the idea that people will want to take active responsibility for their lifestyle choices.*

37 The description of genome-based approaches as unlikely to contribute to understanding asthma was constructed intentionally to provoke the participants to construct genomics as the solution to problems in asthma research. In this way I was looking for the re-creation of the storyline from the review papers (Ch. 4). The opening question of the cardiovascular workshop is likewise formulated to provoke participants to construct the storyline of the reviews where genomics was positioned as a continuation of research into monogenetic conditions. However it is less "provoking" since genomics was not positioned as I the solution in that storyline.

In the same way, two statements were used to initiate the discussion in the cardiovascular workshop. The statement for the first session was meant to encourage the participants to recreate the storyline genomics as a continuation of genetic research on monogenetic conditions as a central goal of cardiovascular disease research. Furthermore, the statement implies a narrow definition of the goal of cardiovascular disease research. It does not include goals like risk assessment and prevention. Genomics was positioned as an approach leading to improved opportunities for risk assessment in clinical practice. The statement is open for participants to correct it and to recreate the storyline from the review papers, or to introduce alternative ones.

> *Genome-based research strategies are crucial for reaching the two primary goals of cardiovascular disease research: understanding the biology and increased understanding of treatment response.*

As with asthma, the second statement was formulated to get at storylines on genomics and clinical practice. In the review papers genomics was positioned as an addition to current methods of risk assessment (Framingham risk score) or as presenting possibilities for new screening programs. Guidelines were developed on how to implement and prepare for genomics in clinical practice. The guidelines addressed the changes in responsibilities and roles by pointing to the need of educating clinicians as well as the public. The second statement was therefore designed to allow the researchers to recreate this part of the storyline.

> *Prospective and predictive personalised health care for people susceptible to heart disease cannot be successful, unless genome-based information will motivate lifestyle change on a large scale.*

5.2 The asthma workshop

The participants in the workshop assessed genomics in relation to its contribution to understanding asthma as well as its future contributions to improved therapies. For the main part of the discussion, alignment with asthma research was sought by positioning genomics as key to understanding asthma. It was also this central positioning of genomics and genes, which was at moments challenged. One attempt came from the establishment of an epidemiological approach for studying environmental influences. Contestation was brief, as this challenge to the position of genomics was reformulated as a question of a yet-to-be-invented (gen)omics approach to studying gene-environment interaction. A second attempt turned out to be more difficult to reformulate in relation to a central

role for genomics. This attempt involved challenging the centrality of genomics by positioning a behavioural component to asthma as more important. The second challenge was reformulated as a question of clinical practice. However, an interstice between a behavioural component to asthma and what I refer to as a 'molecular'[38] understanding of asthma continued to shape the interaction throughout the workshop. The interstice became particularly visible when the theme shifted from research to clinical practice. The discussion of genomics reveals that the space of assessment is structured on specific formulations of environmental influences as well as of how to understand behaviours.

5.2.1 Aligning genomics with asthma research practice

The question of the kind of improvements which genome-based approaches would lead to, was set up to provoke a reaction and it did. The participants directed the first part of the discussion on the relevance of genomics to me as an organiser, and as an outsider (I had presented myself as such) as well as a representative of a broader public. In the first part of the discussion the researchers were therefore concerned with identifying the source of contestation. The first explanation of critical attitudes to genomics sought that source in misunderstood expectations to what genomics would contribute to asthma research and practice.

> **[W1_P4]** *I would like to begin with a general remark. I really like this initiative and think it is highly interesting, but regretfully, when I read your invitation, I find the approach rather negative. The invitation says: frustration, lack of progress, tension, while I see it the other way around. I think it is a fascinating period, over let us say the last 5 years, where we, thanks to the genome-wide association studies have gotten enormous new insights. Maybe not yet for asthma, but definitely in other disease areas [...] Thus an important goal of genomic information is not just diagnosis and identifying susceptible individuals and lifestyle changes, but first and foremost to find new biological pathways involved in the pathogenesis of disease. Therefore I would provide a much more positive description of the state of genomics.*[39]

38 For lack of a better term I call this version 'molecular', since it emerged as a contested mix between: organs (like the lung), molecules (like proteins), cells, the genome and environmental factors.

39 All excerpts from the workshop are translated from Dutch to English by the author of this thesis. All excerpts from the workshop are written up to convey the main message of what was said. That is, I excluded breaks and cleaned up messy sentences by deleting repetitions and exclamations like ah, hmm and the like. Where shorter stretches of speech are left out I have marked it with [...]. Places where the speaker could not be identified are marked with an *.

The orientation to the people organising the workshop (the present author) is established in the first part of the comment. The invitational letter and the opening question is first positioned as negative and even misunderstood in terms of what genomics is.[40] This positioning is necessary for introducing genomics as a promise of future insights into disease mechanisms. Genomics is then established as the method for insight into (new) biological pathways. The success of which is demonstrated through a number of insights achieved in other fields (although not yet for asthma). Disappointment (and in a sense also hype) is negotiated by creating a link with genomics as a contribution to research on biological pathways in asthma. The construction of past achievements of genomics as successful in terms of confirming a role for genes and pointing towards new pathways justifies the re-construction of expectations to contributions of genomics for understanding asthma. With this description, the participant established genomics as central to progress in understanding asthma.

Other participants responded to this opening by introducing a second source of misunderstanding and disappointment. They constructed a failure to communicate the potential of genomics to a public defined as funding institutions and asthma patients as the reason for disappointment. A general description of asthma and clinical practice was mobilised to justify why funding institutions and asthma patients should be interested and excited about the exploration of the role and function of genes for asthma. In this general description, asthma is presented as a chronic condition and clinical practice is presented as struggling with a persistent problem of providing therapy to part of the patient group. In this explanation, the contribution of genomics is constructed in relation to a certain version of asthma clinical practice. In this version the key problem of practice, is a group of 5 to 10 percent with difficult to control asthma. A second variation (not shown in the following excerpt), which also included widening the goal of genomics to developing new medication, explained disappointment in relation to a public that has not experienced any innovation in therapy for a longer period of time. In this version asthma was constructed as a stable, yet chronic condition, which people can live with.

> **[W1_P1]** *That the urgency of research into asthma is not present in the public because someone like Phillip Cocu*[41] *has a fantastic soccer career with*

40 While this is certainly a legitimate interpretation of the invitational letter and the opening question, the response reveals the participants understanding of genomics and how it fits into asthma research.

41 Phillip Cocu (1970) used to play for the Dutch soccer team, and is currently a trainer with PSV Eindhoven.

his asthma, as has other athletes with asthma, but that is a different point

[W1_P7] *No, but my point is, I completely agree, and that is what I am trying to say, we must not lose the public. The statement that the public is lagging behind, I agree with, but we could also do more to disseminate our point of view, without promising that everything will be amazing. If you forget that, and you talk mostly among each other it is a shame because you lose a lot of the positive atmosphere and we have to exude that not just towards each other but also to the outside*

[W1_P4] *[...] We still do not have a cure for asthma. It is a chronic condition, where we can treat a large part of the patient group, but we cannot cure them. That is one point, and second, there remains a group of 5-10 per cent of the patient group, which have serious asthma that is not under control despite the best treatments that we have to offer. Third it is an extremely prevalent condition that perhaps is not increasing, but keeps at a high plateau of incidents. [...]*

[W1_P2] *[...] I think that it just is not clear to people what you can do with research on genes. To speak for myself, what I have learned from researching genes is about the heterogeneity of asthma and how to approach it differently [...] it just takes time before we can pluck the fruits of this type of research*

In the above excerpt genomics and asthma were created as a dual pair. Asthma researchers are struggling to understand why the asthma of some patients cannot be controlled. Genomics offers a solution to this problem. Not only is research into genes cast as a solution, but the asthma researchers are also constructed as just needing time to translate what they know into valuable applications. In addition, athletes with asthma are constructed as the ones to blame for creating an image of asthma as something that one can live with (even with the opportunity to perform sport at an elite level). Finally, the researchers themselves are responsible for communicating the positive message of what genomics research can contribute. Together, these reasons draw away attention from the question of potential of genomics research. Instead genomics remains central to solving problems in asthma research. The exchange reveals more of the storyline that structures the space of assessment, and how alignment is achieved between genomics and the purpose and problems of asthma research and clinical practice. Genomics is given shape in relation to asthma as a disease about which much is not known, and which in up to 10 percent of all cases is not under control. Patients and funding associations are too quick to take a few successful athletes with asthma as a sign that the disease is

solved. Asthma researchers however, are partly to blame for this misunderstanding since they have not been good enough at communicating the potential of genomics. The storylines position the asthma researchers working with genomics as the ones, who will eventually solve the mystery of asthma as well as problems in clinical practice. By positioning patients and funding organisations as unaware of the potential of genomics and the actual status of genomics, they are restricted to a role of passive recipients of the eventual outcome of the innovation journey.

In addition to a problem with communicating the positive message of genomics, the researchers also configured other research practices as necessary additions to genomics approaches. Genomics should be complimented with knowledge on how asthma is expressed from the genome, through tissue and organs. Disappointment then, is a consequence of jumping ahead to a conclusion in terms of prevention, diagnosis and treatments. To get there, many more steps need to be taken, steps that include knowledge from other research practices. Still, other research practices were constructed as contributing to, and not replacing or on equal footing with genomics. The construction illustrates another aspect of the space of assessment. Remember how genomics was initially cast as a contribution to established knowledge on environmental factors? Now, the roles have reversed, and researchers from other research practices are constructing their approaches as additions to genomics.

> **[W1_P7]** *I think that the statement misses a number of steps. If you are talking about aetiology, then it is first and foremost about surroundings and "factors". That is incredibly complex. You need to make a step in between, pathogenesis is after all my area of expertise, and how does the disease originate from the genome, from the patient themselves, expression routes in tissues, different organs, and different peripheries versus the lung? I mean that is already incredibly complex. If you skip steps you run a risk of disappointment [...] we now know how complex it is to include surroundings and all the factors at play. So, I would always do both: pathology and aetiology.*

W1_P7 begins with a reference to the opening statement. In this reference two observations are offered; one, aetiology is an extremely complex subject area, and two, the statement misses a number of steps. Next, attention to pathology is offered as a solution to fill out the missing steps, which in turn will complement the understanding of aetiology. The road towards unleashing the full potential of genomics is constructed as including pathology. The alignment that is sought is between genomics and the organ level in asthma research. Misunderstandings or disbelief in the potential of genomics is not as

explicitly located with the broader public. Instead, an explanation is sought in the scientific approach and the failure to combine genomics with other kinds of knowledge of asthma. The relevance of genomics is not disputed, but another approach is suggested as an additional building block for realising its potential.

Not all of the participants in the workshop constructed other research practices as an addition to genomics. In chapter 4, I showed how the development of a storyline for genomics in asthma research implied a general model of gene-environment interaction as the explanation for asthma. In the development of this model, environmental factors were reduced to the one side of the gene-environment interaction model, with the gene side being the one authors in the review papers would elaborate on. The environmental epidemiologist attempted to revert that balance, and introduce environmental factors as at least as important as genes for understanding asthma.

> **[W1_P6]** *[...] The question is important to consider what we actually know about environmental factors in relation to certain genetic variants when it comes to asthma. Knowledge that would lend us the support to say to people what they can and cannot do. Ultimately that knowledge is very limited [...] and if I can be very disrespectful [...] what is proven here is the phenomena of gene-environment interactions, and where there is little systematic attention being paid to the environmental side of the story [...] gene-environment interactions wonderful, give half of the money to genetics and half of the money to environment, but that is not how it goes of course*

> **[W1_P2]** *It is not that there is no attention [to the environment] [...] the fact is that we first have to learn what genetics is, that is one reason, and secondly environment has not said hey come on we really want to work with genetics, and genetics have not said hey come on*

> **[W1_P6]** *I do not know if that kind of opposition exists, it is also not about advocating for the one the other bandwagon [...] but yeah on the other hand it is about systematically thinking about how exactly are we going to do it [work on gene-environment interactions]*

In this excerpt an attack is mounted on the positioning of genomics and genetic factors, and thus on the storyline that positions genomics as central to understanding asthma. It is an attempt to introduce other types of expertise as relevant for the storyline on genomics, only this time not as an addition to genomics. In the excerpt, W1_P6 takes advantage of the introduction of lifestyle by the other participants to argue for the relevance of explicit attention to

environmental factors. Environmental factors are introduced as a crucial part of the equation on understanding asthma, and as a part about which relatively little is known. The argument is used to construct environmental factors as equally important to understanding asthma. Furthermore, much knowledge is still missing on the role of environmental factors in asthma. Therefore more funding should be directed to research on environmental factors. The mission is clear: to (re)establish the importance of environmental factors. In the response, the dramatic construction of the epidemiologist is played down, and part of the blame for the current situation is shifted towards the researchers performing research on environmental factors. The controversy is seemingly solved with reference to a future collaboration and learning.

In the opening statement, however, W1_P6 did not implicate a desire for collaboration. Rather the message was a plea for more support. The swiftness, with which mutual collaboration ends up as the outcome of the confrontation, testifies to the structuring influence of the storyline that places genomics as central to developing a new (improved) understanding of asthma. Environmental factors have a place in the space, but only in relation to genes. In the discussion, which erupted after the exchange, prevention as a future opportunity emerged as a reference point for the assessment of environmental factors versus genomics or rather genome-based research methodologies versus population based methodologies. Other participants framed the problem with research on the gene-environment model, as the difficulty of performing hypothesis-free research on environmental influences. The hypothesis-free approach to research is part of the study design of genome-wide association studies. Thinking about future options for exploration of a gene-environment model of asthma is cast in the terminology of genome-wide approaches. Furthermore, participants commented on the population studies approach of environmental epidemiology. The argument was advanced, that such studies were not helpful, as they do not contribute to knowledge on individuals that can be used for prevention. These arguments, while seemingly incorporating research on environmental factors, cast approaches to research in terms of genome-based research methodologies. The promise of genomics, and the Human Genome Project, was information on individual susceptibilities. The reference to the need for information on individual susceptibilities mirrors this expectation, and makes it a central element for the assessment of genomics as well as environmental approach. Information on individual susceptibilities is thus an element of the space of assessment that structure storylines, and one that only allows a gene-environment interpretation of environmental factors. Even the epidemiologist draws on the concept gene-environment interaction to introduce the importance of environmental factors, which shows the structuring effect of the storyline that introduced gene-environment interaction as the central

aetiological model of asthma (see also chapter 4, section 4.3.1 and section 4.3.2)

What I referred to in the introduction as a molecular model of asthma thus emerged as a contested category. The bone of contention is what should be considered as relevant for understanding biological pathways, and the role of genomics and different groups of researchers. It was not only the fixation on genomics as the sole solution to problems in asthma research that come under scrutiny, so also did also the groups performing genomics research. Instead of disputing the importance of other research directions, a discussion erupted on how genomics has so far been used, and in particular the kind of researchers carrying out genomics research. The category of amateurs was constructed to refer to the researchers who perform research on hyped topics like genomics without the necessary expertise. They were portrayed as the researchers who have researched a disease for a longer period of time, but who have not necessarily worked with genetics/genomics before. This construction countered the following response:

> **[W1_P7]** *But is it also the other way around right? It is also that the basic genetics groups have just as well thrown themselves at diseases. It keeps coming back, what you called multi-disciplinary collaboration. To move further you need both levels of knowledge.*
>
> **[W1_P11]** *But the more complex a disease gets, the more multifactorial, the more difficult it becomes to incorporate genome-wide approaches into those kinds of trajectories.*
>
> **[W1_P7]** *It has to become clear that you need all levels of knowledge. That genomics knowledge is very popular, but you need all levels of knowledge to discover the good associations, and to check that you keep your eye on real phenomena that also really take place and not just phenomena that could theoretically happen.*

The quote opens with W1_P7 proposing the opposite scenario, that also basic genetic research groups have thrown themselves at specific disease areas. Implying that the accusation of amateurism could also be directed towards geneticists. In each the replies of W1_P7, an attempt of solving the problem with amateurs is made. Instead of arguing priority for one or the other research direction, the commentary is that every discipline is needed. W1_P11 throws in a subtle warning, by stating that the more complex a disease is (and earlier in the discussion asthma has been characterised as complex) the more difficult it is to incorporate genome-based methods in multi-disciplinary trajectories. In the final comment, the statement that all areas of expertise are necessary is repeated,

but this time it contains a subtle accusation that genomics needs to be checked for dealing with theoretically imaginable events and not the "reality" of asthma. The construction of amateurs as a category for explaining disappointment in genomics is an example of demarcation of an area of expertise. It shows the influence of the storyline on the relevance of genomics, as researchers who might not have been that involved with genomics attempt to create a place for their expertise in the continued development of genomics. The category of amateurs is thus designed to keep others out of genomics research on asthma. The question of who should contribute to realising the storyline of genomics is a structural element in the space of assessment. When other research groups and perspectives would be added to the storyline of genomics, this structural elements would change and thus also the actors and interactions in the space.

The discussion in the workshop so far reveals a more nuanced picture of the structure of the space of assessment than the picture that emerged in chapter 4. The storyline that genomics will provide the solution to understanding asthma is recognised as a collective expectation, as it functions as a gradient constraining and enabling specific explanations of asthma and asthma research. The researchers position genomics centrally in relation to the problems of asthma clinical practice and research, and they position their perspective as additions to this storyline. However, they produce different perspectives on how the storyline should be written in terms of what groups should lead research efforts and what sub-disciplines would be involved and how. The central position of genomics is hardly contested. Only in the discussion on environmental factor did some contestation occur. It was promptly closed down as environmental factors were repositioned as relevant in relation to genes and genomic methods. However, towards the end of the first session the relevance of genomics as such was challenged, when a participant introduced a description of asthma where the key problem was the behaviour of asthma patients. The behaviour of asthma patient is another element, like environmental factors, where an alternative story of opportunities of alignment with genomics emerges.

[W1_P3] *You are all going to the left, and you know what you are*

talking about, so it might not be so wise of me to go to the right

[W1_P2] *You have been hired for something?*

[W1_P3] *Yes, to be the dissenting voice!*

[...]

[W1_P3] *And for a large part we keep ignoring a behavioural component and we leave it untreated. Fortunately we are going to talk about lifestyle in the next session, and I am very much looking forward to that, but if you would say now that you are actually disappointed in what has come out of genomics*

 # No, absolutely not

[Everyone talking amongst each other]

In the excerpt, a behavioural component to asthma is constructed as a key concern by portraying the previous discussion in the workshop as directed in the opposite direction. The reference to two opposite directions introduces behaviour as an alternative storyline in the space of assessment. The problem is not the composition of a molecular component to asthma, but rather why asthma patients behave as they do. In the following section I show how the researchers struggled to align the behaviour of asthma patients with genomics. As a result several storylines emerged for structuring the space of assessment and future options for genomics and clinical practice. Like with environmental factors, prevention turned out to be the central element of the space of assessment against which behaviour in combination with genomics was positioned.

5.2.2 Storylines of improved clinical practice

In the second part of the workshop, the behavioural and environmental problem definitions proved challenging for aligning genomics with a storyline of improved clinical practice. That genomics is relevant to an improved health care system geared towards personalised prevention and cure, is an essential expectation introduced with the HGP (Collins 1999; The White House 2000; Collins et al. 2003; National Institute of Health 2008, Collins 2010). The workshop discussion split into two groups. One group attempting to reconcile explanations of patient behaviour with the expectation to genomics and its potential for clinical practice, and another drawing on those same explanations

to discredit genomics as relevant for clinical practice. The crucial questions under discussion were how to understand the behaviour of asthma patients, and if genomics would contribute to changing it in a desired direction.

The workshop participants constructed or contested the alignment of genomics with clinical practice through specific descriptions of the (problematic) behaviour of asthma patients, and their (problematic) surroundings. They thus introduced more than one storyline on the position of genomics in future clinical practice. Examples of behaviours that were drawn on to construct or contest the relevance of genomics involved habits such as smoking, alcohol and not taking medication, whereas examples of surroundings included social influences/norms, the availability of fast food and pollution. The contestation on how to align genomics with asthma clinical practice testifies to the existence of more opportunities for genomics to develop. The interaction in the workshop thus nuances the unspecified and generalised description of how genomics would lead to opportunities for prevention diagnosis and therapies, which was introduced in the review papers.

In chapter 1, I introduced Francis Collins' 2010 future scenario of how genomics would contribute clinical practice. In this scenario, the individual being treated is presented as pro-active, interested and able to act on information on a future risk. In general, individuals want to live healthy, they know what a healthy lifestyle is, but they lack the proper tools to go through with a healthy lifestyle. This is where genomics comes in. Information on people's genetic make-up will enable these motivated people to target interventions and lifestyle choices to their specific situation. Genomics will be that special tool. (Collins 2010) This construction of motivated individuals runs contrary to a storyline on prevention, treatment and individual behaviours and attitudes that emerged during the workshop.

> **[W1_P5]** *We already have a whole group of preventions, where if you know you have a certain gene you can do something preventative about it. A lot of people do not want to though [act preventatively]. So, on the one hand prevention is desirable, but on the other hand people do not want to, because they do not see, or only barely see the effect – take the example of smoking – because they cannot oversee the effects of prevention. That makes it very difficult to prevent by relying on information, and with that make a difference in treatment.*

In this storyline, the problem is not a lack of preventative options or information, but the attitude of people in general. People do not want to take advantage of already available preventative options. The reason, in this example, is that the benefits of preventative measures are not clear. In general, the point of clarity

and tangibility of information was raised over and over again. Information must be clear, precise and with concrete implications for people in order for them to act on it. Smoking cessation was used as an example of how difficult it is to motivate behavioural change. Since the effects of smoking only appear later in life, it is difficult to motivate immediate behavioural change. Information, genomics or otherwise, is not positioned as that which will make a difference for clinical practice. That of course creates a problem for arguing genome-based information as relevant for prevention or other clinical practices. Clearly, the researchers in the workshop live in world where prevention as desirable, is a dominant construction. However, they interpret attempts with prevention in clinical practice as frustrating and not very successful. In addition to the above explanation, another way of understanding the frustration on prevention was put forward. In this explanation, the behaviour of the asthma patients should also be seen in relation how much their opportunities to act are restricted by social and environmental influences. Not only did these participants draw in environmental and social factors as explanation for why prevention is difficult, they also used this explanation to contest the relevance of genomics for clinical practice.

> **[W1_P6]** *[...] I think that for prevention. Lifestyle and environment, then the point is what people can and cannot decide and act on themselves. In addition to that are environmental factors [...] like fast food chains, in the direct surroundings [...] or letting children play outside. So if we are talking about general public health that is the ultimate direction we are moving towards*
>
> **[W1_P11]** *But if you do not take that coaching aspect into account, and I think that then there could be an important gain in health care [...] and you can say that everyone knows that you should not eat too much fast food, and as you make sure that there are not too many fast food restaurants in the vicinity, then that is possible to avoid. It starts however with influencing the way people think, in health care and in education [...]*
>
> **[W1_P9]** *Still the question remains if you need genomics to achieve that*
>
> **[W1_P11]** *That is one part of it*
>
> **[W1_P9]** *I am for example generally interested in a healthy lifestyle. My sister has asthma and we lived in Zaandam next to the highway, and already 45 years ago, we were told by the doctors to live on dry sand, and that is what we did, and that helped my sister. So, the question is, do you need genomics to change your lifestyle?*

This part of the discussion opens with a characterisation of lifestyle and environment as the primary factors for a healthy life. These factors are described as partly outside of people's control. For prevention to be successful it is not people, as much as their environment, which needs to change. When lifestyle and environment are the individual's control, then more information is unlikely to make a difference. The construction is a contestation of the relevance of information on genes for treatment and prevention. The follow-up construction of coaching by another participants in turn suggests that some choices are within the control of individuals. Coaching was presented as the scenario that in a future prevention oriented health care system, doctors would become more like coaches. Instead of treating illness, they would motivate and guide individuals in personalised trajectories for optimal health. If people already know what a healthy lifestyle is, then it is just a matter of supporting them in what they already know they should do. The representation of individuals in the coaching example comes close to how individuals are presented in the scenario of Francis Collins. The coaching example is answered with a personal example. In this example, a family moved to a different area to help a sister that was asthmatic. The example is potent because it illustrates how genomics is not relevant for accomplishing changes that make a difference for treatment and prevention.

In addition to the unsuccessful picture of prevention, the participants also presented current treatment trajectories as problematic. They painted a picture of a clinical practice where it is very difficult to persuade patients to take their medication. Even when adverse effect, like nightly asthma attacks are experienced, patients still do not take their medication as prescribed. Again explanations for this behaviour centred on the attitude of the patients. They were described as just wanting to be left alone, or as having an aversion against medication. One participant divided all patients into four quadrants. The one quadrant contained the patients who take their medication. Another quadrant with patients who think medication is poison, and who do not want to take it. The last two quadrants were described as a mix in between these two extremes. The message was, to concentrate on the two quadrants with patients with a positive disposition towards medications. Again, coaching was advanced as a solution to motivate these two patient groups. The exchange reveals that the space of assessment is structured by several storylines on the potential of genomics for future clinical practice.

In the workshop, several storyline of how genomics will contribute to clinical practice emerged. On the one hand, the interpretation that prevention and treatment is not as successful as it could be is shared among the participants. On the other hand, they draw on different explanations for how to understand this lack of success. Their explanations range from people simply not being interested in, or able to understand the long-term effects of their behaviour, to

the influence of environmental, lifestyle and social factors as constraining the possibilities of individuals to act. Coaching based on personalised information emerged as a storyline for the space of assessment, since it is the only attempt at aligning genomics with clinical practice. In this storyline, the configuration of future genome-based applications for clinical practice is shaped by the researchers explanation of current patient behaviours. In addition, the presentation of asthma as a chronic condition influences the choice of application. With a chronic condition is created a necessity for a life-long relation between the patient and the clinician. Such an understanding of the clinical trajectory also shapes the emergence of coaching as the solution to how genomics could make a difference for clinical practice. However, as the interaction shows, coaching was a contested solution. The place and relevance of genomics in asthma clinical practice is therefore still uncertain as no storyline (apart from prevention and a need for better compliance with treatment) functioned as a common reference point.

5.3 The cardiovascular disease workshop

As in the asthma workshop, the discussion on genomics in relation to CVD revealed much about the storylines that structure the space of assessment. In this space, the difference between monogenetic and complex CVD is used as an explanation for the difficulty in finding the genes for complex CVD. At the same time, it is the existence of a genetic component for the monogenetic conditions that guarantee the presence of a relevant genetic component for the complex conditions. In this storyline complexity was created as a central touchstone in constructing accounts of the present as well as of future opportunities. Complexity is a challenge to be solved by future research methodologies, especially new approaches based in bioinformatics. All of these explanations did not challenge the relevance of genomics or genetic information as such. Instead the explanations configured genomics as part of an evolving storyline where genetics has been key to increased understandings of cardiovascular disease. As in the asthma workshop, the central positioning of genomics was contested. An alternative storyline advanced environmental factors as equally, if not more important, to understanding and more importantly, treat and prevent, complex CVD.

In the second part of the workshop, it proved challenging to fit explanations of the behaviour of patients with storylines of genomics' contribution to clinical practice. Three storylines on the relevance of genomics developed in the workshop. In the first version, the contribution of genomics was limited to CVDs with a strong genetic component. That meant that questions of a behavioural component were dismissed as not relevant. In the second version, the need for genomics was questioned, since

a general healthy lifestyle is the best prevention. In this version, people could be free to choose what to do, since just doing something was better than doing nothing. Finally, the third version aligned genomics with clinical practice through a storyline of a personalised approach to patients. This suggestion is similar to the coaching idea in the asthma workshop. Also here, people were presented as difficult to reach with health information and even more difficult to actually persuade to change behaviours. The multitudes of ways in which the expectations to genomics are assessed testify to the evolving nature of the storyline on the relevance of genomics for clinical practice. However, in their interactions during the workshop the participants shaped the contribution of genomics mostly in terms of risk prediction and prevention. For the space of assessment, genomics, as part of individualised trajectories emerged as the only storyline aligning genomics with clinical practice.

5.3.1 Aligning genomics with cardiovascular research practice

In the cardiovascular disease workshop the assessment of genomics was closely related to the characterisation of the monogenetic and complex cardiovascular conditions. A key reference in establishing the relevance of genomics for common complex CVD was the reference to the genes of monogenetic conditions. As in the review papers, the argument that the genes for the monogenetic conditions is also relevant for exploring the biological pathway of the more common forms was drawn on to position genomics. The genes found for monogenetic forms were referred to as the 'low hanging fruit' (excerpt below), indicating that the genetic component for common CVD would be less easy to find. The metaphor helps assert that there is a relevant genetic component for the complex cardiovascular conditions, however it will just take a bit more effort to find.

> **[W2_P6]** *The reason you are now saying "what have we now actually found?" is that the low-hanging fruit has already been plucked. We are of course focused on the complex diseases and then you cannot expect that a certain tool like GWAS or sequencing is going to solve everything. As scientists, we have to be realistic and go against the hype and just be honest about the problems with complex diseases like the cardiovascular ones.*

> **[W2_P2]** *I think that GWAS could, well because now GWAS are often brushed under the carpet with reference to the variability, the amount of variability that is explained by genetic variations is quite small, but I really do not agree with this critique. All the causes of monogenetic diseases come forth with absolute clarity in the GWAS. So all loci that come forth*

with the same clarity are potential relevant biological pathways. [...]

In this exchange the participants assess the relevance of genomics in relation to the different kinds of CVD. To begin, W2_P6 differentiates disappointment of the outcome of GWAS studies to refer to the complex CVDs. Before this comment, W2_P2 has complained about the amount and complexity of data produced for the monogenetic diseases with exome sequencing.[42] As W2_P6 rephrases it, this is only a momentary low, and it is only brought on by the fact that 'the low hanging fruit', the "easy stuff", has been found. Therefore it is not realistic to expect that the remaining genes for cardiovascular disease can be found as easily. Finally, W2_P6 constructs hype as an external phenomenon, which the researchers must simply address by honestly explaining the difficulties in transferring genetic studies to complex conditions. W2_P2 picks up on the defence of GWAS as a method, and refers back to the monogenetic conditions to defend the potential of genomics for the complex conditions. For the monogenetic diseases the genetic causes of disease show up very strongly in GWAS studies, and this gives decisive clues to biological pathways. The application of genome-based data is thus assessed as relevant in relation to discovering biological pathways. In the assessment of the relevance of genomics, these researchers handle shifting criteria. The presence of strong signals for genomic studies of monogenetic conditions is a success as it can be used to discover more about the biology of these conditions. In contrast, the absence of such strong associations for complex cardiovascular conditions is not a problem, and does not indicate problems with the genome-based approach. Instead the expectation that GWAS would deliver immediate insight into complex CVD is constructed as part of hype created by outsiders. The storyline, drawing on the success of monogenetic conditions to argue the relevance of genomics for complex conditions, was not entirely uncontested.

> **[W2_P5]** *But then you have addressed 40.000 of the 16 million people in the Netherlands. So, if you look at how often mutations occur then it only relates to a very small group. You have to present that in your story.*

The response to this contestation was similar to the one above, arguing that rare mutations associated with monogenetic conditions are also relevant for common cardiovascular diseases. The comment by W2_P5 was not recognised as a valid critique, and show the strength of the storyline in structuring the space of assessment. It also reveals that other storylines exist in cardiovascular disease research, where the genes of monogenetic diseases is not seen

42 Please see appendix A for a glossary.

as guarantee of a relevant genetic component to the complex ones.

In addition to resistance to the assumption that genomics would provide data relevant for common cardiovascular diseases, contestation also developed on the role of environmental factors in explaining disease. In the asthma workshop, the storyline on a central role of genomics in understanding asthma was meet with a storyline on the central importance of environmental factors. Likewise in the cardiovascular workshop, environmental factors were pushed as relevant for further developments. However, instead of trying to think along on how to work together, the participants instead talked past each other. The following excerpt is part of a discussion on the importance of defining the phenotype (expression) of a disease for deciding what cases to include in a genomics study approach.

> **[W2_P5]** *But also because you forget the effect of all kinds of environmental factors*
>
> **[W2_P6]** *Environmental factors – in an exploratory study we found that the genes that influence blood pressure at night are different than the ones that influence blood pressure during the day*
>
> **[W2_P5]** *Yes, that is very likely, but there is also an effect of alcohol intake, semen and other factors, and if you take all that together, that can add to a considerable difference in blood pressure*
>
> **[W2_P2]** *But for cardiovascular diseases, if you correct for all present risk factors, then a positive family history is still predictive. That means that there are other important mechanisms than the normal risk factors, and they are hidden in the genome [...]*

In this exchange the participants draw on the example of blood pressure to discuss difficulties in determining the phenotype. The first comment is a reaction to the rest of the participant's construction of blood pressure as something to be primarily explained in terms of heritability. In the response W2_P6 signals to have heard the comment, but then immediately proceeds to establish genes as the key focus for a better understanding CVD. The back and forth takes place once again, before the discussion continues along the storyline of the importance of genes. For cardiovascular disease, the storyline of the contribution of genomics for a better understanding of the disease is also contested. However, in contrast to the asthma workshop, the participants did not attempt to unite the two storylines. Environmental factors are collected in tools like the Framingham risk score. They are known (not uncertain like in the asthma case). That makes

it possible to align genomics with cardiovascular disease research through a storyline on genomics as a contribution to an existing tool, and at the same time separate this research from research on environmental factors.

Complexity, as a challenge and as a feature of complex cardiovascular conditions formed a central touchstone in the storyline aligning genomics with cardiovascular research practice. The sequencing methodologies developed with genomics produce large amounts of data. The participants constructed the data challenge, not only as the challenge of handling the large set of data, but also in terms of the large amount of studies still necessary to explore and confirm the function of polymorphisms indicated in the data. During the workshop, the situation was referred to as 'so complex that the human brain can no longer keep up' (W2_P2 in the excerpt below). Bioinformatics offers a solution to this complexity through computer models and simulations. The introduction of bioinformatics as a solution enforces the usefulness of the data produced with GWAS and exome sequencing. However, even as bioinformatics was introduced as a solution, it was immediately repositioned as just part of solution along with other approaches. Similarly to the asthma workshop, genomics was thus configured as of central importance and other approaches were positioned as relevant in relation to uncovering a genetic (molecular) component.

> **[W2_P6]** *Bioinformatics is a very wide concept. As a genetic epidemiologist I am interested in environment and genes and their interaction. A bioinformatician is for example busy with the processing of sequence data. [...] So, bioinformaticians are busy with gene expression, for example building networks often only focused on gene expression [...] There will always be other people necessary to create the bigger picture, and those people will be for example people clinical experience or doctors.*

> **[W2_P4]** *But you also need a translation. Look, here we have the statement on genome-based research methodologies, it seems clear to me that with the monogenetic diseases and small families, that there, a rapid development will take place. But when it comes to their outcome, GWAS are still in their infancy, because we still do not know what gene is responsible. That is the first challenge, which one is it? [...] For that I think bioinformatics has an important role to play, and if you then want to penetrate further into the biology, well then we have to move to model systems like mice, worms, flies and zebra fish [...]*

> **[W2_P2]** *This makes it extremely complicated. I am participating in an NIH grant [...] I am lucky to be able to sit at the table with people who have an extreme brain and big track records, but what I notice every time*

in our teleconferences, is that we are not really getting any further.

[W2_P9] *That is the same message that you get in many places I heard.*

Bioinformatics is placed in context of the general aetiological model of gene-environment interaction. Since bioinformatics is just a tool for ordering data, and creating networks of how different model systems interact, the approach is not suitable for sketching gene-environment interactions. However, in order to learn more about the biology of cardiovascular conditions, a simulation model from bioinformatics is a nice start, but will have to be tested in model systems like mice, worms, flies and zebra fish. So far, the participants managed the challenge of the amount of data by reference to a technological solution and the need for additional studies. Two answers that avoids addressing the relevance of the data as such. Even further, the positioning of bioinformatics and model systems as the next step avoids addressing the relevance of exploring the function and role of genes for complex CVD. Towards the end of the excerpt, the comment of W2_P2, and the follow-up reply by W2_P9, however opens up for discussing the potential of the data, but only in relation to the motivation of the researchers. In their comment they sketch a general situation where even the best researchers are not getting any further with the data that has so far been produced with genomics.

Following the exchange shown in the excerpt above, W2_P9 continued the comment by asking the rest of the participants how long they would keep their enthusiasm for genome-based research. Since the data is so complex, and the findings do not reveal a lot about the chance of a disease developing. Next, differentiation was made between the relevance of genomics for complex and monogenetic cardiovascular diseases. For monogenetic diseases finding a polymorphism is a certain success, whereas the interpretations of finding a polymorphism for a complex cardiovascular disease is much more uncertain. The relevance of genomics data was saved in the last part of the commentary by again referencing the monogenetic cardiovascular conditions, where a lot has been learned about risk. Eventually, genomics is thus configured as relevant in relation to what it can contribute in terms of information on future risk. The exploration of a genes and the elaboration on possible biological pathways is therefore shaped as interesting in relation to its use in risk prediction. The other participants picked up the configuration of genomics as relevant in relation to risk information. They in turn provided examples of cases where genome-based information is relevant or might be relevant. W2_P9 then constructed complexity not as a problem for research as such, but more a problem for securing investment. Complexity is thus constructed as problematic in different ways: either in relation to the goal of producing information on future risk, in terms of the motivation of researchers

to carry out the work involved and in terms of the interests of investors. In turn, each of these explanations creates storylines for the space of assessment that aligns genomics with cardiovascular disease research. The choice to construct genomics as relevant for a clinical practice of risk prediction reveals another part of the world that the participants live in. They could also just argue for the intrinsic value of more insight into the biology of complex cardiovascular disease. Instead, the argument that genomics will also be relevant for understanding complex disease is linked to its contribution to clinical practice. In the review papers, authors also repeatedly stated that the main concern was the clinical implication of the information produced by genomics. The connection with clinical practice is thus important for the alignment of genomics with cardiovascular disease research.

So far, the discussion in the workshop shows that the participants recognise and reproduce the storyline of the relevance of genomics for complex cardiovascular conditions based on successes with monogenetic conditions. This storyline positions genomics as a contribution to established knowledge on environmental factors. The storyline therefore does not have to incorporate a part on collaborations or further explorations of environment. Finally, a storyline is constructed on complexity as a challenge and a promise. Complexity is at once the cause of the challenges with data interpretation and the basis of a promise of important future findings.

5.3.2 Genomics, clinical practice and a personalised approach

The statement, that genome-based information would necessarily have to lead to behavioural change on a large scale for the possibility of prospective and predictive health care, encountered resistance from the start. The immediate response by the workshop participants was to construct smoking as the number one issue to be dealt with. If people would stop smoking, then the effect would be greater than what could be achieved with research. Motivating people to stop smoking was constructed as a near to impossible job. Either the government would have to ban cigarettes all together, or researchers would have to locate the gene for addiction. Smoking cessation was, like in the asthma workshop, used as an example of how difficult it is to motivate behavioural change. Information, genomics or otherwise, is not positioned as that which will make a difference for clinical practice. This creates a problem when arguing for genome-based information as relevant for prevention or other clinical practices. Clearly, the cardiovascular disease researchers also interpret prevention as desirable goal. However, like the participants of the asthma workshop they present attempts with prevention in clinical practice as frustrating and not very successful. This leaves the participants

of the workshop with the same dilemma for explaining how genome-based information will make a difference in clinical practice. One solution was to simply construct behaviour as irrelevant to clinical practice and disease outcomes.

> **[W2_P1]** *And something else, if I turn back to my own area of expertise, to the families with monogenetic disease, there it [lifestyle] does not play a role [...]*
>
> **[W2_P5]** *But how do you mean W2_P1?*
>
> **[W2_P1]** *Well, as I just said to begin with, if our efforts to map families with monogenetic diseases succeed, then I think we have the problem of sudden cardiac death at a young age under control. Then you do not need sport screenings, or help by premature new-borns or school children [...] and all those discussion on population screening all of that you wouldn't need it anymore if we could just map those families.*
>
> **[W2_P5]** *But the challenge is still, once you identify these people, to tell them to quit smoking*
>
> *[Everyone laughing]*
>
> **[W2_P3]** *and to quit sport, that is also a counter intuitive advice*

In the above excerpt, behaviour is constructed as irrelevant for clinical practice. The move is possible as the group of CVDs is limited to the monogenetic conditions. However, the other participants immediately open up the dismissal to questioning. In the replies, two different explanations of cases when lifestyle information is relevant are at play. W2_P5's reply to the elaborated answer of W2_P1 indicates that lifestyle changes are always relevant independent of the kind of cardiovascular condition. The general storyline in the workshop on what a healthy lifestyle is summarised as: not to smoke, to have a moderate alcohol intake and to sport regularly. The follow-up by W2_P3 also hints to the advice 'to quit sport' (excerpt above) is counter intuitive.[43] However, it also shows an understanding of lifestyle advice that should be tailored to the specific situation of the patient. As the discussion continued, the consequences of these different understanding for the construction of genomics became more obvious (as I will explain in more detail below). These replies already outline different approaches to the construction of prevention and the role of

43 The comment should be understood as a reference to advice given to patients with a specific heart muscle defect (HCM).

genomics. In the one construction of monogenetic conditions, good organisation, monitoring and identification of genes are key to prevention. The patients themselves are impossible to reason with, and so their role in prevention is eliminated. The latter two approaches open up a role for patients, by constructing behavioural change as a relevant element to prevention in clinical practice.

The construction of a behavioural component as relevant to the prevention of CVD brought with it the problem of how to bridge the gap between patient lifestyle and information. One solution was to dismiss genomics information as relevant for complex cardiovascular disease. This dismissal followed the same argumentative course as in the argumentation for monogenetic conditions. The difference here is that it is not the behavioural component that is presented as irrelevant for clinical practice, but genome-based information. Motivating behavioural change in practice was again constructed as problematic. Examples were given of how even showing pictures of blocked arteries could not motivate people to stop smoking. When graphic information could not make a change, then it was argued that information on mutations that might or might not influence future risk certainly would also not make a difference. However, this line of argument was met with a counter example of people who are motivated by information.

> **[W2_P8]** *Well, I do not completely agree with you, because I more and more often experience that people come to me with their story, they hear it in the media, or read the stories of others in a magazine, and now they want to do something with that information. People get scared in some way, and then they want their cholesterol level measured.*

In this construction, people are presented as motivated due to stories they have read or seen in the media. This construction thus counters the argumentation that it is impossible to motivate people with information. As in the asthma workshop, a form of coaching based on personalised information was suggested. Here the interstice between different ways of thinking about the relevance of lifestyle change and information again showed up. Key to the coaching approach would be to enforce positive messages in interactions with patients instead of emphasising what not to do. The messages would, in addition to focusing on positive messages, be personalised and targeted to the individual. The expectation of personalised advice is a major expectation attached to genome analysis. Personalised information would allow the development of more effective therapeutic trajectories, as well as better diagnosis. Such personalised advice is also imagined to motivate individuals to a higher degree than general advice.

However, personalisation was not equally popular with all participants:

> **[W2_P5]** *Yes, but if you look at personalised advice in the area of lifestyle, then is would be very bad if you on the basis of genetic information would say to one person, well you need to change your diet, but you do not need to do so much about your exercise habits [...] You simply have to tell what you know about how these factors relate to cardiovascular disease and then everyone has to make up their own mind what to do, but the fact is the more you do the better the result, so if you are adequately physically active, do not smoke and are moderately in your alcohol intake and also eat reasonably, then the effect is greater than if you would do 2 or 3 of those, and I think we have to communicate that much more, so the total package, but if people want to follow that advice*

> **[W2_P3]** *Well, the people will never conform to the total package, we know that, but I think it could motivate by saying well for you exercise is important while for you*

In the excerpt W2_P5 responds to coaching as a solution to overcome problem concerning people's behaviour. The objection in the response is directed towards the idea of personalisation. Instead the 'total package' no smoking, be physically active, drink moderately and eat reasonably should be promoted generally. Whether or not people will then take up such advice is up to them. The two responses carry with them a subtle but important difference in the understanding of how and what kind of choices people can and should be allowed to make. Aiming at general advice, W2_P5 concludes that it is up to people themselves to decide what to do, while the coaching approach indicates a strategy to "push" people to make the right choice. Division points to different practice with giving advice.

5.4 The storylines that structure the spaces of assessment

The analysis of the review papers in chapter 4 raised the question of how spaces of assessment would be recreated in interaction among asthma and cardiovascular disease researchers. The workshop opened up an access point to the space of assessment. It offered an opportunity for alternative storylines on the alignment between genomics and asthma and cardiovascular research and clinical practice, and thus for a more complex picture of the storyline from chapter 4. In both workshops, storylines of the review papers were recreated,

and complimented with additional elements that did not show up in the reviews. The interaction in the asthma workshop revealed how the argumentation of a central place for genomics was supplemented with a description of a public and funding agencies that do not see the urgency of genomics. As a consequence genomics was made relevant in relation to a sub-group of 5-10 percent that suffer from asthma that is not under control with current medications. Furthermore, alternative storylines emerged establishing environmental factors and the behaviour of asthma patients as important unknown factors. However, the storyline on the importance of environmental factors was phrased drawing on the concept of the gene-environment interaction model. The changing storyline on genomics from the review papers —from the relevance of genes being established in relation to knowledge on environmental factors, to knowledge on environmental factors being established in relation to genes and genomics – thus structured the interaction during the workshop. It shows that this storyline of the space of assessment is a structuring gradient for organising interactions.

In the cardiovascular workshop, the storyline on investigation of monogenetic CVD as relevant for multifactorial diseases was recreated. However, it was challenged by an alternative storyline that positioned such research as only relevant for a very small group in the overall Dutch population. Furthermore, the workshop showed how researchers struggled to fit the concept of data translation into the storyline of genomics as relevant for clinical practice. To guard the future potential of genomics data, investors and bioinformatics were introduced, the former as impatient and result-oriented, the latter as the solution to the translation of data. This storyline was specific for the cardiovascular disease workshop.

In both workshops, the storylines of genomics for clinical practice were influenced by explanations of patient behaviour that challenge the relevance of genome-based applications. To take advantage of genomics information for better health, patients and individuals must be pro-active and able to act. However, alternative storylines emerged that described patient and individuals as either unwilling or unable to act on information on future risks. Coaching, as a third storyline, becomes a way to overcome the limitations of patients, and a way to align genomics with clinical practice. The drawn out contestation on this solution however, shows that the spaces of assessment are structured on storylines, each with their own future implications. The interactions in the workshop offer a glimpse of opportunities, but ones that are contested and unstable. In the reviews papers, expectations to future clinical practice portrayed change as following naturally from the results of genomics and other ‘omic’ technologies. However as the storylines emerging from the workshop show, change is starting to look a bit more problematic and complex. At the centre of this complexity are the opportunities and abilities of patients

(and people more broadly) to respond to and act on genomic information. The difference between the storylines that emerge in reviews and in workshops show the influence of the setting in which they emerge. In the review papers, alignment between genomics and research and clinical practice has been achieved to quite some extent. Alternative approaches or opposing positions to the storyline are not presented. Problems with collaborations, patient organisation, investors or patients are left out or only mentioned in passing. The workshops as described above, provide a more nuanced picture of these storylines and of the spaces of assessment. By sampling the macro space through the workshop I found that not just one, but a number of storylines are used to align genomics. Table 7 provides an overview of the storylines of the spaces of assessment as they emerged in the workshops.

Table 7: Storylines emerging in the workshops

	Research	Clinical Practice
Asthma	• Genomic approaches are key to investigating asthma as an outcome of gene-environment interaction • There is an important behavioural component to asthma that we need to learn more about	• If genomics would become part of coaching trajectories we could change practice, to be more preventive and patients would take their medications • There are important social and personal factors involved in determining if patients can act on health information.
Cardiovascular disease	• Data translation is a challenge, but can be solved with new technology and bioinformatics • Genes for monogenetic conditions are (not) relevant for complex CVD	• Genomics would be successful as part of coaching or advice-giving trajectories • We can provide information on how to minimise risk, but it is up to people themselves what to do • There is no incentive to provide people with more information. It does not motivate behavioural change.

So far, I have analysed the emergence and configuration of spaces of assessment and the storylines of the future potential of genomics that structure them. During the workshops, these spaces were structured on storylines that aligned genomics with asthma and cardiovascular disease research and clinical practice. However, in both workshops, storylines of patient behaviour turned out to be a challenge for aligning genomics with clinical practice. The description of patients as passive, not following recommendations and not understanding medical information seem rooted in established clinical practice. In established practice, roles and responsibilities are clearly distributed. The clinician makes the diagnosis, and prognosis, informs the patient, and sends the patient home with a treatment. The role and responsibility of the clinician is to diagnose and advise. It is the role and the responsibility of the patient to follow that advice and to trust in the diagnosis of the clinician. The storylines of the participants in the workshop suggest that researchers experience reality differently. Clinicians and patients already have difficulties living up to their roles as it is. In the interpretation of the workshop participants, this means that patients are very badly equipped to handle even more responsibility and to take on a bigger role in their treatment trajectories. However, this is exactly what the scenario of Francis Collins in chapter 1 suggests. It describes a future health care practice with patients that are proactive and engaged. The scenario describes patients as consumers, who pick and choose what advice they like to hear, and what diagnosis and treatment they want to follow. These descriptions run counter to how the researchers in the workshops interpret their experiences with patients. In the next chapter, I will show how representations of patients (as passive and irrational beings when it comes to their choices of lifestyle) function as a way to solve the tension between promises and expectations of how genomics will change clinical practice, and the researchers' own role and responsibility in such a change. As I will show in the following chapter, all of the representations of patient behaviour function to negotiate the question of the potential of genomics for clinical practice. This function, as part of the storyline of genomics, becomes clear when the analytical focus moves to the inter-personal level.

6 About patients and genome-based revolutions: how scientists negotiate expectations concerning the potential of genomics for common diseases[44]

Genomics, as a general approach to researching common diseases, is promoted as that which will lay the foundation for a revolution in research and understanding of common diseases. Furthermore, scenarios, like the one in chapter 1, present expectations about how genomics will enable citizens to engage with their health in order to prevent or better manage disease trajectories (Collins 1999; The White House 2000; Collins et al. 2003; National Institute of Health 2008; Collins 2010 European Science Foundation 2012). General expectations as to how genomics will change health care practices were also part of the storyline of the review papers analysed in chapter 4. In the reviews these storylines functioned to align genomics with established research practice and created a structure for realising changes towards a personalised approach in future clinical practice. Chapter 5 brought nuance to the storylines that structure the space of assessment. It showed that although the potential of genomics was generally recognised, different storylines emerged on the direction and contribution of genomics. Each of these storylines opened up different futures for the potential of genomics in clinical practice. For some, patients' behaviour seem to form too big an obstacle for genomics to overcome, while others imagined coaching trajectories drawing on more or less personalised genomics information.

The aim of this chapter is to examine more closely some of the dominant discursive resources that scientists draw on as part of the general storyline that they put forward, that is, the potential of personalised genomics (or lack thereof). Rather than determining the truth-value of what they report, we look at the interactional business performed with these reports. As discourse analysts have pointed out, speakers construct different and sometimes contradictory versions of reality to accomplish a range of goals such as blaming someone,

44 Substantial parts of the text in this chapter have been submitted as: Bitsch, L. and Te Molder, H. (submitted) "About patients and genome-based revolutions: how scientists negotiate expectations concerning the potential of genomics for common diseases."

building facts, and managing their own accountability. Therefore this study examines not only a set of interpretative resources but also the interactional goals for which these resources are deployed. Especially, the aim is to explore how expectations that information on genomic susceptibilities will motivate behavioural change, match or clash with scientist's explanations of established clinical practice. The question is how the scientist's constructions of everyday clinical practice and the role of patients (behaviour) therein affect the scientist's response to genomics as part of an approach to personalised medicine.

Scientists are important actors in shaping the innovation process of new health care technologies. Even in the early stages of the innovation process, they not only produce new knowledge but also envisage a future world, in which this knowledge is part of novel societal practices (Kay 1998; Wynne 2005). In the context of genomics as part of future personalised medicine, we focus on how scientists account for problems in the areas that genomics might affect. The patient-doctor relationship and more particularly, how patients deal with information and advice concerning health risks are the areas we address. Specifically, we focus on what their descriptions of these practices are designed to achieve, such as managing responsibility for a well-functioning doctor-patient relationship and managing roles and responsibilities in relation to the success of genomics and personalised medicine.

The strategic nature of expectations opens room for negotiation. When it comes to negotiating expectations, actors may or may not welcome the role that is implied for them in certain expectations. Genomics, as part of personalised medicine, implies a change in roles and responsibilities within current clinical practices. Patients would become more like consumers, but health-conscious consumers, caring about and actively engaging with their health. These patient-consumers would demand a different type of interaction with their physician, based on the on-going evaluations of future risks in relation to current activities and behaviours. As we will see, in order to realise such expectations, or at least to make them part of a conceivable future, scientists must somehow not only deal with the roles implicated for them in these storylines, but also with those claimed for publics or patients. For example, they are expected to link up with the revolutionary promises of genomics and to promote them towards others. Likewise are expected to support images of a public capable of using genomics information for better health. Bouwman and Te Molder (2009) showed how stakeholders made themselves part of the future of personalised nutrition by establishing themselves as 'gatekeepers of innovation' (p. 258), that is, as experts on what the publics want and can or cannot do. In addition, the stakeholders constructed themselves as unable to move, insofar as they had to wait for better evidence from other researchers.

By doing so, the stakeholders avoided an active role in the development of personalised nutrition, yet still managed a position as responsible experts.

The question is what expectations concerning the potential of genomics for research and clinical practices are constructed here, and what objectives they are designed to achieve. Instead of merely offering a collection of statements from scientific experts about what genomics can do for society, we look at what scientific experts achieve by preferring specific descriptions of the contribution of genomics to research and society over others. For example, by constructing publics as unable to take advantage of risk information, an innovation like a genome-wide test can be presented as not yet ready for use. In this way, scientists may avoid having to address their own role or responsibility in developing their work in a specific direction.

By highlighting what scientists achieve with specific descriptions of conflicts, concerns, and opportunities concerning the incorporation of genomics in clinical practices of asthma and cardiovascular disease, we add to our understanding of the performativity of storylines. It shows how storylines are structured and put to use at the inter-personal level, as part of continuously shrinking and expanding spaces of assessment. Thus the analysis goes further than showing how researchers may or may not draw on the description of genomics as a revolutionary force. We show how participants actively manage the tension between established doctor-patient roles and responsibilities, and the new horizons outlined in this respect by the use of genomics for clinical practice. They do so by establishing themselves as gatekeepers to the innovation process without making themselves responsible for its ultimate success or failure.

6.1 A discourse analytic approach to scientists' accounts of the potential of genomics for clinical practice

The perspective used in this chapter is a form of discourse analysis as developed by Potter and Wetherell (1987). Their approach moves from the perspective of the analyst to the perspective of the research object (in this case: the scientists). In general, the concern of discourse analysis is to make visible how discursive constructions are oriented to action, that is, the way discourse is central in constituting events, settings, and identities. Speech in this sense is constructed and constructive. That is, talk does not simply reflect the world or people's mental state, but it is used actively. People construct descriptions of their

world and mental states in order to achieve interactional goals, like building expertise or certain identities, or to compliment, blame or accuse someone. The descriptions or the discursive resources on which people draw in order to achieve certain interactional goals are referred to as interpretive repertoires: *'An interpretive repertoire is a culturally familiar and habitual line of argument comprised from recognisable themes, common places and tropes'* (Wetherell 1998:409).

6.2 Method and data analysis

The analysis is based on 20 one-hour interviews with medical scientists in the Netherlands and the United States (US).[45] Three of the interviewees are primarily genome researchers (two of them are the US interviewees). Of the remaining group, seven work within asthma research and use genomics methods, and ten work within cardiovascular disease research and use genomics methods. The US interviewees are based in the National Institute of Health (NIH). The Dutch interviewees work within a range of Dutch academic hospitals, research clinics and larger pharmaceutical companies. In the process of locating interviewees we used two strategies. For both research fields, contact with a knowledgeable informant was established as part of writing the proposal for the present research project. These informants were then interviewed, in order to get some information on the structure of their field and about other persons to interview. In each of the interviews the interviewee was solicited for other persons to interview. Furthermore, the Dutch database of researchers and research projects (NARCIS) was searched for persons reporting asthma or cardiovascular disease together with genetics and/or genomics as their field of interest. Their research and bibliographic descriptions formed the basis for deciding whether or not to invite them for an interview. Since we wanted to probe how scientists involved with genomics research projects envisaged genomics' future contribution, the researchers involvement with genomics research projects was a selection criterion. The interviews were structured on four main topics: important developments in research in the last 10-15 years, current challenges for research, perspectives on future developments, and thoughts on future contributions of research to clinical practice. These categories remained stable during the whole interview process. However, in each interview the questions were adjusted to fit the context of the interviewee.

For our analysis, we employ the analytical principles of discursive psychology. Discursive psychology shares with other discourse analytical approaches an understanding of language as an actively constructed tool. Accounts of reality are

45 The present author conducted all the interviews.

necessarily selective, and therefore, they should be understood in relation to their situated use and effect (Potter 1996; Sacks 1992). The crux of discursive psychology is to understand how descriptions are made available in talk for particular interactional purposes, such as blaming, shifting responsibility, or building specific forms of expertise. The analysis concentrates on discursive actions in sequence, and draws on the turn-by-turn development of a conversation to make sense of the social actions achieved by participants. The way conversational partners treat and understand each other's talk is therefore an important point of focus for the analyst. In addition to the turn-by-turn development of a conversation discursive psychologists use the rhetorical principle (Potter and Hepburn 2005; Wooffitt 1992). The analyst considers why a specific version of reality is produced at certain moments in the conversation. A claim to a certain version of reality functions to undermine alternative versions and alerts the analyst to the interactive purpose of a specific construction. It is important to notice that we do not make any claims with regards to the truth-value of accounts, nor report on what people really think or feel. Instead the aim is to analyse the interactional achievements of the participants' talk by the active deployment of particular interpretive repertoires.

Discursive psychologists preferably work with naturalistic data, where the researcher does not influence the turn-by-turn development of a conversation. The disadvantage of interviews is precisely that the interviewer is likely to influence the turn-by-turn development of the conversation. However, in order to compensate for this disadvantage, the talk of the interviewee is analysed in relation to the input of the interviewer. The interviews are therefore analysed as a conversation (Potter and Hepburn 2005). Furthermore, open-ended interviews provide plenty of room for interviewees to bring up their own topics, which already structures the interview as a conversation.

The use of interviews for a discourse analytical project depends on the research questions, the availability of naturalistic data, and the kind of interactions that are studied (Potter and Hepburn 2005). In this case, the scientists' descriptions of expectations to genomics are less likely to be invoked in naturalistic settings. Scientists' expectations concerning the potential of genomics for research and clinical practice are less likely discussed among groups of researchers. Indeed, in their daily practice they are more likely to discuss experimental details and challenges than expectations of the wider impact of genomics. Interviews therefore allow for a probing and exploration of narratives, which scientists themselves might take for granted. Most of the interviews were conducted in English, but two were carried out in Dutch. The interviews were tape-recorded and transcribed by the author of the present thesis to word-level accuracy, including speech errors, pauses and overlapping speech. A standard interview

protocol can be found in appendix D. To assist in reading the excerpt the transcription notation used to transcribe the interviews is included below.

Transcription notation, Based on (Jefferson 2004)

[text]	Overlapping speech
(x)	Pause of x seconds
(.)	Micropause, less than one second
word	Emphasized
(text)	Transcriber's remarks
=	No pause between turns or words
?	Questioning intonation
Ah::	Colons mark the prolongation of the sound immediately before
-	Cut-off, self-repair by starting a sentence anew

6.3 Results

When analysing the interviews with the asthma and cardiovascular disease researchers we found four different descriptions of patients, which included four different opportunities of applying genomics in clinical practice. These descriptions are all versions of what has been referred to as the 'gatekeeper repertoire' by Bouwman and Te Molder (2009). In a study of personalised nutrition, they showed how stakeholders negotiated their role in innovation trajectories on personalised nutrition by displaying themselves as experts on the wants, needs and capacities of the public. In so doing, they could present themselves as controlling access to the innovation process, without however being responsible for its end result. In one version, the public was described as not ready for the innovation, because publics cannot deal with information on risk. Instead, information with no uncertainty is needed, but since that is not available, the public should be protected. This version made it possible for stakeholders to avoid taking an active role in developing the innovation. An alternative version also emerged, although only in two interviews, where publics were described as wanting personalised nutrition advice. That made it possible for the stakeholders to take a proactive attitude to innovation.

In response to our question concerning the future use of genomics, the interviewees also drew on the gatekeeper repertoire for these two purposes. However, we found two additional versions of the repertoire. In one version, the "problematic" behaviour of the public was used to argue for a technological fix like a pill or the need for broader social and cultural change. In the other

additional version, publics were portrayed as unreliable, that is, unpredictable in adhering to genomics-based advice or information. Each of these descriptions allowed the scientists to explain the success of genomics in clinical practice, or lack thereof, for that matter, without carrying responsibility for these outcomes.

6.4 Gatekeepers of personalised genomics medicine

The scientists solved the tension between the role and responsibilities implied by the patient-doctor relationship in current practice, and the proactive consumer of future genomics, by constructing four different descriptions of patients. Each description was matched with an opportunity for the clinical application of genomics. Except for one scientist, all the interviewees constructed the behaviour of publics as a problem. Only the genome scientist based in the US constructed an alternative version. In the first of these dominant versions, the scientists solved the problem of clinical applicability by suggesting that genomics could and should be used to provide more personalised advice to people or to improve treatment trajectories. In the second version, information on genomics susceptibilities combined with knowledge on environmental risk factors should lead to large-scale societal and cultural change. Finally, the third version constructed genomics as not what is needed in clinical practice. As I will show below, each of these versions were tied up with a specific description of patients. Each of the repertoires allowed the scientists not only to account for the current state of genomics in clinical practice, but also to avoid having to take a role in making genomics a success in future clinical practice. The scientists achieved a position as protector of the public and reader of their needs and wants. In the fourth version of the repertoire, the US genome researcher constructed publics as proactive and capable of taking advantage of genomics information. In this version, publics were created as being similar to the scientist. Publics, where, as the scientist, interested in their health, and aware of what a healthy lifestyle is, but yet somehow not quite able to take the last step and actually change their lifestyle. This is where genomics comes in as the tool that enables people to live the life they always wanted. With this version of the gatekeeper repertoire, the genome scientist manages issues of responsibility in terms of promoting genomics as useful for clinical practice. The evidence of usefulness is already there in the form of the scientist himself as a model of how the general public thinks and behaves. In each of the uses of the gatekeeper repertoire, the scientists are established as the evaluator of what should and should not be pursued for clinical practice. The repertoire eliminates the need to consult publics on their needs and wants, since the scientists already know them.

6.4.1 Version 1: the success of genomics and personalised medicine depends on unreliable patients

In this version of the gatekeeper repertoire, the scientists construct information on genomic susceptibilities as useful. Whether or not this potential will unfold in clinical practice, depends on the patients. Information on genomic susceptibilities combined with advice from clinicians, would in principle, facilitate patients in making healthier choices. However, patients are unreliable, and it is difficult to say whether or not they would be able to improve their situation. Thus they emerge as the weak link. In these accounts, patients need a coach or a clinician to help them interpret, understand, and act on genomic information. The descriptions reveal the difference in the capabilities prescribed to health care professionals versus patients in understanding health information. Patients do not interpret this information the way they should. This can be seen from the way they behave, by still engaging in unhealthy behaviour, even though they are aware of its adverse effects. However, if the clinician and the patient take responsibility together —the clinician for delivering the information and the patient for making the right choices— genomics may become a valuable tool in clinical practice. This repertoire reinforces the distribution of roles and responsibilities embedded in current patient-doctor relationships, but expands the relationship to also containing activities of prevention and risk assessment. Drawing on this version of the repertoire, the scientists watch over the boundary between doctors and patients, while being also able to account for how genomics could be successful in clinical practice. At the same time, the construction of patients as the weak link counters speculations on the skills and capabilities of doctors in giving advice and on the adequacy of the current set-up of roles in doctor-patient relationships.

Excerpt 1 illustrates the construction of the difference in capacities between health care professionals and patients. The scientist being interviewed is a professor in genetic epidemiology specialised in cardiovascular disease.

Excerpt 1

(L=interviewer, S19=interviewed scientist)

370	L:	Do you-do you think that (.) the health care system
371		would have to change to take up this new information
372		or do you see it more as an extra tool for the clinician
373		or the general practitioner (.) to guide people?
374	S19:	(0.2) You mean at this stage already or?
375	L:	No in the future (.)
376	S19:	I think yeah in the future (.)
		(377-380 omitted)
381		But there is no treatment (.) so it doesn't really make sense
382		to offer a test (0.2) aaahhm (0.3) but yeah if there is a
383		treatment and eeh I think (.) those types of tests may at
384		one point become feasible and (0.2) informative
385	L:	Hmm treatment or even prevention if you could do
386		something (.) to advise people to yeah
387	S19:	Yes yes potentially (.) but then you know there is (0.2) then it
388		involves behavioural change and that is a different science and
389		that is also very difficult to (.) even now it is very difficult to have
390		influence on the public and to have them change their behaviour
391		become more-take up healthier lifestyle (.) so that is a different
392		issue but you know what I am saying is eh (0.2) you know
393		everyone that smokes knows it is eeh it is bad for you but still
394		they smoke right so eeh you can provide people with knowledge
395		about their genetic risk but then will they do something with it?
396		or I don't know you know so it is eh is-but it works in the
397		same way (.) I think but maybe the general practitioners
398		may be able to use it to (.) eeh (.) you know more tailor-made
399		treatment for example or tailor-made prevention (.) and give
400		them more direct advice on what they should (.) should do

The interviewee constructs genomic information as something that might be useful in the future (lines 374-384). Then the interviewee proceeds to elaborate on the different capacities of health care professionals and patients in dealing with this kind of information (lines 385-400). Understanding people's behaviour is characterized as 'a different science' (line 388) – suggesting that one cannot be held accountable for not grasping it, let alone for not being able to change it —but then, the difference is nonetheless portrayed as clear and readily available. The description of a general public that smokes, while knowing that it is not beneficial for their health, functions as a contrast to the health care professional, who is capable of using such information in clinical practice. By expanding the group of people that behave irrationally to include publics in general, the scientist creates a

sharp boundary between the health care professional and everyone else, and in the last instance, the interviewee as the evaluator of this behaviour. At the same time, patients and others become part of the same homogeneous mass with the same characteristics. At several places in the fragment, the scientist uses the discourse marker 'you know' (lines 387, 392, 396, 398), as to invite the listener to accept the description as generally accepted knowledge. It is not only that the interviewee maintains that people smoke even though they should not, it is common knowledge that they do. Furthermore, the reference to tailor-made prevention and treatment is put forward with reference to a commonly shared understanding "you know tailor-made prevention and treatment, you probably heard that as well" (my paraphrase). All of this may work, provided that the unpredictable patients collaborate (lines 394-395). Thus the scientist achieves a position from where it is not necessary to account for the potential of genomics in clinical practice. The public is in charge of making (or not making) genomics and tailor-made prevention and treatment a success. The potential is certainly there when it comes to genomics and the health care professionals, but when it comes to the public, only time will tell.

6.4.2 Version 2: The success of genomics and personalised medicine depends on broader social and cultural change — or a pill

In this version of the gatekeeper repertoire, the scientists construct genomics either as part of broader social and cultural change, or as contributing to a technological fix in terms of a pill. This version functions to solve the unsolvable problem of patient behaviour. Changing patient behaviour is constructed as a difficult if not impossible problem to manage. Therefore, a pill or social and cultural change would be the only solution to make people change and behave in a healthier way. This version of the repertoire places the responsibility for making genomics work in the hands of the patients as well as with the wider society. The difference between this version and the former one concern the specific discursive resources the interviewees draw on. In this version, patients are more than unreliable; they are without a chance to change their behaviours. Therefore genomics is not suitable for use in treatment or prevention trajectories like the ones suggested in the first version of the repertoire. Again, the scientists maintain the boundary between genomics and its possible use in clinical practice by constructing a description of patients as unable to use it. By using this version of the repertoire, the scientists achieve a position where they do not have to account for the potential of genomics in clinical practice. In fact, it is not information on genomic susceptibilities that is needed. What is needed is a full proof solution to the problem of people's behaviour

and the overwhelming amount of temptations of our society to act unhealthy. A pill or broader social and cultural change, may overcome that challenge.

Excerpt 2 illustrates how a technological solution like a pill is constructed as the only solution to help people live healthier lives. The interviewed scientist is a professor in human genetics.

Excerpt 2

(L=interviewer, S7=interviewed scientist)

764	L:	People would also have to change I guess?
765	S7:	Well=it=depends so I-so I don't think it is easy
766		if people are obese to put them on a diet that's=
767		not=gonna=work but if we could-so if we
768		understand better (.) why some obese people
769		develop diabetes and others don't (.) so if we
770		understand the molecular mechanisms maybe
771		we can develop a pill (.) that can-although you are
772		obese-can prevent you from going to this diabetic
773		end stage then you are still obese which is (.) has all=
774		kinds=of=other=drawbacks but still you would
775		be kind of healthy obese (.) because I think we
776		have=to accept that we live in a world where
777		there is simply too much food

In response to the question regarding whether people would have to change, we are told that it is difficult to get people to go on a diet (765-767). This characterisation is then substantiated by the description of our world as one where there is 'simply too much food' (line 777). Such a description implies that people are not able to control themselves in the face of food. Furthermore, such a lack of impulse control is constructed as bad insofar as it leads to disease and obesity. However, as it is constructed in lines 770-775, diabetes is the more serious of the two. Therefore even though obesity is not desirable, a pill can help you to be a 'kind of healthy obese' (line 775), which at the same time suggests that it is not really possible to be a healthy and obese. In the face of this challenge, a pill is the best solution because people can keep up their lifestyle, but still avoid disease. In this excerpt, the scientist carefully constructs the disease, diabetes, as that which we need to know more about. People's behaviour on the other hand, is not much of a mystery: they simply lack control over their instincts.

In addition to a pill, broader social and cultural change was suggested as a

solution to the difficult problem of patient behaviours. The following excerpt has been split in two. First we go through the part that illustrates the construction of social and cultural change as a desirable and even necessary extension of information on genomics susceptibilities. The interviewee is professor of molecular genetics with a special interest in cardiovascular disease and diabetes.

Excerpt 3a

(L=interviewer, S14=interviewed scientist)

447	L:	The next thing is eeh once you have the-these
448		predictions what to do with the information?
449:	S14	Mhm (.) well the ni::ce part is of course
450		that it-that it is so sensitive to the environment
451		I like that much=more than if you would need
452		medication (0.2) I mean cardiovascular disease
453		and also diabetes are-for a main part also
454		gene environment interaction
455	L:	Yeah so what you are saying that it is nice
456		that because you can actually just say "well
457		this is diet related or exercise"=
458	S14:	=Yeah you can motivate people that is what I hope
459		but then that might be more maybe (0.2) closer to
460		your area than to mine what you need
461		what you need to pump into the general public I
462		think there is a web site on it that in the UK they
463		a::lso eeh (.) have (.) multidisciplinary team from
464		the government (.) that thinks that obesity is not
465		a problem of the food industry but of also everybody
466		so they think of staircases that are steeper
467		or-something to get people automatically more
468		active-motivate people to move
469	L:	So-it is actually-it is culturally constituted in the
470		way that eh society-buildings are built and (.)
471	S14:	Absolutely you need to tackle everything
472		it is such a-you will never get there by advertising
473		dietary discipline (0.2) but I think it would be a
474		good start but you need to do much=more

The need for more than individual change is created in lines 458-68. Before that, the interviewee establishes information on genomic susceptibilities as a reason to be optimistic about dealing with complex conditions (in this example, diabetes as part of co-morbidity in relation to cardiovascular disease). Optimism is warranted as results from genomics point to the influence of the environment.

Here, environmental change is contrasted to medication as a different route for change. Initially, this opening points to the possibility for people to become motivated and to change their behaviour as the reason to prefer environmental change. However, when the interviewee continues, it is no longer the motivation of individuals that is put forward as the true solution, but rather, broader social and cultural change. Motivation is nice, but 'you need to do much more' (line 474). This 'much more' is, for example, a change in the architecture of buildings, which need to be designed in such a way as to motivate people to climb the stairs.[46]

In the following passage, the interviewee also provides a description of the group that makes such thorough measures necessary. Thus excerpt 3b illustrates the construction of a public whose behaviour is impossible to change.

Excerpt 3b

(L=interviewer, S14=interviewed scientist)

467	L:	Do you think there are misunderstandings in the public
468		around what eeh what you-what you can do with
469		genetic or genomic information?
470	S14:	I=think=so yeah (0.3) yeah because eeh the nicest
471		example is once I eeh (.) I told my eeh (.) cleaning=lady
472		what I was doing for work (.) a::nd I see her as a
473		representative of half the Dutch population (.) and she
474		tells me: "Well (name of interviewee) you know when
475		my time comes it will come", it's that easy so it is
476		like-it is more like a Japanese belief in fate so I
477		think; "Okay so that is what we are up against"=
478	L:	=Yeah
479	S14:	How can you motivate these people (.) they smoke like
480		crazy drink like idiots and eeh and and-the good part is
481		that they usually have a more active lifestyle(.) in terms of
482		moving-not everybody but many of them-so (.) but still
483		they are of course-there is a huge difference in morbidity
484		with the lower social classes in Holland so (0.2) but yeah (.)
485	L:	Yeah it's a complicated problem because you can also ask
486		like how much is up to the responsibility of the individual
487		person how much is eeh=
488	S14:	=Yeah but if=they=don't=know (.) they don't understand it

46 Actually many of the interviewees insisted on taking the stairs when we walked to the meeting rooms where the interview would take place.

In response to the question about misunderstandings of genomics, the interviewee offers a personal example. It features the cleaning lady who works for the interviewee. She is described as typical of half of the Dutch population (line 473), and as not quite having understood the meaning of genomics information. The cleaning lady's response to the interviewee's account of genomics is to delegate the responsibility of future outcomes to chance. This reply is constructed as not matching up with the kind of response a rational person would have in the light of such information. The interviewee creates further distance to this half of the Dutch population by describing it as 'the lower social classes' (line 484), a general description of which is given in lines 479-484. This group displays a behaviour that defies rational explanation: 'smoke like crazy and drink like idiots' (479-80). When the interviewer suggests that the issue might be more complicated, the brief reply in line 488 claims that people (simply) do not understand. Well in first instance people might not even know, but when they are told, they do not understand genomics information. The rather drastic measures of changing people's surroundings so they will have no choice but to take the stairs are thus justified (at least for one half of the population).

In both excerpts the interviewees identify a specific group to illustrate the need for broader changes. In excerpt 2, it is 'the obese', and in excerpt 3b it is the 'lower social classes'. It is interesting to note that this does not happen in the other versions of the repertoire, where the interviewees talk much more generally of publics, people, or patients.

6.4.3 Version 3: Genomics and personalised medicine is not what the public wants

In this version of the gatekeeper repertoire, people are constructed as unable to interpret (uncertain and complex) information on risk. Typically patients are constructed as wanting clear and definite answers on disease risk. However, even if they had these answers, they would still not be willing to change: they 'prefer their own disease' (excerpt 4, lines 709-10) to making an effort to be healthy. On the basis of this experiential knowledge, scientists created a bird's eye view from where to judge what kind of innovations should be transferred to clinical practice. As a consequence the option of exploring genomics as a possible clinical application together with patients/publics or the interviewer for that matter is closed down. This description is based on a construction of publics as unable to make use of risk information in order to improve their health. With it the scientists create a distance between the success of genomics in clinical practice and their own responsibility for it. Instead, responsibility for the success of genomics

in clinical practice is transferred to patients. The repertoire implies that the scientists are better able to deal with information on risk. That, in combination with their knowledge of the public, is why they are in the position to evaluate whether or not genomics is ready for clinical practice. The repertoire mirrors the established roles and responsibilities of current doctor-patient relationships. However, in contrast to the other uses of the gatekeeper repertoire, no solutions are proposed. Rather the scientists judge the condition of current interactions and the potential of genomics as what is not needed (now). In fact, if patients would just live up to their responsibility, current practice is good enough.

The following excerpt illustrates how people's behaviour is interpreted as showing a preference for being ill in the face of having to choose between future risk and immediate change. The interviewee is a professor in paediatric pulmonology.

Excerpt 4

(L=interviewer, S6=interviewed scientist)

698	L:	Perhaps you could imagine (.) a new role for general
699		practitioners ehm I have heard someone mention
700		this idea of eeh of doctors more as coaches for
701		people eeh?
702	S6:	Yeah yeah they may not be doctors (0.2)
703		I think doctors are not very good in doing this
704	L:	ah no well it=
705	S6:	=they may play a role in de-defining how this should
706		happen (.) and eehm (.) especially in our society I am
707		not convinced that people would like to have this
708	L:	hm ok (.) you-you mean the doctors or the patients?
709	S6:	the patients
710	L:	ok (.)
711	S6:	I think in the end they may prefer to have their
712		own disease and (.) and be wheezy from time to
713		time but not have a coach
714	L:	and is that-is that because you have experience
715		with-with people (.) that you say this
716	S6:	Absolutely (.) yes

The interviewee establishes patients as the key problem in two steps. The immediate reply to the suggestion that genomics could be part of coaching trajectories is to point out that doctors are not very good at coaching (lines 702-703). However, the interviewee continues, a second reason why 'people' and 'society' are obstacles in the road to change is being put forward (lines 706-07). In fact, patients are the ones

who prefer to have their disease above behavioural change (lines 711-716). With the closing remark, the interviewee builds on the suggestion of the interviewer to ground the description of patients in experiential knowledge (lines 714-716). This closing strengthens the earlier description of patients' preferences, and turns it from a personal opinion into a fact proved by many years of experience. The admission that doctors are bad coaches, as well as the description of patients as preferring their disease above difficult behavioural change, helps to establish a position where the scientist is not responsible for the success or failure of genomics in clinical practice. Genomics information is simply not what is needed or wanted.

Excerpt 5 illustrates how scientists create an insurmountable difference between themselves and lay people when it comes to understanding risk information. The interviewee is a professor physician and epidemiologist and occupies a higher-level function in the National Human Genome Institute at the US National Institute of Health (NIH).

Excerpt 5

(L=interviewer, S2=interviewed scientist)

162	L:	Yeah yeah I guess it can be quite difficult to relate to this
163		idea that you know in 10 years you have 10 per cent
164		chance or 15 per cent chance to develop eh (.)
165		yeah some-some disease eeh?
166	S2:	Yeah well yeah that's particularly difficult as most
167		people if you tell them you know you have a 10 percent
168		chance of developing heart disease they'll say: "well fine,
169		you know 9 to 1 I won't get it" so quite great=
170	L:	=Yeah
171	S2:	=and then ehm you try to explain to them well that
172		you know probably 20 times the risk of somebody
173		your= age should=have eeh they still don't get terribly
174		excited about it so-so it is a real challenge to communicate really

The difference, between how a health care professional, and how a lay person interpret risk is established in lines 166-169. The interviewee uses the example of telling someone the risk of developing heart disease. Upon learning a risk of 10 per cent, people tend to react relieved and to rely on not getting a heart disease themselves. Next, the interviewee establishes that as a sign of misunderstanding risk information (lines 171-174), by contrasting the response of the layperson with a professional interpretation of the information. A 10 per cent chance (at that age, an

age we are not told, but presumably young) is more than 20 times the average. Still, people do not 'get terribly excited' (line 173-74). To not get excited is clearly the wrong response as the interviewee ends the description by re-stating how difficult it is to communicate risk information (seen in the light that people seemingly do not understand and respond correctly to it). Together these descriptions of the doctor-patient relationship and the limited capacity of patients to correctly interpret and follow up on risk information, allow the scientists to present themselves as not being the spindle that matters in making genomics work for clinical practice. Instead the doctor-patient relationship, or the approach to communication, emerges as solutions to problems in clinical practice. However, at the end of the day it is really people's attitudes and cognitive abilities, which should be worked on.

6.4.4 Version 4: Genomics and personalised medicine is what the public wants

An exception or so-called deviant case in the interviews was the construction of a public, which is not lacking in ability, but rather in tools for making healthy choices. The US genome scientist was the only interviewee to use this version of the gatekeeper repertoire. This construction —to a certain extent— presents the interviewee as part of the public. This is accomplished by equating the experiences and behaviour of the scientist with that of a broader public. The effect is a powerful description of how even a cynical expert scientist is transformed by genomic information into a citizen who actively takes responsibility for his/her own health. As a result genomic information receives a special status as the tool, which will enable people to lead a healthy live. With this description the scientist achieves a position where it is possible to account for genomics as useful for healthier practices. Simultaneously the scientist does not have to defend the positive image of genomics to accusations of being uncritical of, or perhaps even promoting genomics. The evidence is already there, it works, and people want it. Note how again the scientist positions himself as a gatekeeper to the innovation process, as he is not only a scientist but also an ordinary human being with the same drives and limitations as anyone else.

The interviewee is what can be called a frontrunner in genomics with a prominent position in the NIH. In other words, it was to be expected that genomics would be promoted. Interestingly enough, however, the construction of a brighter future of genomics went hand in hand with a role for publics and patients that was strikingly different from how the other participants designed it. In this sense, the fourth version of the gatekeeper repertoire was a deviant case that confirmed rather than disconfirmed the pattern as found with the other participants: it showed

that a brighter genomics future goes together with a more active and independent patient image, whereas a more indeterminate or even gloomy future requires more passive, unwilling or less capable patients. Excerpt 6 illustrates how a public is created that is capable of using genomics for initiating a healthier lifestyle.

Excerpt 6

(S1=interviewed scientist, L=interviewer)

192	L:	Is it enough to know the genetic
193		variations that a person has?
194	S1:	(.) owh it is not enough but it is
195		helpful in terms of making some
196		predictions about risk and getting
197		insight into pathogenesis
(198-201 omitted)		
202	S1:	If we find out about our risk and know
203		therefore that we could modify our
204		environment in a way that would be
205		beneficial that seems like an
206		empowering mo::ment and something
207		people might be interested in=I have had
208		my own DNA analy::sed and this is all
209		described in that book (a book of the
210		interviewee that was due to be published in
211		soon after the interview) a little bit and
212		it actually (.) to my surprise it did
213		have more of an impact on me than
214		I expected=
215	L:	=hm
216	S1:	=I kind of was a little bit of a cynic about all this

The empowering nature of information on genomic susceptibilities is constructed in lines 202-06. Environmental influences are important and malleable influences over which people have power. Even so, the interviewee is at first careful in constructing people as empowered by this information, as we are first told that it is 'something people might be interested in' (lines 206-07). However, he then suggests that merely receiving the information turned him from a sceptic into a believer. If even a scientist is convinced by genomics information it must be powerful information. Indeed as the scientists continues (not included here), the example is broadened to how this information has provided the scientist with the motivation to get involved with an exercise program and lose weight. By describing how people equipped

with genomic information are able to deal with their environment in such a way as to become healthy again, genomic information becomes the determining factor, which makes people capable of such action. Showing how genomic information also changed the behaviour of the interviewee, who had serious doubts about the force of such information in the first place, supports the claim. This narrative counters the idea that the researcher's claim about the force of genomics is the product of some stake or fixed expectation — it must be the product of the facts themselves. This move both makes the interviewee knowledgeable about the public as such as well as creates a standard for how to measure the applicability of genomics. The public in general is like the scientific expert. Deep down everyone wants to change their lifestyle and behaviour, however the right tools are lacking. With the emergence of genomics, this gap between desire and ability is finally bridged. The capable public as a discursive resource thus functions to account for a proactive attitude of the scientist towards genomics and its applicability in clinical practice.

6.5 In conclusion

In this chapter we explored how scientists account for the expectations that information on genomic susceptibilities will, or will not, motivate behavioural change and lead to changes in the roles and responsibilities of established clinical practice. In general the scientists judged the possibility that information on genomics susceptibilities would change patient behaviour in relation to what they constructed as typical patient behaviour in current clinical practice. In doing so, the scientists established themselves as gatekeepers to the clinic and as experts on patients and publics. They accomplished this position by constructing four different versions of the so-called gatekeeper repertoire. In each version the scientists drew on descriptions of patients and the wider public as to motivate opportunities for clinical applications of genomics, or a lack of opportunities for that matter. All versions placed final responsibility for the success or failure of the innovation process with the patients or the general public, rather than focusing on the scientists' responsibilities.

The four versions differed from each other in the ways in which patients or the publics were depicted. This difference in discursive resources also led to different implications for clinical practice. In the first version of the repertoire, patients and the public were described as unpredictable. Genomics can motivate behavioural change provided that it is made part of coaching and/or advice trajectories, and only if patients and publics take up their own responsibility in changing their behaviour. With this version of the gatekeeper repertoire, a potential application for genomic information is created. The construction of

patients as unreliable but possibly able to change aligns genomics as personalised medicine with the roles and responsibilities of established clinical practice.

In the second version of the gatekeeper repertoire, little space however was left open for patients to change their behaviours. Instead a technological fix, like a pill, or broader social and cultural change was claimed necessary. Genomics might lay the groundwork for research into a pill, or provide information for incentives to social change. However one should not count on publics changing their life on the basis of genomics information.

In the third version of the gatekeeper repertoire, genomics was constructed as something that patient do not want. Patients and the wider public are unable to deal with or interpret information on health risks. They also prefer to live with their disease over having to make changes to their behaviour. In addition doctors are not very good coaches, so information to be used in motivational talk would not land either.

Finally, a fourth version of the gatekeeper repertoire was distinguished. This version went against the pattern found in the other fragments where participants undermined patients' capacities or desires for behavioural change in such a way as to avoid responsibility for the route that genomics might take, and the opportunities that may or may not be realised. Instead, the public was constructed as interested in and able to act on information about future risks. Genomics was positioned as just the tool needed for motivating people to live their lives healthier. On a higher level, one may conclude that this 'deviant case' confirmed rather than disconfirmed the pattern as identified earlier, namely by showing that the foreseeing of a particular future for genomics in clinical practice goes together with the construction of particular patients and publics. Whereas drawing on a passive, untrustworthy and somewhat unwilling public seems to fit in seamlessly with undermining or displaying reluctance concerning the innovative potential of genomics, sketching an active and self-responsible public seems to go along with constructing a far brighter future for genomics. In other words, the outline of different futures provides for or requires different publics to emerge. In this sense, the deviant case shows why the pattern takes the form that it does: the creation of certain prospects goes together with the creation of certain publics, and once the need for a cautious or reluctant attitude concerning genomics has gone, the corresponding 'passive publics' seem to disappear as well.

Interestingly, in each case, the scientist is established as the evaluator of what should and should not be pursued for clinical practice. The need to consult publics on their needs and wants is made

redundant, since the scientists already know what they are.

Analysing participants' achievements at the interpersonal level adds to our understanding of storylines, by looking at what resources they are made of and how these are actively drawn upon as to structure the spaces of assessment. Descriptions of patients as well as publics are invoked by scientists so as not having to be personally responsible for the success or failure of genomics in clinical practice. Furthermore, by establishing reasons for patients' behaviour, like preferring disease over action, being idiots, lower social class, obesity, having no discipline and so forth, the scientists also close down any need to consult the publics on their ideas and desires for future clinical practice. The future opportunities for genomics in clinical practice thus remain narrowly shaped by scientists' notions of how clinical practice should look like, as well as how patients should behave.

Part 3

7 Discussion and conclusion

In this concluding chapter of the thesis, I return to my guiding research question.

> *How do researchers of common disease respond to expectations of genomics and what role do elements of established practice play in their response, and how does that shape future options of prevention, therapy and diagnosis?*

I address the question in two parts. In the first part (section 7.1), I look back on the story of the spaces of genomics. First by discussing what can be learned about genomics and its potential for transforming research and clinical practice by also paying attention to the influence of established practices in shaping expectations of genomics. Second, I will reflect on the usefulness of the concept of spaces of assessment as an addition to the literature on the innovation journey and to the sociology of expectations (section 7.2).

In the second part of the chapter, I take a forward look, and reflect on my findings in relation to the opportunities for future innovation journeys of genomics and health care. I discuss how my findings modify the dystopian image of geneticisation as well as the utopian ideas of personalised genomics medicine (section 7.3).

7.1 The transformative potential of genomics

In this section, I return to the question of genomics' influence on understandings of common disease, and future opportunities of prevention, therapy and diagnosis. In the two cases I studied, researchers responded to these general expectations with various storylines. Genomics was made part of storylines of research and clinical practice specific to asthma and cardiovascular disease. The contribution of the empirical investigation is to show how storylines of genomics are constructed in different fields, and how that leads to different descriptions of the future social order, and thus a contextualisation of genomics' claim of a wholesale transformation of health care.

My research strategy was a three-step approach, where each step builds upon information from the previous step. The first step in the research design was the analysis of scientific review papers. The second and third step consisted of interviews and workshops; they provided two additional

access points to the spaces of assessment and the emerging storylines. The workshops helped to probe interactions at the level of storylines and how they structure interaction among researchers. The interviews shifted the focus to how certain elements from storylines are mobilised in interpersonal interaction. Each of the three methods opened a window onto on-going dynamics, together helping to answer the question how researchers construct a space of assessment for exploring genomics and how their interactions shape opportunities for genomics in research and clinical practice.

I begin with the claim that genomics would lead to new understandings of disease. In the scientific review papers, genomics was made part of two different storylines for asthma and cardiovascular disease (CVD). For asthma, genomics was eventually positioned as part of a storyline of developing a profound new understanding of asthma. The emergence of new omic technologies was incorporated into the storyline as what would make it possible to arrive at a new understanding of asthma. For cardiovascular disease, the potential of genomics was argued by creating a connection between the genes involved with monogenetic and complex CVD. The creation of this connection was possible, as complex CVD were already (before the introduction of genomics, see chapter 4) positioned as the outcome of gene-environment interactions.

The workshop discussions introduced several additional storylines on the position of genomics as relevant for understanding disease. The discussion in the asthma workshop revealed that the gene-environment interaction model is the dominant model of thinking about asthma. However, the positioning of genomics as having the potential to lead to a profound new understanding of disease was contested. Epidemiological studies on population-level differences were suggested as an alternative. The suggestion was countered with reference to the kind of data that it would produce. A contestation that revealed a difference in storylines on what kind of data is needed to understand asthma: data on group or individual risks or data on population-wide risks? The response in the cardiovascular disease workshop showed resistance to the suggestion of a connection between monogenetic CVD and complex CVD based on genes. Denying the relevance of this link made for a storyline where environmental and lifestyle factors were placed as central to understanding complex CVD. There are signs that the model of gene-environment interaction structures interactions among researchers. The order between the elements of genomics, environment and gene-environment interaction (what is central and what data is relevant) is not settled, and the structure of the spaces thus reveals the potential for different future directions. For asthma as well as for cardiovascular disease, the opportunity still exists of genomics research continuing to develop in parallel with other types of research.

In the review papers, personalised medicine was presented as the ultimate goal of genomics (chapter 4). However, the claims of a transformation of diagnostic, therapeutic and preventative practices were developed differently in the two cases. For CVD, genomics was positioned as a contribution to established clinical practice and on-going concerns (Framingham risk score and more precise prescription practices). For asthma the expectations to what genomics can contribute to clinical practice were not modified into specific examples of innovation journeys. Instead an ideal image of clinical practice was created. Prevention and cure was presented as the ultimate goal, while improvements in diagnosis and therapy were treated as more short-term contributions.

The interaction in the workshops problematized certain aspects of the storylines on clinical practice from the reviews. Especially the ideal of personalised genomics medicine as motivating and allowing patients to take more responsibility for their own health was contested. New elements, like patient behaviour emerged as an important part of storylines on the desirability and plausibility of genomics and its possible applications in clinical practice. Genomics' contribution to personalised medicine was given shape mainly as an opportunity for clinicians. Clinicians would be able to provide more accurate diagnosis and prescribe medications developed specifically for sub-types of patients. The workshops showed that prevention and notions of personalised medicine structured the interaction between the participants. It is against the backdrop of these notions that the researchers developed their storylines of genomics. The role of genomics in such storylines was far from settled and several suggestions were discussed in each of the workshops. The discussions in the workshops were rather similar on this point. The key difference was in the description of what choices patients can and cannot take control of. In the asthma workshops, the suggestion of coaching was met with examples of smoking, lifestyle habits and environment as factors that people cannot fully control. In the cardiovascular workshop, following general recommendations on lifestyle was presented as a free choice. The participants did not make a differentiation between choices within or outside the control of individuals. In terms of introducing genomics in clinical practice, some participants suggested to use genomics as part of advice or coaching trajectories.

In chapter 6, I further explored how scientists explained the role of genomics in clinical practice. The descriptions of patients as the obstacle in implementing new forms of health care functioned as a dominant discursive resource for researchers. By constructing patients and their choices as irrational, they avoided having to engage with questions of their own responsibility in transforming health care, or with questions of the desirability or eventual success of genomics and personalised medicine. The ideal of personalised genomic medicine was problematic at the

interpersonal level because it suggests changing roles, not only for patients but for researchers and clinicians as well. The outcome of the clash between the storyline of genomics as part of a personalised medicine approach and the researchers' explanation of patient behaviour are four versions of the gatekeeper repertoire. Each version implies a different social order. One version suggests that people can be coached to follow recommendations, a second version that surroundings should be changed to steer people in healthy directions, a third version suggests that there is no place for genomics in clinical practice and a fourth version that genomics is already initiating lifestyle changes, and thus it is exactly what is needed.

The creation of a connection between genomics and the two fields of common disease research was motivated in relation to elements of established practice. So, how did the presence or absence of a monogenetic disease influence the development of the storylines and what about established practice organised on risk prediction, prevention, diagnosis or treatment? Clearly, the presence of monogenetic CVD provides a stable element against which to motivate the positioning of genomics as a possible contribution to understanding complex CVD. Without such a monogenetic subset of disease, the choice for genomics must be motivated against other elements of practice. For asthma, that is initially knowledge on the influence of the environment. Eventually, the absence of a monogenetic subset of disease thus affords the creation of a storyline claiming a profound new understanding of disease. The ideal of genomics as contributing to personalised medicine, and personalised medicine as a radical change in health care practice was produced in the review articles. The description of future practice was however far more detailed for CVD, as it could build on existing practices of risk prediction and screening. The expectation that genomics would shift clinical practice in new directions was modified for both cases in the workshops, but it was not completely abandoned. The workshops showed the similarities in how particular constructions of patients were used to situate genomics as a likely or unlikely part of future clinical practice.

In terms of the implications of the storylines that are developing on the potential of genomics, different conclusions can be drawn for asthma and for cardiovascular disease. For asthma, genomics has found a place in a storyline on the creation of a profound new understanding of disease. The opportunity for a new understanding of asthma is creating by constructing a connection between this opportunity and the emergence of 'omic' technologies. The storyline implies the possibility for a development of a new classification of asthma based on the so called endophenotype model emphasising non-linear discrete pathogenic pathways connected to groups of genes and ending in different sub-sets of disease (Chapter 4, section 4.3.2). Asthma would then transform into asthmas. For CVD, genomics is

predominantly woven into a story of developing drugs or improving risk prediction in clinical practice. Genomics is thus not so much positioned as a change, but as a strengthening of on-going practices. Genomics combined with elements of practice thus affords the emergence of two differing storylines in asthma and CVD research.

7.2 Spaces of assessment

The conceptual approach in this thesis is a contribution to the literature on innovation journeys as well as to the literature of the sociology of expectations. The stylised description of the innovation journey draws attention to patterns and typical activities of the journey (Rip and Schot 2002; Rip 2010; Rip 2012). In these descriptions, it is mentioned how the identification of a novelty as a solution to problems in a field, and resource mobilisation through promises and expectations, are key activities in the first phase of the innovation journey. However, these descriptions do not go much further in explaining how a novelty is identified as promising or how actors acquire support for their work. I therefore zoom in on the first phase of the innovation journey (build-up of a protected space). The contribution is thus one of describing a process that contributes to the overall innovation journeys. The space of assessment centres on the discursive work of creating a space for exploring a novelty. In contrast to the idea of a protected space, that is developed to describe a space created for a group to work without much interference from the "outside", the space of assessment refers to actors developing an opportunity for exploration and inviting other to join in. A space of assessment is structured as much by positive as well as negative storylines on the potential of novelty within an area. It shows how actors use contextual elements as a resource as to construct storylines of a social order in which the novelty will fit. What I found is the emergence of several storylines, differing between, as well as in, the spaces of assessment. The approach adds to previous attempts of drawing attention to discourse in innovation journeys (see for example Lowell 2008; Geels and Verhees 2011). By delving into the discursive work of creating storylines in specific fields, I can highlight the elements of established practice, which are used to create a storyline of a novelty. The concept of spaces of assessment draws attention to the actors and the structure they build together, and it includes the actors who do not necessarily construct favourable storylines of the novelty. Actors construct their storylines in relation to the storylines of others. This is illustrated in my case studies. Genomics is assessed and given a place in storylines that create connections with elements of established practice. It is also these connections that are contested. For example, in the asthma workshop, it is the centrality of genomics as an approach to researching asthma, which is contested (Chapter 5, section 5.3.1). Environmental factors is exactly the element

against which the space for genomics was first created in the review papers, and also the element that disappeared from view as the storyline was reconstructed with genomics as contributing to a profound new understanding of disease.

Within the sociology of expectations, a desire has been formulated to investigate dynamics of how expectations are modulated in specific settings (Borup et al. 2006; Konrad 2010). The concept of spaces of assessment could be tool for such an investigation. Spaces of assessment pay specific attention to how expectations of a novelty are received, and what role contextual elements of specific settings play in how these expectations are modified. Konrad argues, for a reflexive relationship between the production of expectations and the emergence of structure that govern actors and in turn the production of new rounds of expectations. The relationship is reflexive since the form of expectations is dependent on the context in which they are produced. So, while expectations contribute to coordinating the work of actors, their form is also dependent on the way the work of actors is coordinated in established practices. This implies that the new combinations of expectations and elements of practice, feed back onto the practices that shaped them and change them. In my case studies I show this reflexive relationship at the level of storylines. For example in cardiovascular disease research, a genomic approach for common complex CVD was justified with reference to an expected relationship between the genes involved with monogenetic CVD and complex CVD. In the workshop, what was first claimed to be a possible connection in the review papers, now structures the interaction between a nutritional epidemiologist (W2_P5) and a genetic epidemiologist (W2_P6). They disagree on the connection, but nonetheless it structures their interaction (Chapter 5, section 5.4.1).

Spaces of assessment refer to the discursive work of actors that recognise a novelty as promising. They do so by developing storylines on its potential and by configuring the novelty in relation to elements of their established practice. The concept of spaces of assessment is thus particularly useful for analysing the phase of the innovation journey where a space is created and a novelty is explored. The concept could also be tested by analysing how promises and expectations of genomics have been received and potentially modified in society, for example among policy makers, patient organisation and insurance companies. Preferably such analyses should be performed in parallel, so as not to lose sight of how the space constructed in a field like asthma or cardiovascular disease research, is also influenced by and influences the creation of spaces in other fields and spheres. The spaces of assessment concept allows a focus on a specific process of the innovation journey in a field, but one should keep in mind the interconnections and co-evolutionary dynamics between spaces and spheres. A next step building on my analysis would be to analyse the parallel emergence of spaces in other spheres,

and based on that information to point to emerging patterns in the structuring of spaces and the configuration of genomics. Such an analysis would give a more inclusive impression of the possibility of future innovation journeys for genomics and health care. In the context of the present thesis, I will briefly introduce a storyline from the context of policy on the future of Dutch health care, and use it to situate the storylines from asthma and cardiovascular disease. On this background I will provide a 'controlled speculation' on future opportunities for innovation journeys of genomics in health care and for asthma and cardiovascular disease.

7.3 Future innovation journeys

The storylines of the spaces of genomics in asthma and cardiovascular disease are examples of how the future of genomics in research and clinical practice is configured in science. Parallel with the discursive construction of storylines in these spaces, storylines emerge in the spheres of technology, society, market and regulation spheres (Figure 1, Chapter 1). In this chapter, I take a look at one of the storylines emerging in the society sphere; a storyline on the future goal of health care in the Netherlands. Every four years, the Dutch Ministry of Health, Welfare and Sport has a report drawn up by the National Institute for Public Health and Environment (RIVM) on future vision of health care. The next report is due in 2014, but already the key directions and arguments have been published. The Ministry sets the tone for initiatives and developments in health care. The RIVM report is developed in collaboration with select experts from various groups in the health care sector. The storyline of the report gives an impression of the selection environment for the storylines of the asthma and cardiovascular disease researchers. How do the storylines match up and in what ways do they diverge? What can they tell about future opportunities for the innovation journey of genomics?

In the report, a picture is drawn of a health care system with changing roles and a new definition of health. Health, according to the report will be defined in positive terms, not as the absence of disease, but as a dynamic equilibrium and the capacity to deal with ambitions as well as threats (RIVM 2011). The report justifies the definition, by pointing out that it provides the opportunity to understand what drives people to stay healthy, and to strive for a healthy life. Changing the definition in this way opens up for categorising people with a chronic condition as healthy. The goal in the end is to provide the conditions for individuals to control their health. Genes are mentioned in connection with prospects for personalised medicine. The desirable future is described as one where information on individuals risk can be used to target specific interventions to their risk group. When it comes

to describing the changing roles of the clinicians and patients, the storyline matches up with the "coaching" ideas that were seen in the workshops and in the interviews. The report sketches out a role for the clinician as an aid in self-management trajectories of patients that take control of their health. However, aiding is not necessarily coaching, but can also imply a one-time responsibility to refer the patient to relevant information. Social, educational, and economic factors are mentioned as obstacles for people to take control of their health. The report does describes it as people's own choice if they want to take responsibility for their health as *'The government does not tell people what do to or what not to do, that is up to people's own choices. The surrounding environment should however be designed in way as to make healthy choices easier than unhealthy ones.'* (RIVM 2011:28)[47] This way of describing health care is similar to the version of the gatekeeper repertoire from the interviews, where the scientists argued for the necessity of changing surroundings to "guide" people towards healthy choices. However, the descriptions of health care professionals as 'aids' could suggest a shift to coaching. The storyline in the report is thus a combination of the storyline aiding/coaching of unreliable patients and changing surroundings to incite behavioural change.

Coming back to my two cases, what opportunities for future innovation journeys present themselves? The RIVM report opens up for patients to take more responsibility for their own health. In contrast to the asthma and CVD researchers more responsible patients are a plausible and desirable future. The report also sketches a new definition of health, from the absence of disease to the capabilities of individuals to live their life pursuing ambitions and dealing with threats. Developing a cure for asthma or CVD is not an innovation journey supported by such a change in definition. Instead, the individual at the centre implies that responsibility for following prescription of medications and advice on lifestyle and environmental influences to be mitigated will be up to the individual. This implies a specific form of coaching, where responsibility for the outcome is not shared between the individual and a coach. So, what could be imagined as possible innovation journeys for asthma and CVD?

For asthma, an opportunity has emerged for changing the classification of disease into including several sub-types based on a so-called endophenotype model. This type of classification stands in contrast to known divisions such as 'allergy induced' or 'exercise induced' asthma. A classification based on the endophenotype model shifts attention from the influence of environmental factors as triggers, to an individual's body. One could imagine that if such a reclassification would

47 The quote is translated from Dutch to English by the author.

happen, then patients would be sub-divided according to individual body and lifestyle specific divisions, instead of general categories based on outside triggers. At present asthma patients are told to adapt their home environments and lifestyle to their status as chronically ill patients. Increased attention to the responsibility of individuals would strengthen this trend. However, in the quote from the RIVM report above, the option is mentioned to change environments as well. In combination with the storylines from the asthma workshop, where some researchers argued for attention to the choices that an individual can and cannot control, one could imagine devices or other measures to change the environment of asthma patients. One problem is the difficult in getting patients to take their medication. An option could for example be an application on mobile devices that remind a patient to take his or her medication. Another idea could be a device that would warn asthma patients of critical substances in the air.

For cardiovascular disease, a slightly different opportunity emerges. Here an opportunity rather emerges for giving advice on risk and providing information on how to avoid such risk. Information on risk could include information on a person's genome in combination with data from the Framingham risk score on social status, age, sex and lifestyle. Responsible patients are then the ones that deal with this future threat by modifying their lifestyle to minimise risks of CVD. In contrast to asthma, self-management is directed to the phase before as well as after the event of a CVD. In both cases genomics is imagined as an addition to existing practices, which account for the difference in timing of when individuals should become responsible. The role of genomics in these future innovation journeys is however highly uncertain.

The inclusion of genomics in clinical practice of asthma and CVD would depend on how it is judged in terms of enabling patients to be more responsible, or to provide more precise diagnosis and medication. When it comes to motivating individuals to become more responsible, the only option was seen in developing coaching trajectories. Coaching could be seen as an option for aiding individuals in becoming responsible, but so could technical devices. Least controversial in the workshops and the report is a future where genomics acts as additional information in practices of diagnosing disease and of prescribing medications. For asthma, that would require a reclassification of disease: an opportunity that is opened with the storyline on genomics as leading to a new understanding of disease. For cardiovascular disease genomics would have to be seen to perform better then the Framingham risk score in terms of predicting risk. The expectations and promises of genomics have been modified in the responses of the asthma and cardiovascular disease researchers. However, they have also initiated research and conceptual changes, which could one day influence clinical

practice: for asthma in terms of behaviour modification after the manifestation of disease, and for CVD behaviour modification as a life task for risk groups.

To conclude this thesis, I want to discuss the storylines on patient behaviour from the workshops and the RIVM report, in two ways: first in terms of the dystopian concerns of Lippman's geneticisation thesis (chapter 1) and two, in terms of the values of the "good life" underlying the utopian ideal of personalised medicine as self-management (Komduur, Korthals and Te Molder 2008).

Returning to the geneticisation thesis introduced in chapter 1, there are no indications that genes are becoming the sole factor for distinguishing individuals or classifying disease. Instead a more complex model is emerging, which includes genes together with other molecular factors. The transformative power of genomics may not so much lie with its introduction of an understanding of disease based on genes, but rather with a 'molecular'[48] understanding of disease where the individual body is the central focus. Still the geneticisation thesis predicted that economic, social and political factors would disappear as explanatory factors of disease. Shostak (2003) commented that such an 'inward focus' would result in individualised notions of risk. She argued that it would go together with public policies focused on individual responsibility for health and intervention strategies. From the RIVM report, it seems that part of the equation is institutionalising as a dominant scenario of desirable future health care. In this storyline economic and social factors are however not disappearing from view. Instead they are part of an effort to change societal structures to promote what is defined as healthy choices. In the last part of this section I take brief look at the values health that are promoted in the RIVM report and that also are part of the responses of the scientists in the workshops and interviews.

There are two entrance points: the first is about the vision of the good life implied in the storylines of personalised (genomics) medicine, and the second remark ties back to my conceptual framework of spaces and their storylines. A healthy lifestyle is described as an important part of taking control of one's health. In the workshops and in the interviews, food was given an important role in keeping people healthy. Komduur et al. (2008), described three assumptions behind the storyline on personalised health care using nutrigenomics: the good life is a healthy life, to achieve health one needs to minimise risk, and prevention is in the hands of the individual. These assumptions are recognizable

48 Like in chapter 5, I refer to this version as 'molecular' in lack of a better term. It is a version that sees disease as the outcome of interactions between genes, cell, organs, metabolites, proteins and environmental influences as a complex non-linear model.

in the workshop discussions in chapter 5 and in my interviews from chapter 6, as well as in the report from RIVM. The problem is, that what seems good, can have perverse effects if it becomes the primary purpose of life. Once health becomes connected to everyday activities it may become an all-consuming goal, taking over people's lives and preventing them from pursuing other goals. Instead Komduur et al. argue that striving for health should be in balance with other values in life like the social, cultural and religious meanings of food.

The constructions of the patients and the general public, as they emerged in the workshops and in the interviews, reflect the same narrow boundaries in defining a good life as a healthy life. In these constructions people and patients emerged as irresponsible and unreliable, as drinking too much, as being obese and having unhealthy eating habits, all behaviours, that people were constructed as unable to control. It is possible to understand these images when we look at the researchers' narrow definition of responsible and rational behaviour. Since they define a healthy life as a life where the responsible persons actively pursues health through lifestyle choices, the only way to explain behaviours that do not live up to this ideal is as deviant.

Herein lies the irony. It is the narrow definition of responsible behaviour, combined with the researchers confrontation with their experiences of actual patient behaviour that leads them to question personalised genomics medicine. When a responsible patient, one who understands risk information, is portrayed as taking specific actions as a result, the patient that does not follow this pattern of behaviour must necessarily not have understood what is at stake or be simply irresponsible. Following my empirical findings it is this that makes it difficult for the researchers to embrace the specific version of personalised medicine as introducing more responsibility for patients, and thereby to entertain notions of patients as taking control of their own health. However, if one was to broaden the notion of what constitutes a healthy, good life and thus responsible action to include other values, both the interpretations of patient behaviour by researchers and policy makers as well as the goals of personalised medicine might change.

The policy report already offers an opening to such a broadened understanding. By changing the definition of health towards a focus on the actions a person is able to take towards fulfilling ambitions and overcoming difficulties in life, the healthy life becomes about more than just the absence of disease or the choice of foods. The question is how the suggestion will be filled in. One option, would indeed allow for people to pursue other values than a life free of disease and to balance food and lifestyle choices with other values. Whether or not the eventual report due in 2014 will follow this suggestion is not known. The quote above, on enabling healthy

choices, however leads one to suspect that free choice is not so free after all.

I want to end this discussion with a comment on the storylines, the 'grammar', of the spaces where genomics as a part of personalised medicine is taking shape. The storylines from the workshops and interviews presented a vision that position patients as responsible for realising a role of genomics in personalised health care trajectories. In this position the only choice for patients (and people) is to take up and follow the prescriptions of responsible and healthy behaviour. If they do not, they are irresponsible and not capable of living healthy and good lives. Crawford (2006) described this as a society-level storyline with health as a 'super-value'. As a super value health, collects everything that is worth to pursue in life under its wings. Health has expanded to include mind, body and spirit. To pursue a good life has become equated with the pursuit of a healthy life. To be ill, or not engaged with finding health is interpreted as a failure to live well, and so being ill is something that can and should be avoided. (Crawford 2006) The new definition of health from the RIVM report is such an expansive version of health. It refers to health as a life-task, as continuously striving for ambitious goals, overcoming ones own limitations and fighting off temptation and threats, and so links up with the storyline described by Crawford. The price to pay for this development is the loss of concerns for society as a whole (Crawford 2006). With the researchers descriptions of experiences with patient behaviour in mind, perhaps the storylines need to be opened up to other interpretations of patient behaviour. Such an opening up would allow alternative interpretations of patient behaviour and what constitutes a healthy life. Activities like eating healthy, quitting smoking or taking part in sports, should be balanced with emphasis on the cultural value and meaning and the pure enjoyment of food and social activities. Those values should be recognised and examined. Perhaps a new storyline of genomics and personalised health care would emerge where health would be broadened to include social, economic and cultural values as well.

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Appendix A

Glossary of key terms associated with genomics

Allele	Alternate sequence of a gene. One version is inherited from each parent.
Biomarker	Is a protein, a molecule, a dye, blood levels, cholesterol levels or any change in the physiological state of the body that can be measured. Biomarkers can provide information on if an individual is at risk for develop a disease, or can be used to measure the progression of a disease.
Candidate gene association study	A candidate gene association study focuses the association between a gene of interest and a specific phenotype. The question to be answered by this type of study is if the suspected gene appears more frequently in the people expressing the disease phenotype.
Case-control study design	The case-control study design relies on comparing to groups on the basis of an expressed trait in order to test if a factor of interest influences the expression of that trait.
Chromosome	Are structures of DNA and protein found in cells. Humans have 23 pairs.
DNA	Are the structures that contain hereditary information (genes). This information is coiled up in two strings that run anti-parallel to each other. Each string contains the so called base-pairs made up of the amino acids A (adenine), C (cytosine), G (guanine), and T (thymine).
Epigenetics	Is the study of heritable changes in gene activity, which occur without a change in the sequence of the hereditary material.
Exome	Is a term for the part of the genome harbouring exoms. Exoms are the part of the genes, which are actually expressed.

Linkage analysis	Is a method for following patterns of inheritance in families with high risk of a certain trait. The aim is to identify causative genes, which would be inherited with the trait.
Gene	A subunit of DNA, which code for a product such as proteins or enzymes. Humans have ca. 20.000 genes, and they make up just about 1-2 % of the genome.
Genome	Is the total of all the genetic material in an organism. That is it includes both coding and non-coding regions of the DNA/RNA.
Genome-wide association study	A method where the statistical variation between a trait and a large number of genetic markers is investigated. This type of study does not rely on a priori hypothesis of possible causative genes, and is therefore said to be able to identify novel pathways.
Genotype	Is the constitution of alleles that an individual inherits from its parents. More specifically it can also refer to the combination of alleles at a certain loci.
Mendelian disease	Are conditions caused by a single mutation. They are inherited from parent to child following Mendel's laws. Depending on whether the parents mutation is dominant or recessive the children have varying percentiles of risk for getting the disorder.
Metabolomics	Is the analysis of intermediate -and end products involved in metabolic processes in cells.
Phenotype	A phenotype, is the observable manifestation of a genetic trait, which results from specific genotypes and their interaction with the environment.
Polymorphism	A polymorphism is a common variation in the DNA sequence that occur among individuals in a population. Polymorphism refers to variations on the level of populations, while mutations refer to variations among individuals.

Proteomics	Proteomics is the study of proteins, their structure and function on a large scale. Contrary to the genome, which is largely constant, the proteomic profile changes with time and environmental influences.
RNA	RNA molecules can play active roles in cell processes by directing the synthesis of proteins, controlling gene expression and sensing and responding to signals within a cell.
Single nucleotide polymorphisms (SNPs)	SNPs are a variation in the DNA sequence, which occur when one base in a pair is changed. Most such changes have no effect, but some influence protein production. SNPs underlie our susceptibility to disease and response to drugs. SNPs are crucial for comparison of DNA sequences and for the genome-wide association strategy.
Loci	A specific region on the DNA.
Systems biology	The term covers an interdisciplinary field, with the aim of creating an overview and understanding of the whole of biological systems. The discipline is anti-reductionist in its aim to put-together instead of taking apart biological systems. The approach is often focused on bringing metabolic or cellular network into view.

Appendix B

Invitation asthma workshop

Dear Prof. X,

Despite much hard work, a clear definition of the asthmatic phenotype(s) is still lacking. Even with the availability of medications for control and management of asthma, there is frustration on the lack of progress in understanding the condition. Seeing that asthma is a chronic condition, prevention or cure would be preferable for the patient, as the health care system at large. Medical genomics emerged some 10 years ago with the promise of providing novel understandings of asthma together with possibilities for prevention and cure. Still not much has changed in asthma clinical care.

We would hereby like to invite you to attend the expert workshop "Future Visions of Prevention, Diagnosis and Therapy for Asthma: priorities in asthma research" taking place on Friday February 4 2011. The workshop is part of research carried out in connection with a PhD project **1**.

In the light of the emergence of genomics as a research tool, we want to probe into difficult questions facing asthma research. These questions include: How can asthma research and asthma researchers best profit from current developments? What does the future hold for asthma research? Should research priorities be different? What fruitful combinations can be made between different approaches? What choices can or would you yourself be willing to make?

We think that you will be able to provide a valuable contribution to this discussion.

The workshop will take place on Friday February 4 2011 from 9.30-12.30 at Brasserie & Restaurant De Rechtbank, Korte Nieuwstraat 14, 3512 NM Utrecht, and will be held in Dutch. Lunch will be provided at 12. Please see the detailed program attached.

Confirmed participants include: (List)

Please let us know of your plans to attend (workshop and lunch) before November 29 2010 at: l.bitsch@utwente.nl or 053 489 4235/0644318194

Sincerely,

The workshop organisation:

Lise Bitsch, MSc. (Twente University)

On behalf of,

Dr. Dirk Stemerding (Rathenau/Twente University)

Prof. Hedwig te Molder (Wageningen University/Twente University)

1 The background for this workshop is research, carried out in the PhD project "Future Scenarios of Genomics and Health Care" at the Centre for Society and Genomics (CSG). Through analysis of scientific review articles on asthma research and genomics, and interviews with asthma researchers in the Netherlands, as well as genomics researchers in the Netherlands and the US, it has been found, that research into a genetic component in asthma, using genomic methods, has rapidly emerged as an approach within asthma research in the last 10 years. However such developments are not undisputed. Opinions among researchers are especially divided on the cost-effectiveness of prioritising genomic research. Opponents doubt that the effort will cash out in terms of valuable contributions to asthma clinical practice. Proponents certify that on the long term insights acquired through genomics research will lead to significant improvement of treatment, diagnosis and prevention of asthma. Such claims are countered by opponents who seriously doubt patient's ability to take advantage of the results. By opening the discussion on these topics, we hope to contribute to a clarification of the issues that separates researchers, leading to improved consensus on the future priorities of asthma research.

Invitation cardiovascular workshop

Dear Prof. x

Genome-based research on monogenetic and multifactorial cardiovascular conditions has been successful in confirming a role for many genes involved. The initial expectation was, that unravelling the genetic basis of these conditions would lead to options of prediction and timely prevention. Current expectations for complex disorders are of better understanding of pathophysiology, improved diagnosis, prognosis and better assessment of treatment responses. Due to the complex nature of the most common cardiovascular conditions, prevention as such is no longer as highly anticipated. The most likely candidates for prevention would be lifestyle changes, but it is unclear if genomics can contribute in any way to such already established interventions.

We would hereby like to invite you to participate in the expert workshop "Future Visions of Prevention, Diagnosis and Therapy for Cardiovascular Disease: priorities in cardiovascular disease research" taking place on June 1 2012. The workshop is part of research carried out in connection my PhD project **1**.

In the light of the emergence of genomics as a research tool, we want to probe into difficult questions facing cardiovascular disease research. These questions include: How can cardiovascular disease research and its researchers best profit from current developments? What does the future hold for cardiovascular disease research? Should research priorities be different? What fruitful combinations can be made between different approaches? What choices can or would you yourself be willing to make?

We offer an opportunity to discuss with distinguished colleagues in a 'free space'. The outcome of the discussion could be a publication co-authored between organizers and participants.

The workshop is free of charge and will take place on June 1 2012, from 9.30-12 at Brasserie & Restaurant De Rechtbank, Korte Nieuwstraat 14, 3512 NM Utrecht, and will be held in Dutch. Lunch will be provided at 12.00. Please see the detailed program attached. Compensation for travel costs is also a possibility.

Please let us know of your plans to attend (workshop and lunch) before March 1 2012 at: l.bitsch@utwente.nl or 053 489 4248/0644318194

Sincerely,

The workshop organisation:

Lise Bitsch, MSc. (Twente University)

On behalf of,

Dr. Kornelia Konrad (University of Twente)

Prof. Irene van Langen (Groningen University Medical Centre)

1 The background for this workshop is research, carried out in the PhD project "Future Scenarios of Genomics and Health Care" at the Centre for Society and Genomics (CSG). Through analysis of scientific review articles on cardiovascular disease research and genomics, and interviews with cardiovascular researchers in the Netherlands, as well as genomics researchers in the Netherlands and the US, it has been found, that research into a genetic component in multifactorial cardiovascular diseases, using genomic methods, has rapidly emerged as an approach within cardiovascular disease research in the last 10 years. However such developments are not undisputed. Opinions among researchers are especially divided on the cost-effectiveness of prioritising genomic research. Opponents doubt that the effort will cash out in terms of valuable contributions to clinical practice. Proponents certify that on the long term insights acquired through genomics research will lead to significant improvement of treatment, diagnosis and prevention. Such claims are countered by opponents who seriously doubt patient's ability to take advantage of the results. By opening the discussion on these topics, we hope to contribute to a clarification of the issues that separates researchers, leading to improved consensus on the future priorities of cardiovascular disease research.

Appendix C

Program Asthma workshop

Expert workshop:

Future Visions of Prevention, Diagnosis and Therapy for asthma: priorities in asthma research

Brasserie & Restaurant De Rechtbank, Korte Nieuwstraat 14, 3512 NM Utrecht

February 4 2011

Chair: (name of moderator), PhD (CSG)

Despite much hard work, a clear definition of the asthmatic phenotype(s) is still lacking. Even with the availability of medications for control and management of asthma, there is frustration on the lack of progress in understanding the condition. Seeing that asthma is a chronic condition, prevention or cure would be preferable for the patient, as well as for the health care system at large. Medical genomics emerged some 10 years ago with the promise of providing novel understandings of asthma, together with possibilities for prevention and cure. Still not much has changed in asthma clinical care. How should these developments be interpreted? In this workshop leading experts in asthma research address the tension between promises and reality, and discuss visions of the future of asthma research and clinical practice.

09:30-09:45: Introduction by Lise Bitsch, MSc (University of Twente)

09:45-10:20: Session 1: Asthma research and the promises of new technologies; what is a proper strategy?

10:20-10:35: Break

10:35-11:10: Session 2: Prevention and treatment; how do we get there?

11.10-11.40: Reflection with W1_P11

12.00 Lunch

Program cardiovascular workshop

Expert workshop:

Future Visions of Prevention, Diagnosis and Therapy for Cardiovascular Disease: priorities in research

In de Driehoek, Willemsplantsoen 1c, 3511 LA Utrecht

June 1 2012

Chair: (name moderator), PhD (CSG)

Genome-based research on monogenetic and multifactorial cardiovascular conditions has been successful in confirming a role for many genes contributing to risk and outcome of cardiovascular conditions. The initial expectation was, that unravelling the genetic basis of these conditions would lead to options of prediction and timely prevention. These promises have been more readily fulfilled for the monogenetic conditions. Currently main expectations for all complex disorders, including cardiovascular diseases, are of better understanding of pathophysiology, improved diagnosis, prognosis and better assessment of treatment responses. Due to the complex nature of the most common cardiovascular conditions prevention as such is no longer as highly anticipated. The most likely candidates for prevention here would be lifestyle changes, but it is unclear if genomics can contribute in any way to such already established interventions.

How should these developments be interpreted? In this workshop leading experts in cardiovascular research address the tension between promises and reality, and discuss visions of the future of research and clinical practice.

10:30-10:45: Introduction by Lise Bitsch, MSc (University of Twente)

10:45-11:20: Session 1: Cardiovascular disease research and the promises of new technologies; what is a proper strategy?

11:20-11:35: Break

11:35-12:10: Session 2: Prevention and prognoses: A monogenetic model for multifactorial cardiovascular diseases?

12.10-12.40: Reflection with W2_P9

12.40: Lunch

Appendix D

Standard Interview Guide

1. What is, according to you, the most important development in the field of x disease research in the last 10 years?

Probes: Ask details in how this development came about, or an example of what it has meant, why it is seen as important by the interviewee.

Follow-up: Why would you consider xx to be the most important development?

What about XX? (genomics, development in epidemiological observations of animals and farm surroundings, the hygiene hypothesis, technological developments, such as chip technology and computer/software technology, conceptual developments such as major gene to many genes, gene-environment interactions, gene-gene interactions, phenotypic classification)

If not mentioned ask about the impact of genomics on past development

2. Are there any issues in the field of x disease research you find particularly challenging?

Probes: Why, could you give me and example of the way in which this particular feature is challenging?

Follow-up: Is this an issue which is widely considered to be a challenge/ important question to solve in common complex disease research?

Could you imagine any solutions to this issue? (if so how)

What about complexity – is this an issue which

3. What are your expectations to the way x disease research might develop in the future?

Probes: Could you describe how this development would take place? What might be important contributions of such development (in research (understanding mechanisms), in the clinic (tests, prediction possibilities for prevention), for classification (phenotypes))?

Follow-up: What would be a list of important people who decide on what developments should be supported?

Why are these people important?

Are you one of these people (why, why not)

4. The general public is often said to be the group who will have the most to gain from research into x disease – What are according to you the gains that the public will have?

Probe: Could you give an example of how the public would benefit?

Follow-up: What is, according to you, one of the biggest misunderstandings in the public about the contribution of genomic knowledge to health care?

Can you imagine that the Dutch health care system would have to change to accommodate such changes?

In what ways can you imagine the health care system would change?

5. Is there anything that you think is important to know that I did not ask that we did not talk about?

6. Ask about others to interview

Appendix E

List of analysed asthma reviews

Year	Author	Title	Journal	ISI Web of Knowledge category and rank
1999	Anderson, G.G. and Cookson, W.O.C.M.	Recent advances in the genetics of allergy and asthma	Molecular Medicine Today	Indexed in Biochemistry and Molecular Biology, Cell Biology and Medicine, Research and Experimental
1999	Los, H., Koppelman, G.H. and Postma, D.S.	The importance of genetic influences in asthma	European Respiratory Research	3/34 in Respiratory Research
1999	Moffatt, M.F. and Cookson, W.O.C.M.	Genetics of asthma and inflammation: the status	Current Opinion in Immunology	8/119 in Immunology
1999	Wiesch, D., Meyers, D.A. and Bleecker, E.R.	Genetics of asthma	Journal of Allergy and Clinical Immunology	1/17 in Allergy and 9/119 in Immunology
2002	Hoffjan, S. and Ober, C.	Present status on the genetic studies of asthma	Current Opinion in Immunology	8/119 in Immunology
2002	Vercelli, D.	The functional genomics of CD14 and its role in IgE responses: an integrated review	Journal of Allergy and Clinical Immunology	1/17 in Allergy and 9/119 in Immunology
2004	Kaufmann, F. and the Post Humane Genome Respiratory Epidemiology Group	Post-genome respiratory epidemiology: a multi-disciplinary challenge	European Respiratory Journal	3/34 in Respiratory Research
2004	Wills-Karp, M. and Ewart, S.L.	Time to draw breath: asthma susceptibility genes have been found	Nature Reviews. Genetics	2/132 in Genetics and Heredity
2006	Ober, C. and Hoffjan, S.	Asthma genetics 2006: the long and winding road to gene discovery	Genes and Immunity	28/119 in Immunology and 37/132 in Genes and Heredity
2008	Anderson, G.P.	Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease	Lancet	2/100 in Medicine, General and Internal
2008	Koppelman, G.H., Te Meerman, G.J. and Postma, D.S.	Genetic testing for asthma	European Respiratory Journal	3/34 in Respiratory Research
2008	Moffatt, M.F.	Genes in asthma: new genes and new ways	Current Opinion in Allergy and Clinical Immunology	Indexed in Allergy and Immunology
2008	Vercelli, D.	Discovering susceptibility genes for asthma and allergy	Nature Reviews. Immunology	2/119 in Immunology

List of analysed cardiovascular interviews

Year	Author	Title	Journal	ISI Web of Knowledge category and rank
2000	Ferrari, P. and Bianchi, G.	The genomics of cardiovascular disorders – Therapeutic implications	Drugs	Pharmacology & Pharmacy (36/219), Toxicology (6/75)
2002	Mukherjee, D. and Topol, E. J.	Pharmacogenomics in cardiovascular diseases	Progress in Cardiovascular Diseases	Cardiac and Cardiovascular Systems (10/79)
2003	Stephens, J. W. and Humphries, S. E.	The molecular genetics of cardiovascular disease: clinical implications	Journal of Internal Medicine	Medicine, General and Internal (11/107)
2004	Gibbons, G. H. Liew, C. C. Goodarzi, M. O. Rotter, J. I. Hsueh, W. A. Siragy, H. M. Pratt, R. and Dzau, V. J.	Genetic markers: progress and potential cardiovascular disease	Circulation	1/117 Cardiac and cardiovascular systems, 1/68 Hematology, 1/68 Peripheral vascular disease
2005	Ginsburg, G.S. Donahue, M.P. and Newby, L.K.	Prospects for personalized cardiovascular medicine — The impact of genomics	Journal of the American College of Cardiology	Cardiac and Cardiovascular Systems (2/79)
2005	Podgoreanu, M. V and Schwinn, D. A.	New paradigms in cardiovascular medicine — Emerging technologies and practices: Perioperative genomics	Journal of the American College of Cardiology	Cardiac and Cardiovascular Systems (2/79)
2007	Arnett, D. K. Baird, A. E. Barkley, R. A. Basson, C. T. Boerwinkle, E. Ganesh, S. K. Herrington, D. M. Hong, Y. Jaquish, C. McDermott, D. A. O'Donnell, C. J.	Relevance of genetics and genomics for prevention and treatment of cardiovascular disease — A scientific statement from the American Heart Association Council on Epidemiology and Prevention, the Stroke Council, and the Functional Genomics and Translational Biology Interdisciplinary Working Group	Circulation	1/117 Cardiac and cardiovascular systems, 1/68 Hematology, 1/68 Peripheral vascular disease
2007	Seo, D. M. and Goldschmidt-Clermont, P. J.	Unravelling the genetics of atherosclerosis: implications for diagnosis and treatment	Expert Review of Molecular Diagnostics	Pathology (15/69)
2007	Ashrafian, H. and Watkins, H.	Reviews of translational medicine and genomics in cardiovascular disease: New disease taxonomy and therapeutic implications — Cardiomyopathies: Therapeutics based on molecular phenotype	Journal of the American College of Cardiology	Cardiac and Cardiovascular Systems (2/79)
2009	Bos, J. M. Towbin, J. A. and Ackerman, M. J.	Diagnostic, Prognostic, and Therapeutic Implications of Genetic Testing for Hypertrophic Cardiomyopathy	Journal of the American College of Cardiology	Cardiac and Cardiovascular Systems (2/79)
2009	Arking, D. E. and Chakravarti, A.	Understanding cardiovascular disease through the lens of genome-wide association studies	Trends in Genetics	Genetics and Heredity (11/138)

Year	Author	Title	Journal	ISI Web of Knowledge category and rank
2009	Pereira, N. L. and Weinshilboum, R. M.	Cardiovascular pharmacogenomics and individualized drug therapy	Nature Reviews Cardiology	5/117 Cardiac and Cardiovascular Systems
2010	Chico, T. J. A. Milo, M. and Crossman, D. C.	The genetics of cardiovascular disease: new insights from emerging approaches	Journal of Pathology	Oncology (22/143), Pathology (6/69)

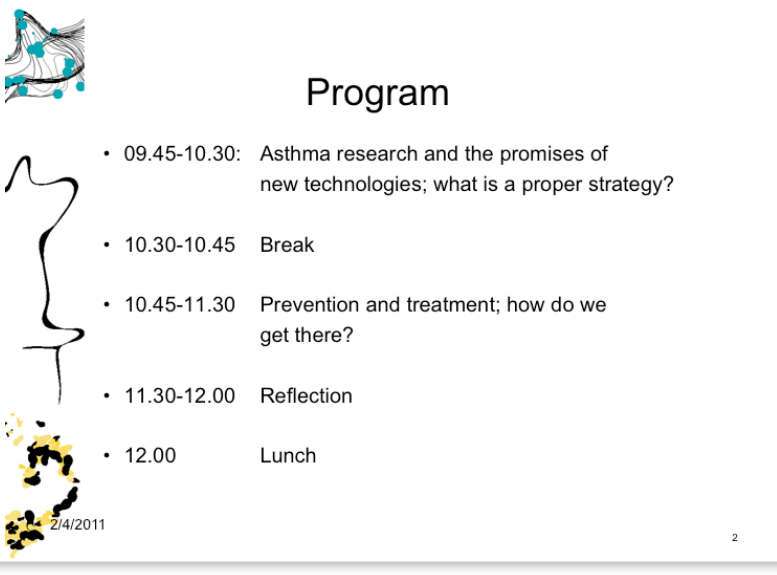
Appendix F

The following images are slides from the presentation *"Future Visions of Prevention, Diagnosis, and Therapy for asthma: Priorities in asthma research"* and the presentation *"Future Visions of Prevention, Diagnosis, and Therapy for cardiovascular disease: priorities in research"*.

Future Visions of Prevention, Diagnosis, and Therapy for asthma: Priorities in asthma research

Slide 1

Slide 2



Slide 3

Welcome

2/4/2011

3

Slide 4

Asthma research; what do I see?

- Whole-genome information as well as whole-genome methods have become established in asthma research
- Persistent expectations that improved understanding, diagnosis, therapy and prevention will result from these approaches
- So far clinically useful associations have not been found
- Not everyone is impressed with new technological approaches

2/4/2011

4

Slide 5

Asthma research; what do I see?

- Genomic information could be used by clinicians to support diagnosis and decide on treatment
- Susceptible individuals should be identified, so prevention can be targeted towards them
- People want to use genomic information to initiate lifestyle changes

- Genomic information is of no added value in a clinical setting: the patient-doctor relationship is much more important

2/4/2011

5

Slide 6

Asthma research and the promises of new technology – what is a proper strategy?

- Are genome-based approaches unlikely to improve our understanding of the etiology of asthma or lead to improved prevention, diagnosis and therapy?

2/4/2011

6

Slide 7

Prevention and treatment; how do we get there?

- The assumption that genomic information will make a crucial difference in prevention and treatment of asthma, rests on the idea that people will want to take active responsibility for their lifestyle choices.

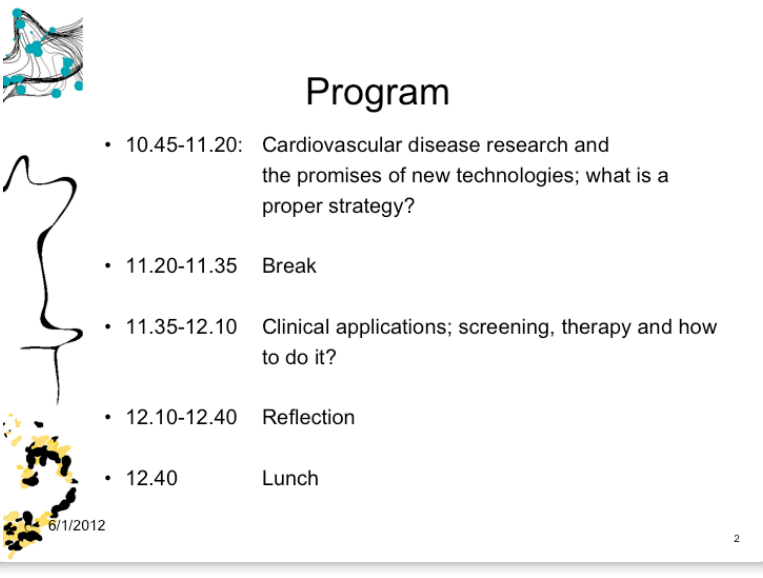
2/4/2011

7

Future Visions of Prevention, Diagnosis, and Therapy for cardiovascular disease: priorities in research

Slide 1

Slide 2



Slide 3

Welcome

Slide 4

Cardiovascular disease research; what do I see?

Review papers

- Whole-genome information / methods have become established
- Two main goals are pursued
  - understanding the biology
  - finding targets for developing (personalised) medicine
- Next generation sequencing in families / systems biology approaches will provide clues to mechanisms of disease
- How to tackle gene-environment interaction?

Summary

The study of the genome was introduced with promises of enabling a revolutionary shift from a care to a prevention-oriented health care system. It was imagined that mapping the whole genome would lead to options for prevention, improved diagnosis and therapies for common diseases, such as Alzheimer's, cardiovascular disease, cancer, respiratory conditions and mental illnesses. Doctors would be able to let individuals know of their risk of disease. With this risk information individuals would be able to take preventative action in terms of medications and changing lifestyles. However, opponents argued that genomics would eventually benefit a much smaller group of people with rare diseases. Furthermore, the usefulness of genetic tests for common disease was questioned with reference to the relative uncertainty of the test results. The desirability of an increased focus on genes in dealing with common disease was also questioned. Especially prominent were concerns with reductionism, and concern with a related shift in responsibilities for preventing and managing disease to individuals.

This thesis explored how the expectations and promises of genomics have been taken up and given shape by researchers of common disease. Genomics presents itself as a novel opportunity for exploring a possible genetic component to disease. However, researchers of common disease are embedded in established research practices. Researchers are therefore seen as constrained – as well as enabled – in the way they can make connections with the expectations and promises of genomics. Established practices might therefore afford researchers different opportunities to respond to the promises and expectations of genomics. I used a comparative approach to investigate how researchers responded to genomics and its associated expectations. In particular I focused on how they use elements of established practice in formulating the contribution of genomics to research and clinical practice. The research question is a specification of this aim:

> *How do researchers of common disease respond to expectations of genomics and what role do elements of established practice play in their response, and how does that shape future options of prevention, therapy and diagnosis?*

In chapter 1, I first presented genomics and its related expectations of a revolution in health care. The chapter introduced findings from STS literature on the impact and development of genomics, and related these findings to the aims of the thesis. The concept of 'the innovation journey' was presented. The innovation journey is used as the overarching frame for conceptualising the activities of

researchers as they attempt to develop genomics for their research area. The innovation journey directs attention to non-linear and uncontrollable nature of innovation processes, and thus to the gap between expectations and eventual outcomes. In chapter 1, I developed two criteria for selecting my case studies. The criteria were based on 1) a description of how genetics is used in current health care practice, and 2) on the observation of differences in how prevention and treatment is weighed in clinical practice. The two case studies were asthma and cardiovascular disease (CVD) research. The case studies, and how they relate to the selection criteria, were briefly described at the end of chapter 1.

In chapter 2, I developed a conceptual model for approaching the research question. The model built on insights from evolutionary economics, STS, SSK and innovation studies. The central idea was of the creation of 'spaces of assessment'. Spaces of assessment are social spaces defined by discursive action. In these spaces, storylines for developing a novelty take shape through actors on-going evaluation of the potential of the new option (genomics). Spaces of assessment are created where researchers take up genomics assess and evaluate its contribution to their area of research. Storylines become the main currency in these spaces that structure the interaction of the researchers. Spaces of assessment then are a specification of the development of the innovation journey in a certain context. The concept of spaces of assessment was based on an exploration of the sociotechnical dynamics of innovation journeys, and a description of the specific context of spaces of assessment in science.

In chapter 3, I developed the research design. Spaces of assessment were probed via three different methods: scientific review papers, interviews and expert workshops.

In chapter 4, I explored the creation of spaces of assessment for genomics in asthma and CVD research. I investigated with what storylines the spaces are created, and how these storylines develop. Specifically I investigated the storylines in scientific review articles. The chapter showed the influence of the specific context of asthma and CVD research on how researchers configured genomics in their storylines. For the asthma researchers, genomics became a matter of developing a profound new understanding of asthma. While the CVD researchers developed a storyline on genomics as justified with reference to a genetic component for monogenetic CVD. This observation was then presented as a guarantee that genomics would add to existing knowledge of, not only the common but also the more rare, CVDs. In both cases, the researchers used a storyline that connects genomics with general expectations of improved understandings of disease, opportunities for prevention, and improved diagnosis and therapy. This storyline was used to justify the more specific expectations to genomics, and

to support genomics as a worthwhile approach. The CVD researchers however emphasised practical implications for clinical practice (therapy, diagnosis) as the most important outcome. The asthma researchers were more general in their expectations. In both cases prevention was presented as the ultimate goal.

In chapter 5, I explored how spaces of assessment were created in interaction among asthma and CVD researchers. The workshops offered an opportunity for alternative storylines. The workshops thus opened up for a more nuanced picture of the storylines from chapter 4. In both workshops, storylines of the review papers were recreated, and complimented with additional elements that did not show up in the reviews. The interaction in the asthma workshop revealed how the argumentation of a central place for genomics was supplemented with a description of a public and funding agencies that do not see the urgency of genomics. As a consequence genomics was made relevant in relation to a sub-group of 5-10 percent that suffer from asthma that is not under control with current medications. Furthermore, alternative storylines emerged establishing environmental factors and the behaviour of asthma patients as important unknown factors.

In the CVD workshop, the storyline on investigation of monogenetic CVD as relevant for multifactorial diseases was recreated. However, it was challenged by an alternative storyline that positioned such research as only relevant for a very small group in the overall Dutch population. Furthermore, the workshop showed how researchers struggled to fit the concept of data translation into the storyline of genomics as relevant for clinical practice. To guard the future potential of genomics data, investors and bioinformatics were introduced, the former as impatient and result-oriented, the latter as the solution to the translation of data. This storyline was specific for the CVD workshop.

In both workshops, the storylines of genomics for clinical practice were influenced by explanations of patient behaviour that challenge the relevance of genome-based applications. To take advantage of genomics information for better health, patients and individuals must be pro-active and able to act. However, alternative storylines emerged that described patient and individuals as either unwilling or unable to act on information on future risks. Coaching, as a third storyline, became a way to overcome the limitations of patients, and a way to align genomics with clinical practice.

In chapter 6, I further explored the storylines on patient behaviour by examining them as discursive resources for the researchers. In particular, I explored how researchers accounted for the expectation that information on genomic susceptibilities will, or will not, motivate behavioural change, and lead to

changes in the roles and responsibilities of established clinical practice. To this end, the analysis in this chapter moves to a so-called participant perspective. This shift allowed me to explore what specific discursive resources allow the researchers to do in relation to ”prevention” as a dominant element of storylines on genomics. In general, the scientists judged the possibility that information on genomics susceptibilities would change patient behaviour in relation to what they constructed as typical patient behaviour in current clinical practice. In doing so, the scientists established themselves as gatekeepers to the clinic and as experts on patients and publics. They accomplished this position by constructing four different versions of the so-called gatekeeper repertoire. In each version the scientists drew on descriptions of patients and the wider public as to motivate opportunities for clinical applications of genomics, or a lack of opportunities for that matter. All versions placed final responsibility for the success or failure of the innovation process with the patients or the general public, rather than focusing on the scientists' responsibilities. Analysing participants' achievements at the interpersonal level adds to our understanding of storylines, by looking at what resources they are made of and how these are actively drawn upon as to structure the spaces of assessment.

In my concluding chapter, I reflected on the findings of the thesis. I did so in three steps. First by exploring how elements of established practice influenced the researchers' storylines of genomics. A clear difference was visible in how genomics was positioned in the storylines of asthma and CVD researchers. In asthma, genomics has found a place in a storyline on the creation of a profound new understanding of disease. For CVD, genomics is predominantly woven into a story of developing drugs or improving risk prediction in clinical practice. Genomics is thus not so much positioned as a change, but as a strengthening of on-going practices. Genomics combined with elements of practice thus affords the emergence of two differing storylines in asthma and CVD research.

Second, I discussed the concept of spaces of assessment as en addition to the literature on the innovation journey as well as to the literature on the sociology of expectations. I argued, how spaces of assessments serve to focus the exploration of the innovation journey between the science, society, and technology spheres. The concept draws attention to the specific actors, their storylines and discursive resources. By delving into the discursive work of creating storylines in specific fields, I could highlight the elements of established practice, which were used to create a storyline of a novelty. The contribution to the sociology of expectations was argued as a tool for investigating how expectations are modulated in specific settings. Spaces of assessment pay specific attention to how expectations of a novelty are received, and what role contextual

elements of specific settings play in how these expectations are modified. A so-called reflexive relationship emerged between the production of expectations and the emergence of structure that govern actors and in turn the production of new rounds of expectations. The relationship is reflexive since the form of expectations is dependent on the context in which they are produced. So, while expectations contribute to coordinating the work of actors, their form is also dependent on the way the work of actors is coordinated in established practices. This implies that the new combinations of expectations and elements of practice, feed back onto the practices that shaped them and change them. In my case studies I showed this reflexive relationship at the level of storylines.

Third, I took a forward look. I drew on a recent report by the National Institute for Public Health and Environment (RIVM), to situate the storylines on genomics from asthma and CVD research. I argued that the storylines in the report open up specific opportunities for genomics in asthma and cardiovascular disease. These opportunities would strengthen on-going practice. Asthma patients would become increasingly responsible for mitigating environmental threats: a behaviour, which could be enforced through technical devices. Genomics opened up for the possibility of new classifications of asthma. These might be combined with the technical device. Persons seen as at risk for CVD on the basis of their genome and lifestyle could be increasingly expected to life, and aided towards, a responsible healthy life. Next, I reflected on the version of the healthy life implied in the researchers' visions of genomics as personalised medicine. In these visions, striving for health becomes a 'super-value'. I argued that this vision is what makes it difficult for researchers to judge patient behaviour as anything else than irrational and unhealthy. Such a vision of health excludes other important values of for example food. These are values like; enjoyment, community and tradition. To be truly healthy, the visions on personalised medicine might need to be opened up and broadened to include other values than a narrow definition of health. Perhaps then researchers would judge the behaviour of patients in a different light, and open the way for an inclusive vision of personalised medicine and the role of genomics therein.

Samenvatting

De studie van het genoom werd geïntroduceerd met de belofte van het mogelijk maken van een revolutionaire verschuiving van een zorg naar een preventief georiënteerd gezondheidszorg systeem. Er werd een inbeelding gemaakt dat het in kaart brengen van het gehele genoom zou leiden tot mogelijkheden tot preventie, verbeterde diagnoses, en therapieën voor wijd verspreide aandoeningen, zoals Alzheimer's, hart- en vaatziekten, kanker, ademhaling- en psychische aandoeningen. Doktoren zouden in staat zijn patiënten individueel op de hoogte te brengen van het risico op een aandoening. Met deze informatie zouden de patiënten zelf preventieve actie kunnen ondernemen in termen van medicatie of verandering van de levensstijl. Echter, tegenstanders beredeneerden dat genomica uiteindelijk voor een veel kleinere groep van mensen met een zeldzame aandoening nuttig kan zijn. Bovendien, werden er vraagtekens gezet bij de bruikbaarheid van genetische tests voor veelvoorkomende ziekten met betrekking tot de relatieve onzekerheid van de resultaten. De wenselijkheid van een verhoogde focus op genen en hun rol in veelvoorkomende ziekten werd ook in twijfel getrokken. Het meest prominent, waren zorgen over reductionisme en een gerelateerde verschuiving van verantwoordelijkheden voor de preventie en managing van ziekten naar de individuele persoon.

Deze thesis onderzoekt hoe de verwachtingen en beloften van genomica zijn opgepakt en hoe ze vorm zijn gegeven door onderzoekers van veelvoorkomende ziekten. Genomica presenteert zichzelf als de nieuwe mogelijkheid tot het verkennen van het mogelijke genetische component behorende bij een aandoening. Echter, onderzoekers van veelvoorkomende aandoeningen zijn ingebed in gevestigde onderzoeksmethoden. Onderzoekers worden om die reden gezien als beperkt – als ook het mogelijk maken – op de manier dat ze connecties kunnen maken met de verwachtingen en beloften van genomica. Gevestigde methoden kunnen daarom onderzoekers toelaten met verschillende mogelijkheden om te reageren op de verwachtingen en beloften van genomica. In het bijzonder heb ik mijn focus gelogd in hoe ze elementen van gevestigde methoden gebruiken in het formuleren van de bijdrage van genomica voor onderzoek en klinische praktijk. De onderzoeksvraag is een specificatie met het volgende doel:

> *Hoe reageren onderzoekers van veelvoorkomende ziekten op de verwachtingen van genomica en welke rol spelen daarbij de elementen van gevestigde onderzoeksmethoden in hun reactie, en hoe geeft dat vorm aan de toekomstige mogelijkheden van preventie, therapie en diagnose?*

In hoofdstuk 1, ben ik begonnen met het presenteren van genomica en de gerelateerde verwachtingen van een revolutie in de gezondheidszorg. Het hoofdstuk introduceert bevindingen van STS literatuur op de impact en ontwikkeling van genomica, en relateert deze bevindingen aan de doelen van de thesis. Het concept van 'the innovation journey' is gepresenteerd. The innovation journey is gebruikt als overkoepelend geraamte voor het conceptualiseren van de activiteiten van onderzoekers terwijl ze trachten om genomica te ontwikkelen voor hun onderzoeksveld. The innovation journey richt de aandacht naar niet-lineaire en oncontroleerbare aard van innovatie processen, en dus ook het gat tussen verwachtingen en uiteindelijke uitkomst. In hoofdstuk 1 heb ik twee criteria ontwikkeld voor het selecteren van mijn 'case studies'. De criteria waren gebaseerd op 1) een beschrijving van hoe genetica wordt gebruikt in de huidige gezondheidszorg methoden, en 2) op de observatie van de verschillen in hoe preventie en behandeling wordt afgewogen in klinische praktijken. De twee 'case studies' waren de onderzoeksgebieden van astma en hart- en vaatziekten (HVZ). De 'case studies', en hoe ze relateren tot de selectiecriteria, werden kort beschreven aan het eind van hoofdstuk 1.

In hoofdstuk 2, heb ik een conceptueel model ontwikkeld voor het aanpakken van de onderzoeksvraag. Het model is gebouwd op inzichten van evolutionaire economie, STS, SSK en innovatie studies. Het centrale idee was het creëren van 'spaces of assessment. Spaces of assessment zijn sociale ruimtes gedefinieerd door discursieve acties. In deze ruimtes worden verhaallijnen voor de ontwikkeling van iets nieuws vorm gegeven door de 'actors' doorgaande evaluatie van de potentie van een nieuwe optie (genomica). Spaces of assessment worden gecreëerd waar onderzoekers ingaan op genomica en de bijdrage voor hun onderzoeksveld beoordelen en evalueren. Spaces of assessment zijn vervolgens een specificatie van de ontwikkeling van een innovation journey in een bepaalde context. Het concept spaces of assessment is gebaseerd op de verkenning van de sociotechnische dynamiek van innovation journeys, en een beschrijving van de specifieke context van spaces of assessment in wetenschap.

In hoofdstuk 3 heb ik het ontwerp van het onderzoek ontwikkeld. Spaces of assessment zijn onderzocht via drie verschillende methoden: wetenschappelijke review publicaties, interviews, en expert workshops.

In hoofdstuk 4 heb ik het creëren van spaces of assessment voor genomica in astma en HVZ onderzoek verkend. Ik heb onderzocht met welke verhaallijnen de ruimtes zijn gecreëerd, en vervolgens deze verhaallijnen zich ontwikkelen. Meer specifiek heb ik de verhaallijnen in wetenschappelijke review publicaties onderzocht. Het hoofdstuk laat de invloed zien van de specifieke context van astma

en HVZ onderzoek op hoe onderzoekers genomica in hun verhaallijnen hebben geconfigureerd. Voor de astma onderzoekers werd genomica een aangelegenheid van de ontwikkeling van een volledig nieuw begrip van astma. Terwijl de HVZ onderzoekers een verhaallijn op genomica ontwikkelden gerechtvaardigd met betrekking tot een genetische component voor monogenetische HVZ. Deze observatie werd vervolgens gepresenteerd als een garantie dat genomica iets zou toevoegen aan bestaande kennis van, niet alleen de gemeenschappelijke, maar ook de meer zeldzame, HVZ's. In beide gevallen gebruikten de onderzoekers een verhaallijn die genomica verbindt met algemene verwachtingen van verbeterde inzichten van de ziekte, de mogelijkheden voor preventie en betere diagnose en therapie. Deze verhaallijn werd gebruikt om de meer specifieke verwachtingen van genomica te rechtvaardigen, en om genomica te ondersteunen als een waardevolle benadering. De HVZ onderzoekers benadrukte echter praktische implicaties voor de klinische praktijk (therapie, diagnostiek) als het belangrijkste resultaat. De astma onderzoekers waren meer algemeen in hun verwachtingen. In beide gevallen werd de preventie gepresenteerd als het ultieme doel.

In hoofdstuk 5 onderzocht ik hoe spaces of assessment werden gecreëerd in interactie tussen astma en HVZ onderzoekers. De workshops boden een kans voor alternatieve verhaallijnen. De workshops hebben dus gezorgd voor een meer genuanceerd beeld van de verhaallijnen uit hoofdstuk 4. In beide workshops, werden verhaallijnen van de review artikelen opnieuw gevormd, en aangevuld met extra elementen die niet op kwam in de reviews. De interactie in de astma workshop lieten zien hoe de argumentatie van een centrale plaats voor genomica werd aangevuld met een beschrijving van publieks en financieringsinstellingen die niet de urgentie van genomica zien. Als gevolg, werd genomica relevant gemaakt voor een subgroep van 5-10 procent die lijden aan astma en niet onder controle staan van de huidige medicijnen. Bovendien ontstonden er alternatieve verhaallijnen die omgevingsfactoren en het gedrag van astmapatiënten als belangrijke onbekende factoren meenamen.

In de HZV workshop werd opnieuw vorm gegeven aan de verhaallijn voor onderzoek van monogenetische HVZ, relevant voor multifactoriële ziekten. Dit werd echter op de proef gesteld door een alternatieve verhaallijn dat dergelijk onderzoek positioneert als alleen relevant voor een zeer kleine fractie van de totale Nederlandse bevolking. Bovendien, liet de workshop zien hoe onderzoekers moeite hebben om het concept van de gegevens vertaling in te passen in de verhaallijn van genomica als relevant voor de klinische praktijk. Om de toekomstige mogelijkheden van de genomica data te bewaken, werden investeerders en bioinformatica geïntroduceerd, de eerste als ongeduldig en resultaatgericht, de laatste als de oplossing voor de

vertaling van data. Deze verhaallijn was specifiek voor de HVZ workshop.

In beide workshops werden de verhaallijnen van genomics voor de klinische praktijk beïnvloed door de uitleg van het gedrag van de patiënten die de relevantie van genoomgebaseerde applicaties op de proef stelden. Om gebruik te maken van de informatie van genomica voor een betere gezondheid, moeten patiënten en personen pro-actief zijn en in staat zijn om te handelen. Echter, alternatieve verhaallijnen kwamen naar voren die patiënt en individuen beschreven als niet bereid of niet in staat om te reageren op informatie over toekomstige risico's. Coaching, als een derde verhaallijn, werd een manier om de beperkingen van patiënten te overwinnen, en een manier om genomica aan te passen aan de klinische praktijk.

In hoofdstuk 6, heb ik verder de verhaallijnen onderzocht van het gedrag van de patiënt door ze te bestuderen als discursieve middelen voor de onderzoekers. In het bijzonder, heb ik onderzocht hoe onderzoekers omgingen met de verwachting dat informatie over genomische gevoeligheden wel, of geen, gedragsverandering zou motiveren, en zou leiden tot veranderingen in de rollen en verantwoordelijkheden van de gevestigde klinische praktijk. Daartoe is de analyse in dit hoofdstuk verschoven naar een zogenaamd deelnemer perspectief. Deze verschuiving stelde me in staat om te onderzoeken wat de specifieke discursieve middelen onderzoekers toestaan om te doen in verband met 'preventie' als een dominerende bestanddeel van verhaallijnen over genomica. In het algemeen beoordeelden de wetenschappers de mogelijkheid dat gegevens over genomica gevoeligheden het patiëntengedrag zou veranderen in relatie tot wat zij construeerden als typisch patiëntengedrag in de huidige klinische praktijk. Daarbij, hebben de wetenschappers zichzelf neergezet als poortwachters van de kliniek en als deskundigen op het gebied van patiënten en publiek. Zij bereikten deze positie door het construeren van vier verschillende versies van het zogenaamde 'gatekeeper' repertoire. In iedere versie hebben de wetenschappers zich gebaseerd op de omschrijvingen van de patiënten en het grote publiek om de mogelijkheden voor klinische toepassingen van genomica, of een gebrek aan mogelijkheden. Alle versies plaatsen eindverantwoordelijkheid voor het succes of falen van het innovatieproces bij de patiënten of het grote publiek, in plaats van bij de wetenschappers. Het analyseren van de prestaties van de deelnemers op het inter-persoonlijke niveau draagt bij aan ons begrip van verhaallijnen, door te kijken naar welke middelen ze van gemaakt zijn en hoe deze actief worden aangesproken om de spaces of assessment te structureren.

In mijn afsluitende hoofdstuk weerspiegel ik op de bevindingen van de thesis. Eerst door het verkennen hoe elementen van de gevestigde praktijk verhaallijnen van genomica van de onderzoeker heeft beïnvloed. Een duidelijk verschil was

zichtbaar in de manier waarop genomics werd geplaatst in de verhaallijnen van astma en HVZ onderzoekers. Bij astma heeft genomica een plaats gevonden in een verhaallijn over het creëren van een volledig nieuw begrip van de ziekte. Voor HVZ is genomica voornamelijk verweven in een verhaal van de ontwikkeling van geneesmiddelen of het verbeteren van risicovoorspelling in de klinische praktijk. Genomica is dus niet zozeer gepositioneerd als een verandering, maar als het sterker maken van de huidige praktijken. Genomica in combinatie met elementen van de praktijk biedt daarmee het ontstaan van twee verschillende verhaallijnen bij astma en HVZ onderzoek.

Ten tweede, besprak ik het concept van de spaces of assessment als een eigen aanvulling op de literatuur over de innovation journey alsook op de literatuur over de sociologie van de verwachtingen. Ik beredeneerde hoe de spaces of assessment dienen om de verkenning van de innovation journey tussen de wetenschap, de maatschappij, en technologie 'spheres' te focusseren. Het concept vestigt de aandacht op de specifieke 'actors', hun verhaallijnen en discursieve middelen. Door me te verdiepen in de discursieve werk van het creëren van verhaallijnen in specifieke gebieden, kon ik de elementen van de gevestigde praktijk uitlichten die werden gebruikt om een verhaallijn van een noviteit te creëren. De bijdrage tot de sociologie van de verwachtingen werd aangevoerd als een instrument voor het onderzoeken van hoe de verwachtingen zijn gemoduleerd in specifieke settings. Spaces of assessment besteedt bijzondere aandacht aan hoe de verwachtingen van een noviteit worden ontvangen, en welke rol contextuele elementen van specifieke instellingen spelen in hoe deze verwachtingen worden gewijzigd. Een zogenaamde reflexieve relatie ontstond tussen de productie van verwachtingen en de opkomst van structuur die het werk van 'actors' bestuurt en op zijn beurt de productie van nieuwe rondes van verwachtingen. Dus, terwijl de verwachtingen bij dragen aan de coördinatie van het werk van de acteurs, is hun vorm ook afhankelijk van de manier waarop het werk van de actoren wordt gecoördineerd in gevestigde praktijken. Dit houdt in dat de nieuwe combinaties van verwachtingen en de elementen van de praktijk terugkoppelen op de praktijken die hen gevormd heeft en hen veranderen. In mijn 'case studies' heb ik deze reflexieve relatie op het niveau van de verhaallijnen laten zien.

Ten derde, heb vooruit gekeken. Ik heb mij gebaseerd op een recent rapport van het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) om de verhaallijnen over genomica van astma en HVZ onderzoek te situeren. Ik beredeneerde dat de verhaallijnen in het rapport specifieke mogelijkheden openstellen voor genomica in astma en HVZ. Deze mogelijkheden zouden de huidige praktijk versterken. Astmapatiënten zouden in toenemende mate verantwoordelijk worden voor het verminderen van milieubedreigingen: een gedrag, dat kan worden afgedwongen

door middel van technische apparaten. Genomica heeft de mogelijkheid van nieuwe classificaties van astma mogelijk gemaakt. Deze kunnen worden gecombineerd met het technische apparaat. Personen geclassificeerd met een risico op HVZ op basis van genomische informatie en hun levensstijl kan in toenemende mate worden verwacht verantwoordelijk en gezond te leven. Vervolgens heb ik nagedacht over de versie van het gezonde leven geïmpliceerd in de visie van genomica als gepersonaliseerde geneeskunde van de onderzoekers. In deze visies wordt het streven voor gezondheid een 'super-value'. Ik beredeneerde, dat deze visie is wat het moeilijk maakt voor onderzoekers om gedrag van de patiënt te beoordelen als iets anders dan irrationeel en ongezond. Een dergelijke visie van de gezondheid sluit andere belangrijke waarden als van bijvoorbeeld voedsel uit. Dit zijn waarden als, plezier, gemeenschap en traditie. Om echt gezond te zijn, zouden de visies op gepersonaliseerde geneeskunde ter discussie moeten worden gesteld, en uitgebreid naar andere waarden dan een smalle definitie van wat gezondheid omvat. Misschien zouden dan de onderzoekers het gedrag van patiënten in een ander licht te beoordelen, en de weg openen voor een bredere visie van gepersonaliseerde geneeskunde en de rol die genomica daarin speelt.

Slide 5

Cardiovascular disease research; what do I see?

Suggestions of Interviewees

- population screening and division into risk groups
  - modeled on existing successful screening programs
- Genomic information should be used to decide on treatment and provide targeted (lifestyle) advice
- Will genomics support a trend of more chronically ill individuals?
- Cardiologists exited about improved technologies for (surgical) intervention

6/1/2012

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Slide 6

Cardiovascular disease research and the promises of new technology – what is a proper strategy?

- Genome-based research strategies are crucial for reaching the two primary goals of cardiovascular disease research: understanding the biology and increased understanding of treatment response.

6/1/2012

6

Slide 7

Clinical applications; screening, therapy and how to do it?

- Prospective and predictive personalised health care for people susceptible to heart disease cannot be successful, unless genome-based information will motivate lifestyle change on a large scale.

6/1/2012

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Colophon

Book design and Illustration by Mark P. Lindhout

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