Translating the dynamics of genetics into health care practice

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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

GENETICS IN HEALTH CARE PRACTICE

Variation within genes is to a large extent responsible for the great diversity among people, making each of us unique. Furthermore, genetic factors are of paramount importance for normal development and health. Abnormal genes and/or abnormal expression of genes can therefore lead to birth defects and diseases[1]. The rate at which knowledge about genetics has become available in the last decade is enormous, having major consequences for our health care[2]. It has had (and will have) a considerable impact on diagnosis, treatment and prevention of diseases[3]. Examples of the use of genetics in health care (in this thesis all referred to as genetic services) can be found in specialized clinical genetic centres (affiliated to University Medical Centres), public health (e.g. population screening programmes), but also increasingly in "mainstream medicine" (provided e.g. by general practitioners, and non-genetic medical specialists in health centres and local hospitals)[4].

Specialized genetic care: Clinical genetics

Centres for genetic counselling were introduced in most developed countries around 1950/1960[5]. One of the first described goals of genetic counselling, by Sheldon Reed in 1955, described the primary aim as "to provide people with an understanding of genetic problems in their family" and did not include curing, preventing or treating disease[6]. Following significant advances in medical genetics, in the Netherlands clinical genetic centres in academic hospitals have been emerging since the early 1970s. Around that time it was realized that there was a growing need for specialized medical geneticists, eventually leading to the recognition of Clinical Genetics as a specialism in 1987[5,7]. Most of the work in the Clinical Genetic centres started with a focus on pre- and postnatal diagnostics and counselling about hereditary and congenital disorders and accompanying cytogenetic, molecular and biochemical diagnostics[8].

The definition of genetic counselling has changed over time although the ethical concept of non-directiveness became a fundamental doctrine quite early, promoting autonomy and self-determination and personal control of the client. This was especially relevant for reproductive issues, in the years when clinical genetics focussed on pre-and postnatal diagnostics. More recently, clients increasingly have questions about disorders that they themselves might develop later in life[9]. One of the latest definitions of genetic counselling was formulated in 2005, following advances in predictive testing, treatment, and prevention of genetic diseases such as hereditary cancer, by the National Society of Genetic Counsellors in the United States, stating that:

> *"Genetic counselling is the process of helping people understand and adapt to medical, psychosocial, and familial implications of genetic contributions to disease." This process integrates the following: I) Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence, II)*

Education about inheritance, testing management, prevention, resources, and research, III) Counselling to promote informed choices and adaptation to the risk or condition."[7]

Although non-directiveness was still felt to be a guiding principle in genetic counselling, it was not specifically included nor excluded in the definition[7]. Since knowledge about genetics and opportunities for genetic testing are still being developed rapidly, shifts in clinical genetic practice are currently still ongoing (see "dynamics of genetics").

Public health genetic services aimed at newborns: Neonatal screening

Apart from individual healthcare, genetics increasingly plays a role in public health services. An example is neonatal screening, that started around the 1970s in several Western countries with programs to identify infants affected by phenylketonuria (PKU), an autosomal recessively inherited condition. All newborns were offered a test in which some blood was taken, usually from the heel, dried on a card, sent to a laboratory, and analysed (currently) in high-throughput tandem mass spectrometers. One of every 10,000-20,000 infants will turn out to have PKU, and its health gain can be enormous if the diagnosis is made before symptoms occur. Because of the successful improvement in health outcomes from this screening program, the panel of diseases tested has been expanded in most countries with multiple other disorders where prompt treatment in newborns is leading to prevention of serious health damage.

Doing good while not causing too much harm has been the central issue in genetic screening.

"All screening programs do harm. Some do good as well and, of these, some do more good than harm at a reasonable cost."[10]

This quote from Sir Muir Gray, former program's director at the UK National Screening Committee, clearly shows the ethical challenge of balancing pros and cons of screening. More than four decades ago, J.M.G. Wilson and G. Jungner (1968) formulated screening criteria to make sure that the advantages outweigh the disadvantages and that the quality of screening programs offered by public health authorities would be optimal. The criteria include amongst others the availability of treatment, a good test, and the accessibility of treatment in health care. Their list of ten principles is currently still widely used as a basis for evaluation when new opportunities for early diagnostics of treatment become available and expansion of neonatal screening panels is discussed[11].

Genetics of common disorders: Moving to mainstream medicine

Since in clinical genetics the focus on family medicine shifted towards more individual counselling to predict, prevent and/or appropriately treat disorders developing later in life, the distinction between clinical genetics and "mainstream medicine" became blurred. In 2010 the Committee of Ministers from the Council of Europe described that:

"The development of genetics in health care services has a major impact on the organisation of health care, leading to shifting from curative to preventive services, from in-patient to out-patient treatment, from specialised genetic services to genetics as an integral part of general health services."[12]

Mainstream medicine is now increasingly encompassing inherited aspects in a variety of ways and the necessary specialist clinical and laboratory elements are integrated through commissioning of the appropriate clinical pathways[4]. This development is still ongoing and responsibilities of expert geneticists and other specialists are changing. Clear opportunities for integration of genetics in "mainstream medicine" currently exist for genetic testing for monogenic subtypes of common disorders, such as breast cancer due to *BRCA* gene mutations, colon cancer in Lynch syndrome, familial hypercholesterolemia (FH), and cardiac death due to long QT syndrome or hypertrophic cardiomyopathy[13]. Challenges lie, for example, in multidisciplinary cooperation and merging of different cultures and practices (from within and outside clinical genetics)[14,15].

DYNAMICS OF GENETICS: NEW OPPORTUNITIES INDUCING CHANGES

New opportunities for genetics in health care are arising rapidly, due to developments in technology for testing (e.g. whole genome sequencing), changes in organization of health care (e.g. allowing market forces to improve health care), shifts in demand (e.g. because of newly available therapies) and/or changes in culture (e.g. recognition of new facets of utility of testing, such as shortening the "diagnostic odyssey"). These opportunities often induce changes in health care practice, challenging policymakers in different types of health care services that are currently provided. Recent changes within the field of genetics have been described to include a shift from reproductive tests to more predictive testing, from reproductive decision making to personal risk reduction, and from monogenic to common complex disorders[16,17]. The studies presented in this thesis explore the challenges in the processes of these transitions in genetic health care practice, induced by the dynamics of genetics, from different perspectives.

The examples studied in this thesis include the processes of change in response to opportunities, for three different settings:

Next generation sequencing in clinical genetics

Advances in DNA sequencing techniques have intensified the use of sequencing and analysis of large parts of the genome (next-generation sequencing, NGS) in research as well as in diagnostics. While techniques for sequencing have become more and more affordable, rapid developments in bioinformatics have made analysis of the sequence more effective and efficient. In clinical genetics NGS is increasingly being

chosen as a diagnostic tool for cases of expected, but unresolved genetic origin. On the one hand, this technique is leading to a diagnosis in many cases with so far unknown aetiology, for instance developmental delay and rare disease phenotypes. However, when exploring a higher number of genetic variants, there is an increased chance of unsolicited findings. The consequential increased need for decisions on disclosure of these unsolicited findings poses a challenge for the informed consent procedure. This challenge gave rise to an international discussion about *the right to know* and *the right not to know* about personal health information detected in the course of diagnostics with NGS, and *the duty to inform* of the health care professional and the question how to get a proper *informed consent*[18-21].

New opportunities for neonatal screening

Insights in genetics and advances in treatment of several (often monogenic) congenital disorders, in addition to the availability of new high-throughput techniques have provided opportunities for neonatal screening. One of the diseases that is (close to) meeting the screening criteria for national blood-spot screening programs for newborns is Pompe disease. Pompe disease is a rare autosomal recessive lysosomal storage disorder, caused by a deficiency of acid alpha-glucosidase (GAA). Since the introduction of enzyme replacement therapy (ERT) for Pompe disease (around 2006), awareness and early diagnosis have gained importance. Because ERT is most effective when started early, neonatal screening is getting increased attention. Neonatal screening for Pompe disease (offering testing of GAA activity to all newborns) will however not only identify patients who will develop symptoms within a few months after birth, but also babies who will be likely to develop symptoms of Pompe disease at an unpredictable time-point later in life. Challenges in the process of implementation of this example lie in the evaluation of the expected benefits and harms of genetic testing for Pompe disease and the weighing of arguments from different perspectives (e.g. the general public, patients and professionals)[22,23].

Genetic testing in "mainstream medicine"

Amongst the most promising genetic services for the near future is testing for monogenic subtypes of common disorders. Identification of patients with monogenic variants of e.g. diabetes, cancer and cardiac disorders could effectively reduce morbidity and mortality by the ability to offer more appropriate treatment to patients and early detection of family members at increased risk of the disorder. These family members could benefit from genetic testing by an offer of appropriate monitoring, prevention and/or timely treatment. It seems appropriate to integrate this service in "mainstream medicine" because diagnosis and treatment of common disorders has always been the responsibility of non-genetic specialists. Although different initiatives have started to implement such services, they have not been all similarly efficient in

terms of effective implementation, and currently accessibility is still far from optimal in many places[24-28]. While it can be expected that analogous challenges and facilitators are experienced in the process of different genetic service innovations, little practical guidance exists for the planning and execution of such transitions[29-31].

TRANSLATION IN GENETIC HEALTH CARE: "FROM BENCH TO BEDSIDE"

New opportunities in genetics need translation to health care before (patients in) the general public can profit from its potential. These processes of change are sometimes also referred to as "translational pipelines", comprising different steps in the evolution from a new invention or development discovered at the research "bench" to an application that is useful at a patients' "bedside" (or at the public health level). Different steps in this translational pipeline have been described by Khoury et al. (2007) and include: translation of a discovery to a candidate health application, translation of a health application to evidence-based practice guidelines, translation from practice guidelines to health practice, and translation of practice to population health impact[32]. Others have described the phases of development of services as processes of deepening, broadening and scaling up of innovations[33], or have proposed 7 steps for "diffusion of innovation"[34], but they have in common that a chronological order of translational processes is proposed.

Ensuring responsible translation

Challenges can occur in all phases of translation and lie for example in providing evidence for utility of a genetic test and in the development of knowledge, practice and understanding in all different actors involved.

In order to ensure responsible translation, a translational pipeline is aimed at verifying whether a new (or adapted) service is meaningful and appropriate and whether imlementation is efficient (with the least waste of time, effort and finances), effective (producing the intended result) and robust (or sustainable).

To facilitate responsible translation in the first steps in the translational pipeline, scientific data on emerging genetic tests and/or services need to be evaluated. The CDC's Office of Public Health Genomics (OPHG) has developed a framework for collecting, evaluating, interpreting, and reporting data about genetic testing in a format that could aid policy-makers in decision-making. This model of the process is composed of a standard set of targeted questions that address disorder, testing, and clinical scenarios, as well as Analytic and Clinical validity, Clinical utility and associated Ethical, legal, and social issues (ACCE: see figure 1.1).

Furthermore, to enable professionals to quickly evaluate appropriateness of implementation of existing genetic tests in a specific context, multiple tools have been developed, which are still frequently updated. Examples are e.g. the Clinical Utility

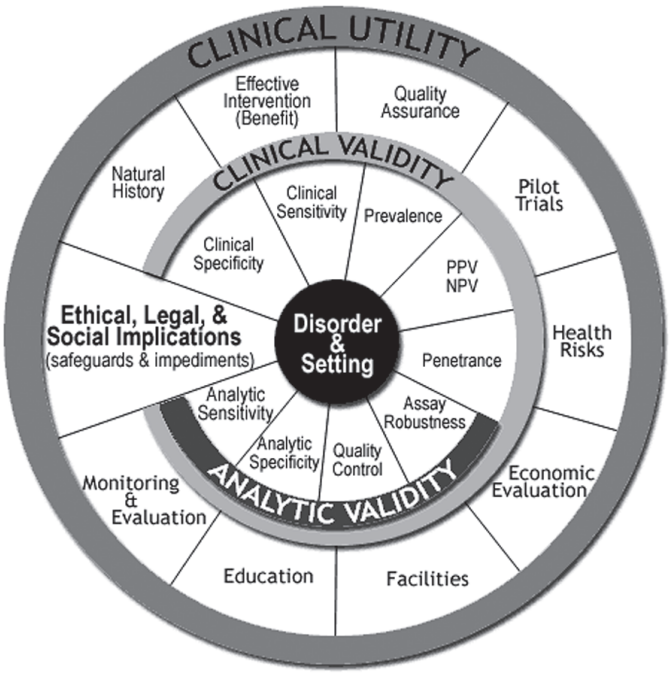

Figure 1.1: ACCE model for evaluation of genetic testing (source: http://www.cdc.gov/genomics/gtesting/acce/acce_proj.htm)

Gene Cards (CUGCs) developed within a European research consortium (EuroGentest) and published in the European Journal of Human Genetics and the GeneReviews available via the National Center for Biotechnology Information (NCBI) of the National Institute of Health (NIH), USA[35-37].

Although clearly guidance exists for the evaluation of genetic tests, the process of implementation of genetic services received little further attention. This was already described by Khoury et al. (2007) who estimated that only 3-4% of published studies in the field of translation research is focussed on the processes beyond the translation of a new gene discovery to candidate health applications (the first phase in the translational pipeline)[32].

Transition management

From studies in the field of Health System Innovation and Translation it is known that to accomplish robust implementation of new or adapted health services, often changes in the existing practice require cultural and structural adaptation. Models for how to sustainably manage these changes are existing for health care in general (adapted from business studies and often referred to as "Transition Management"[38,39]), but what exactly is needed for responsible translation for genetic services remains unclear.

Actors involved

New technology (e.g. genetic tests) or treatment for genetic disorders may be developed by scientists in the laboratory. To be implemented in health care, health care professionals will have to integrate it in the current organization, or develop a new health care setting. The success or uptake will be determined by the question whether or not the patients (or citizens) have a demand. Finally the evaluation of the acceptability, including ethical and legal aspects, may involve regulatory, advisory and governmental agencies. This illustrates the different actors that are involved in the translational pipeline (see figure 1.2) and attuning the different actors is known to be one of the main challenges for efficient, effective and sustainable implementation[40].

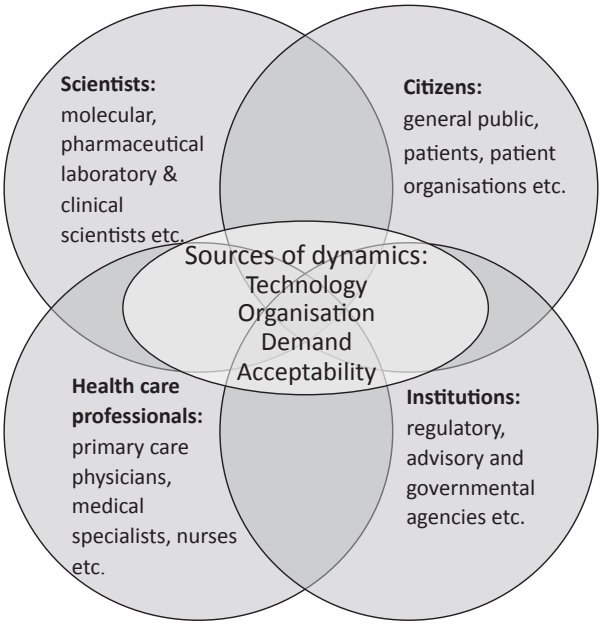

Figure 1.2: Network of actors that need to be attuned in translational processes, which could be initiated by dynamics in technology, organization, demand and/or acceptability in health care systems (Adapted from:[40])

AIM OF THESIS

Valorisation: bridging the gap between "bench and bedside"

Valorisation is currently one of the key themes in the international research agenda: the importance of ensuring responsible translation of fundamental research into practice is generally acknowledged. The EU Horizon 2020 programme for instance aims to tackle societal challenges by helping to bridge the gap between research and

the market (ec.europa.eu/programmes/ horizon2020/). Because little guidance exists for the implementation of genetic health care services, this study aims to explore the barriers, facilitators and needs for this process.

Change processes: providing guidance at different levels

The studies in this thesis aim to explore previous, current, and future change processes within genetic health care practice. Focus has been on recent discussions around the introduction of NGS in diagnostics and its consequences for the informed consent procedure, the potential inclusion of Pompe disease in the neonatal screening panel, and the development of a model for implementation of new genetic services in "mainstream medicine".

Because change processes are complex and could be viewed from different angles, various approaches have been used in the studies described in this thesis, focussing on providing arguments for utility, stakeholder perspectives, and/or earlier experiences with transitions.

RESEARCH QUESTIONS

The main objective of this thesis is to explore what is needed for responsible translation of recent opportunities for genetic health care services. The research questions addressed evolved around the three settings described above (clinical genetic services, population screening programs and mainstream medicine) resulting in discussions of different challenges in the process of translation in three parts:

Part I: Introduction of next generation sequencing (NGS) and -analysis in *clinical genetics* is an example of a *recent change process*. Informed consent is one of the challenging aspects in *attuning different actors* in this process.

Q1: What is needed for optimal informed consent when introducing NGS in clinical genetics?

a. What can be learned so far from experiences with unsolicited findings and informed consent when using NGS for diagnostic purposes in clinical genetics?
b. What are the needs and considerations for an optimal informed consent procedure for NGS in diagnostics, perceived by different actors?

Part II: The introduction of screening for new candidate disorders in the *neonatal screening* program is an example of a *potential change process*. Challenge in this process is the *evaluation of potential advantages and disadvantages* by the actors involved.

Q2: What is the potential utility of neonatal screening for Pompe disease from different perspectives?

a. What are the advantages and disadvantages of neonatal screening for Pompe disease?

b. What are prerequisites for meaningful implementation of neonatal screening for Pompe disease?

Part III: The introduction of testing for monogenic subtypes of common disorders and informing relatives of possibilities for risk-reduction in *"mainstream medicine"* is an example of *on-going change processes*. Many countries experience *challenges in translation*.

Q3: What is needed for responsible implementation of new innovations in genetic health services?

a. What can be learned from recent experiences with implementation of services for monogenic subtypes of common disorders for new innovations in genetic health services?
b. Which questions should be addressed in different phases of transitions to new genetic health services?

OUTLINE OF THE THESIS

Part I of this thesis focusses on recent implementation of next generation sequencing in clinical genetics. In Chapter 2 the consequences of the emerging unsolicited findings on informed consent are explored by reflecting on earlier experiences with unsolicited findings in different contexts and proposing a list of points to consider. Chapter 3 aimed to probe the first experiences with informed consent for next generation sequencing in diagnostics and describes the views of professionals and patients.

The second part (**part II**) of this thesis describes neonatal screening for Pompe disease, serving as an example for potential opportunities in public health. Chapter 4 presents the results of a cross-sectional study of the health status of patients at diagnosis of Pompe disease, to explore the potential utility of neonatal screening. While Chapter 5 describes the support of public and (parents of) patients for neonatal screening for Pompe disease, Chapter 6 explores the views of professionals regarding this issue.

Part III discusses the ongoing implementation of new genetic services in "mainstream medicine", by describing what can be learned from examples of testing of monogenic forms of common diseases in Chapter 7.

The last part (**part IV**) of this thesis reflects on the main findings from the studies by presenting a general discussion in Chapter 8, where methodological considerations are addressed as well as practice implications and further research in this field. The thesis concludes with a summary in Chapter 9.

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