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Translating the dynamics of genetics into health care practice

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GENERAL DISCUSSION

BACKGROUND AND OBJECTIVES

Rapid advances in genetic knowledge hold great promise to impact diagnosis, treatment and prevention of diseases¹. The consequential dynamics in the provision of genetic health care will require changes in the organisation of services². The main objective of this thesis is to describe what is needed for responsible translation* of recent opportunities for genetic health care services. The studies in this thesis therefore aim to explore previous, current, and future change processes within genetic health care practice. The focus is on recent discussions around the current introduction of next generation sequencing in diagnostics and its consequences for the informed consent procedure (Part I), the potential inclusion of new disorders such as Pompe disease in future neonatal screening panels (Part II), and the previous and ongoing development of a model for implementation of new genetic services in “mainstream medicine” (Part III).

The general discussion of this thesis shortly summarizes the main findings, followed by a reflection on these findings and the methods used in the studies presented. A discussion of implications for practice and recommendations for further research will precede the main conclusions of this thesis.

MAIN FINDINGS

Part I: Next generation sequencing in diagnostics

The introduction of next generation sequencing (NGS) and -analysis in clinical genetics is an example of a recent change process. Clinical geneticists have started to offer high-throughput nucleotide sequencing ((whole) exome/genome sequencing (WES/WGS) for diagnostic testing to patients with expected genetic disorders with unresolved etiology, as an element of regular health care. The interpretation of all different variants obtained through WES/WGS by molecular geneticists and bio-informaticians is still a challenge. Incidentally genetic information may be found that is not related to the clinical question, but is still potentially relevant for patients or their relatives. Informed consent is one of the challenging aspects in the context of these so-called “unsolicited findings”. The increased need for decisions on disclosure of unsolicited findings requires attuning of different actors³⁻⁶. Therefore the first part of the thesis (Chapters 2 and 3) aimed to explore what is needed for optimal informed consent when introducing NGS in clinical genetics.

As described in Chapter 2 the ethical challenges encountered in the process of informed consent in this context include balancing between information overload

* Responsible translation is in this thesis used to describe effective, efficient and robust implementation of meaningful and appropriate services.

and uninformed consent. It has proven difficult to find consensus on how to both do justice to the right to be informed about unsolicited findings, while at the same time safeguarding the right not to be informed. Practical needs and considerations identified and discussed in both chapter 2 and 3 include the need for close cooperation and communication among the different actors involved in different phases of the informed consent process. Different actors involved need to realize that there are limits to, and context-dependent differences in, informing and informed decision-making. What is needed furthermore is clear categorization and communication about the possible unsolicited findings, as previously suggested by others^{7,8}. Finally the possibility of the use of an Advisory Board for decisions on which unsolicited findings to disclose was proposed but revealed practical barriers for long term implementation. More experience might teach us about the frequency of unsolicited findings, which is essential information for patients in their decision process^{9,10}.

To guide decisions in the process of developing an informed consent protocol, a set of questions to consider was developed and is presented in chapter 2⁹. It aims to systematically give health care professionals insight in the degree of feedback the patient should and could be able to decide upon, when reporting back results from WES/WGS in diagnostics. Moreover, close collaboration and cooperation between the different actors involved is recommended in multiple steps in this process, in order to ensure an optimal effort to provide good practice.

Part II: Neonatal screening for Pompe disease

The introduction of screening for new candidate disorders in the neonatal screening program is an example of a potential change process¹¹⁻¹³. A challenge in this process is the evaluation of potential advantages and disadvantages by the actors involved^{14,15}. The studies in the second part of the thesis therefore describe the process of gaining insight in, and weighing advantages and disadvantages of, neonatal screening for Pompe disease. Dilemmas involved in screening for Pompe disease can be used as an example for other broad-spectrum phenotype disorders. Current screening tests for Pompe disease not only detect the classic infantile form of Pompe disease - lethal in the first year of life, when untreated - but also less progressive cases, for which the age of onset might vary from infancy to adulthood. Since the traditional focus of neonatal screening does not fit well with the potential outcome of this new kind of screening, introduction of neonatal screening for Pompe disease needs careful consideration from all angles, and screening criteria might need rethinking^{16,17}. The aim of this part of the thesis was therefore to explore the potential utility of neonatal screening for Pompe disease from different perspectives.

The data presented in chapter 4 show that there is utility in early diagnosis of the disease by revealing that the whole spectrum of patients with Pompe disease are significantly impaired in body function and structure, limited in activities, restricted in participation and in some cases dependent on respiratory-, walking- and/or feeding

support already at the time of diagnosis¹⁸. Furthermore the general public and (parents of) patients are shown to be generally positive about potential implementation in chapter 5¹⁹. Professionals described in chapter 6 however seem hesitant and no consensus exists amongst them, although in general they seem to take similar arguments into account. Professionals expect benefits from neonatal screening for Pompe disease, especially for early-onset cases. Some valued screening for more slowly progressive cases as well, while stressing the need for adequate support of pre-symptomatic patients and their families. Others considered the psychological burden and uncertainties regarding treatment as reasons not to screen. Additional to the main findings described in part I, the importance of the search for evidence and arguments on clinical utility is illustrated in the second part of this thesis. Furthermore it is shown that exploring the different perspectives of parents, public and professionals is required early in the process of valuation of early diagnosis.

Part III: Testing for monogenic subtypes of common disorders

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 a previous and on-going change process^{20,21}. Many countries experience challenges in translating new opportunities for genetic health care to practice²²⁻²⁶, and therefore the third part of this thesis aimed to explore what is needed for responsible implementation of new genetic health services.

In order to achieve full translation of an innovation into health care practice (often referred to as a transition), both cultural and structural changes are required. Main barriers encountered and expected in transitions in genetic service provisions (and described in chapter 7) include a lack of essential skills and genetic knowledge amongst non-genetic health care providers, a resistance to new divisions of responsibilities amongst important actors, and a need for closer collaboration and communication between geneticists and non-geneticists. Facilitating factors include statutory registration of genetic specialists, availability of essential staff and equipment, and existence of registries and guidelines for specific genetic services. Other relevant challenges are experienced in the establishment of the appropriate legal and financial structures. Key actors in transitions need to be active in agenda setting, should create coalitions and require negotiation and policy entrepreneurial skills to create room and resources for experimentation.

To give guidance for new and/or developing genetic services the main topics and questions to be addressed in different phases of transitions are summarized in part III (Chapter 7). These include questions on evidence for utility and the perceived need for change as well as exploration of ethical, legal and social issues in the first phase of a transition. Later in the translational process issues as education of stakeholders, cooperation- and communication strategies, evaluation of the new service, and horizon scanning to accommodate for constant dynamics are considered essential.

REFLECTION ON THE MAIN FINDINGS AND METHODS

Part I

The research methods used in the first part of the thesis include the exploration of ethical and practical consideration of various actors, by conducting interviews and observations, and initiating discussion amongst experts in order to give insight into challenges involved in the informed consent process for NGS in clinical diagnostics. While different perspectives, including that of patients, are described in chapter 2 and 3, the case-studies are limited (n=3) and have been conducted in one center. It remains therefore uncertain whether results from chapter 3 can also be applied in other settings. Results of chapter 2 however were mainly obtained through international discussions, suggesting a more international applicability.

Although the challenges and possible solutions for informed consent for WES/WGS in diagnostics have recently received much attention in literature²⁷⁻²⁹, so far, only temporary solutions have been developed and no consensus has been reached on what is best practice^{9,10}. More experience with WES/WGS and unsolicited findings is essential in order to come to definite conclusions on what is best practice for informed consent for WES/WGS in diagnostics, because many of the (long-term) consequences are currently unknown and remain hypothetical so far. More empirical research on how to communicate the complexity of possible outcomes of WES/WGS and the extent of informed decision making is required. Moreover, models for close collaboration between lab and clinic need to be further explored. Until the different key actors have resolved the issues, or at least reached consensus on good practice, a general advice for setting high bars for justification (in terms of necessity and proportionality) and prudence in the use of NGS and analysis seems appropriate^{30,31}.

Part II

In the second part of the thesis different approaches are used in order to provide arguments for utility of neonatal screening for Pompe disease and explore stakeholder perspectives. Increased awareness for the user-perspective has been promoted in the last few years and therefore, even more than in part 1, there has been deliberate attention for the exploration of opinions of (parents of) patients and the general public in chapter 5³². From the studies presented in chapter 5 and 6 it becomes clear that although the advantages and disadvantages may be evident to all actors involved in a change process, the value of the different arguments can differ amongst them, potentially creating tension and difficulty in coming to a general conclusion. This shows the importance of communication amongst the key actors involved in genetic service provision, not only about priorities and division of responsibilities, but also in order to elucidate ethical contexts to create a sense of understanding for each other's' positions, as described in part III. This seems crucial in the process of translation in order to efficiently initiate changes in genetic health services.

Part III

The third part of the thesis aimed to learn from the introduction of testing for monogenic subtypes of common disorders, to gain insight into what factors could facilitate responsible transitioning of genetic health services. Consultation of individual field experts and exchanging experiences amongst them gave an understanding of the main topics and questions that should be addressed in the process of translation. To unravel and structure transition processes related to new (or adapted) genetic health services we have adopted elements of models and concepts used in the field of Health System Innovation and Transition. Although these models have proven applicable for different domains in health care^{33,34} they have so far rarely been applied in analyses of genetic health care. Some of the needs for changes in culture, structure and practice described in chapter 7 overlap with results of studies by others³⁵⁻³⁸. Practical guidance in the form of points to consider (and questions to address), to our knowledge, have so far not been described.

The results in this part of the thesis confirm e.g. that long-term planning of actions and attuning between actors involved (including geneticists and non-genetic specialists) is required for efficient implementation of innovations^{39,40}. Furthermore an analysis of the possibilities and barriers that could be expected in the process of adaption of the culture, structure and practice within the changing constellation could make implementation more efficient, effective and robust³⁴.

General reflection

By exploring three domains of genetic services from different perspectives many aspects of translation of genetic services have received attention in this thesis. Although some context-specific conclusions are drawn in the different parts of the thesis, it is expected that most conclusions concerning the process of implementation (e.g. early involvement and attuning of all actors and planning transition strategies ahead) can be generalized to any transition in genetic health care provision.

Genetic services in general have multiple aspects in common: they are dynamic (subject to rapid advances in possibilities), genetics is often perceived as complex by its users (both by health care professionals and patients), and it often entails sensitive ethical facets (e.g. because of potential predictive properties for patients as well as their families). Moreover, genetic services are often developed for relatively rare disorders, creating a challenge for the establishment of a sense of urgency amongst all actors in a transition. In addition, there is a lack of awareness of the opportunities for genetics for health care among the general public, although when asked they seem very optimistic^{2,20,41}. While in public health many have previously anticipated great impacts of advances in genetic medicine, effective implementation has been disappointing in this field as well, due to a lack of priority for genetics but also because of decreasing expectations in the last few years⁴²⁻⁴⁴. What is observed

in most cases of implementation of genetic services in mainstream medicine is that this requires new division of responsibilities; potentially creating a conflict between the different professionals involved²⁷. While some of these aspects might also be recognized in other fields of health care, especially domains where implementation of new technologies and fast changes are foreseen, it is however unknown whether the results of the studies in this thesis could be generalized this broadly.

Future dynamics in genetics can be expected in all fields described in this thesis. For example it is expected that the use of NGS will be more broadly implemented in clinical genetics. Some even expect that, although many challenges are still to overcome, availability of NGS eventually will also have implications for public health services^{45,46}.

Furthermore, although Pompe disease was chosen in this thesis as an example of the dynamics of adding conditions to neonatal screening panels, the history of neonatal screening for Pompe disease in the United States shows that also in this field changes can occur in a short time period. In 2006 an expert panel commissioned by the American College of Medical Genetics considered many conditions for inclusion in a recommended uniform newborn screening panel (RUSP). Pompe disease was not recommended as a primary or secondary target of screening, indeed it scored next-to-lowest of the 84 conditions considered⁴⁷. In 2013, after two additional evidence reviews had been performed, the Discretionary Advisory committee on Heritable Disorders in Newborns and Children recommended adding Pompe disease to RUSP⁴⁸.

Services for monogenic forms of common diseases will also need (further) development in many countries. Especially the systematic identification of people at increased risk of genetic disorders through cascade screening is shown to currently not be fully effective⁴⁹⁻⁵¹.

IMPLICATIONS FOR PRACTICE

Sources of dynamics in genetics that initiate a need for changes in health care provision currently often originate from new and quickly evolving technological developments (e.g. advances in genetic testing or treatment options). In some cases, however, shifts in the organization of health care (e.g. an increased offer of genetic tests from general clinical laboratories instead of clinical genetic laboratories), demand from users (e.g. more interest in personalized medicine and pregnant women asking for non-invasive prenatal testing) or acceptability (political or cultural) can also induce transitions. In order to objectively review appropriateness and meaningfulness of new services and to efficiently plan strategies for implementation it is important to realize what the initiating cause of the dynamics is.

Structured analysis of the different facets of the translation process can give guidance in the management of transitions. It can aid in decisions to be made and in answering questions to be addressed, without giving clear-cut answers because of

the differences per context e.g. with regard to the relevant actors to be involved and the changes in practice that are required. Moreover, culture, structure and practice in health care constellations are rapidly evolving. To accommodate a constellation for these dynamics, constant communication and close collaboration between different actors is required. Challenges may be experienced in changing the division of responsibilities. To prevent unnecessary misunderstanding and to aid in anticipating potential problems it is important to create timely awareness about priorities and norms and values existing in different domains.

The different “layers of actors” can be depicted as a temple (Figure 8.1). In recent changes often the in-house genetic services are well accommodated for dynamics in genetics. However, to make the required changes visible in the base of the roof of the temple (“mainstream medicine”), where most services are delivered, radical changes in Standard Operating Procedures (the pillars of the temple) are needed. To produce a changed, but stable temple, attuning between the different layers of actors in the temple is crucial.

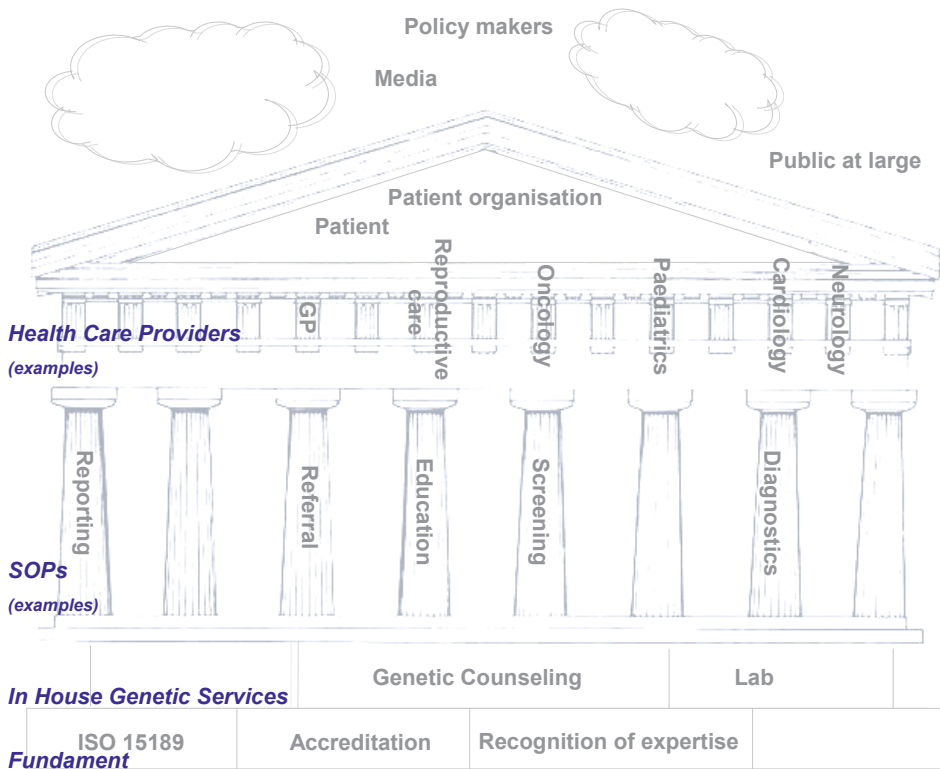


Figure 8.1: Temple of genetic services, depicting the different “layers of actors” and needs that need to attune to form a stable construction. SOP=Standard Operating Procedure. ISO 15189=requirements for quality and competence of medical laboratories.

Based on the results presented in this thesis, the following recommendations for future translations in genetic health provision can be summarized:

1. Identify and be aware of the sources of dynamics: technological innovations in laboratories, organisational changes in health care, changing demands of citizens, legal or ethical requirements
2. Analyze the current practice, structure and culture that requires change
3. Actively plan transition strategies, decide on clinical utility and acceptability, involve relevant stakeholders, scale up from small research setting to landscape level
4. Continually exchange priorities, norms and values between domains (potentially) involved in health service provision
5. Involve all actors early in the change process to avoid unexpected thresholds in later phases of translation
6. Determine needed changes in division of responsibilities between disciplines
7. Plan agenda setting among all actors involved
8. Analyze needs for education and organize training early in the transition process
9. Constantly analyze and evaluate current practice and scan horizon for future changes
10. Be ready for new changes

RECOMMENDATIONS FOR FURTHER RESEARCH

In general this thesis confirms that more attention is required for phases of transitions after providing proof of principle. To guide transitions in genetic service provision, a set of topics and questions to address have been formulated and are presented in chapter 7, but remains unclear which steps are most essential and which aspects require most attention in specific contexts. This would require more in-depth analysis of processes while they are taking place. Furthermore, the lists of points to consider described in this thesis (in chapter 2 and 7) have so far not been evaluated empirically.

More specific recommendations for research on the dynamics in the fields described in this thesis are:

1. Current experiences with next generation sequencing should be evaluated and international debate on informed consent procedures should be stimulated.
2. The current implementation of new neonatal screening panels, including screening for diseases such as Pompe disease, should be thoroughly evaluated, with attention for user-perspectives.
3. In-depth analysis of successful cascade-screening programs should be conducted in order to describe best-practices for this field.

CONCLUSION

To describe what is needed for responsible translation of recent opportunities for genetic health care services, this thesis explored previous, current, and future change processes. Sources of dynamics in genetics that initiate a need for changes in health care provision currently generally originate from new technological developments. To accommodate health care practice for these dynamics, constant communication and close collaboration among different actors is required. Challenges may be experienced in changing the division of responsibilities. To prevent unnecessary misunderstanding and to aid in anticipating potential problems it is important to create timely awareness about priorities and norms and values existing in different domains.

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