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Translating the dynamics of genetics into health care practice

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9

SUMMARY
SAMENVATTING

The enormous rate at which knowledge about genetics has become available in the last decade holds great promise to impact diagnosis, treatment and prevention of diseases. The consequential dynamics in the provision of genetic health care will require changes in the organisation of services. 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 and current change processes within genetic health care practice to optimize future implementation. The examples studied in this thesis describe the processes of change in response to opportunities in three different settings: Clinical genetics (part I), Public health (part II), and "Mainstream medicine" (part III).

Part I: In the first part of this thesis the introduction of next generation sequencing (NGS) and -analysis in clinical genetics is used as an example of a recent (and ongoing) change process. Informed consent is one of the challenging aspects in attuning different actors in this process.

Chapter 2 discusses the ethical and practical dilemmas encountered when contemplating informed consent for NGS in diagnostics from a multidisciplinary point of view. By exploring recent, similar experiences with unsolicited findings in other settings an attempt is made to describe what can be learned so far for the implementation of NGS in standard genetic diagnostics. It is for example shown that challenges are encountered in avoiding both information overload and uninformed consent, and that it is difficult to reach consensus on how to do justice to the right to be informed about unsolicited findings while at the same time safeguarding the right not to be informed. This chapter concludes with a list of points to consider for informed consent for NGS in diagnostics in order to guide decision-making on the extent of return of results.

In **chapter 3** the first experiences with, and needs for, the informed consent procedure in diagnostic exome sequencing are further explored by semi-structured interviews with eleven professionals with different backgrounds, and observation and evaluation of the counselling process with three patient(s) (representatives) and their genetic counsellor. A clear preference for an option not to be informed about unsolicited findings was expressed by the participants in this study, although many challenges were recognized. Complexity of information provision and the need for more experience with exome sequencing and the informed consent procedure are other relevant themes discussed.

The results of chapter 2 and 3 show that close collaboration and cooperation between the different parties involved in NGS in diagnostics is required. Furthermore, it is expected that more experience will help genetic service providers categorize and communicate about potential unsolicited findings in the informed consent process. Finally the use of an Advisory Board for decisions on unsolicited findings is proposed.

Part II: The second part of this thesis explores the potential introduction of screening for new candidate disorders in the neonatal screening program. A challenge in this process is

the evaluation of potential advantages and disadvantages by the actors involved. Pompe disease is used in this part as an example, reflecting the dynamics of the field of neonatal screening. The complexity of neonatal screening for this disorder lies in the fact that it is a broad-phenotype condition that may occur in infancy or manifest later in life.

Chapter 4 presents the results of a cross-sectional study of the health status of patients at the time of diagnosis of Pompe disease, to explore the potential utility of neonatal screening. It reveals that the whole spectrum of patients with Pompe disease is 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 diagnosis. This strongly suggests that there is utility in early diagnosis of the disease.

Chapter 5 describes the support of the public and (parents of) patients for neonatal screening for Pompe disease. Analysis of responses to a questionnaire by 58 Pompe-experienced and 555 neutral respondents demonstrates that 88% of the Pompe group and 87% of the neutral group supported the introduction of screening.

In **chapter 6** the views of professionals regarding expansion of the newborn screening panel to include Pompe disease are explored by describing an interview study with 24 health care and screening professionals, and staff members of patient organisations. It is shown that the participants expect benefits of neonatal screening, especially for early-onset cases, while they also see disadvantages regarding the psychological burden and uncertainties of treatment for more slowly progressive cases. Although they seem to take similar arguments into account, no consensus exists amongst the respondents about the potential implementation of neonatal screening for Pompe disease.

The different approaches used in chapter 4, 5 and 6 to provide arguments for utility of neonatal screening for Pompe disease illustrate the importance of exploring different perspectives of patients (and their parents), public and professionals in the valuation of early diagnosis. There is clear utility in early diagnosis, patients and public support a screening offer but professionals stress the psychological burden and uncertainties of treatment for more slowly progressive cases. Prompt assessment of views and arguments of actors involved could facilitate the translational process and could prevent barriers for implementation.

Part III: The third part of this thesis explores the on-going introduction of testing for monogenic subtypes of common disorders in “mainstream medicine”. It discusses in more detail how to optimize future translation processes in the implementation of new or adapted genetic health services.

Chapter 7 describes a study using mixed methods (including an online questionnaire and an international expert-meeting) aimed at exploring recent experiences with innovations in genetic services and identifying barriers and facilitators in transition processes. Barriers encountered in transitions in the provision of genetic services include: lack of genetic knowledge and skills amongst non-genetic

health care providers, resistance to new divisions of responsibilities, 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. Other challenges are experienced in the establishment of the appropriate legal and financial structures. To provide guidance for new and/or developing genetic services, this chapter ends with the main topics and questions to be addressed in different phases of transitions. 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 process, issues such as education of stakeholders, cooperation- and communication strategies, evaluation of the new service, and horizon scanning to accommodate for constant dynamics within the field are considered essential.

CONCLUDING REMARKS

To responsibly translate the dynamics of genetics into health care practice, 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.