Valorisation
Relevance of this thesis in patient care

The work presented here is not only relevant from a scientific point of view, but is of importance in clinical genetic practice as well, and for patients and patient organizations.

Reproductive options (prenatal diagnosis, PND / preimplantation genetic diagnosis, PGD)

Mitochondrial diseases are often severe hereditary disorders for which couples regularly seek genetic counseling to prevent transmission to a (subsequent) child. In this thesis, guidelines for reproductive testing strategies are provided (General Discussion), which can be applied in reproductive genetic counseling. As such, it serves both the clinician and the patient. For the clinician it is an evidence-based, yet practical guideline in an area of genetics which is often considered complex. The patient can thus be informed in an optimal way regarding available reproductive options and the pros and cons in the couples specific situation, enabling an informed choice. Especially for mitochondrial diseases caused by mutations in the mitochondrial DNA (mtDNA) this adds value to the current situation, as even many health care professionals are unaware of the available options, resulting in incorrect counseling of couples (as illustrated for example in Chapter 7). To further increase knowledge of reproductive options and awareness of the possibility of PGD for mtDNA mutation carriers, we plan to collect the PGD data for mtDNA mutations from our center in an online and continuously curated database, which will be accessible for other centers as well. We expect that the (few) other centers worldwide performing PGD for mtDNA mutations will join and add their data as well, to be able to provide patients and centers offering PGD for mtDNA mutation carriers with the most up-to-date information.

Looking at health care costs, our study showing that a single-blastomere biopsy protocol is sufficient for a reliable PGD diagnosis for mtDNA mutations (Chapter 4) has a direct effect as analysing one blastomere instead of two is cheaper, whereas the success rate of the treatment (chance of a viable/ongoing pregnancy) will increase. Furthermore, our work shows that many mtDNA mutation carriers will benefit from PGD, a cheaper alternative compared to mitochondrial replacement techniques (MRT), which is currently being developed. MRT will only be necessary in a limited and selected carrier subgroup. For those carriers, not having other options for unaffected offspring, the higher costs are justifiable. The successful PGD treatment in a 41-year-old mtDNA mutation carrier (Chapter 5) who produced a quite remarkable number of oocytes considering her age, showed the benefit of establishing ovarian reserve parameters for IVF eligibility. Although not the primary objective of the paper, this illustrates that the use of such fertility markers adds to a more cost-effective
deployment of IVF treatments by selecting the females with a realistic chance of success.

Using whole exome sequencing (WES) for diagnostics

Both in our own experience and that of others,\(^1\) the application of WES as diagnostic tool for mitochondrial diseases, where the mtDNA has been excluded as the cause, enables the identification of the causative gene defect(s) in the majority of patients, instead of the ~16\(^2\)-25\(^3\) that could be solved with conventional diagnostic DNA sequencing methods. As discussed in Chapter 11 (General discussion) this potentially has favourable consequences for the patient (altered patient medical management including treatment options in specific cases) but certainly also for the parents, opting for reproductive testing options to prevent the transmission of the disease to a subsequent child. Not only for individual patients / parent couples the identification of causative mutations is evidently advantageous, also in a broader context this can, and has been shown to, be relevant for subpopulations around the world (see General discussion).

The combination of WES being a generic diagnostic method and having a higher diagnostic yield makes it an efficient and undoubtedly cost-effective approach for genetically diagnosing mitochondrial patients. Costs will be saved due to preventing the conduction of unnecessary investigations. The cost-effectiveness of WES for mitochondrial disorders may further be confirmed in a formal cost-effectiveness (MTA) study, although the clinical impact and cost-effectiveness of WES have already been shown in for example a broader pediatric setting,\(^3\) in the context of four genetically heterogeneous conditions including mitochondrial disease,\(^4\) or in another clinically and genetically heterogeneous pediatric subgroup,\(^5\) respectively.

Preconception carrier screening (PCS)

PCS enables couples at risk of having (severely) affected offspring, for example by a mitochondrial disorder, to be identified prior to their first pregnancy. If a shared carriership is revealed in the parents, an affected child does not need to be born first. The concept of PCS in itself is not new, but PCS based on WES, for which we developed a strategy suitable for the clinical setting, has not been described before. Therefore, WES-based PCS can be viewed as a new ‘product’ for clinical practice, resulting from this thesis. The major advantage compared to existing PCS approaches is the increased sensitivity, because not just a selection of genes, but all genes are included. Our strategy combines the potential of identifying the mutations of interest in the broadest possible way at one hand, and minimizing findings with unknown significance on the other.
Several groups studied the cost-effectiveness of screening for single disorders, sometimes in specific populations, showing cost-effectiveness in certain contexts.\textsuperscript{5-8} Furthermore, for a set of 14 genes, PCS by next-generation sequencing (NGS) was modeled to be cost-effective compared with no screening or targeted mutation analysis of these genes.\textsuperscript{9} Cost-effectiveness of WES-based PCS has not been investigated so far.

As already mentioned above, WES for PCS can be efficiently implemented in the existing diagnostic flow. Moreover, costs for WES are rapidly declining. Considering the tremendous costs of raising a child with a (severe) genetic disorder, PCS is presumed to be cost-effective, although cost-effectiveness is obviously not the main reason to perform PCS. Nevertheless, it is a recurring question when the application of PCS on a broader scale is considered. The most important cost parameters involved are the expenses of the test, the costs (treatment of a patient) that are saved, and the recurrence of the disease(s) in the population. Therefore, a gross indication of cost-effectiveness for WES-based PCS in the Netherlands can already be obtained by comparing carrier frequency and the average patient lifetime costs for the most prevalent disorders. In a hypothetical number of 20,000 couples, ~20 CF carrier couples will be present (carrier frequency 1 in 30,\textsuperscript{10} carrier couple frequency 1 in 900). By identifying them, the birth of 20 unexpected CF patients can potentially be prevented. As lifetime costs for a CF patient are €895,291,\textsuperscript{11} ~€17,905,820 can be saved when only considering this single disorder. For spinal muscular atrophy (SMA) with ~10 carrier couples in this hypothetical population (carrier frequency of ~1 in 45\textsuperscript{12}) and average lifetime costs per patient of €336,726\textsuperscript{13} (calculated from 2009 $), a saving of ~€3,367,260 can be calculated. Accordingly, for Pompe’s disease, with a carrier frequency of 1 in 100\textsuperscript{14} and average costs of €7,032,899 for the classic form when treated with enzyme replacement therapy,\textsuperscript{15} the number is €14,065,798. Smith Lemli Opitz (SLO) and Congenital Disorder of Glycosylation type 1A (CDG1A) are two other relatively frequent autosomal recessive disorders in our population, both with carrier frequencies of ~1 in 70,\textsuperscript{16,17} but unfortunately no data on lifetime costs are available.

However, when considering the lifetime costs per patient ~€500,000 for each disorder (which is probably an underestimation), for these diseases together PCS would save ~€4,000,000. So, in total, only for these five disorders the costs saved would be ~€40,000,000. This means that a PCS test for these disorders combined should not exceed €40,000,000 / 20,000 = €2000 per couple, thus =€1000 per individual. PCS costs include the (whole exome) sequencing and analysis costs, pretest counseling, specific posttest counseling of carrier couples, and the costs for reproductive options (PND or PGD) if a carrier couple opt for these. Exome sequencing can currently be performed for well below €750 per individual and costs are rapidly declining . Only including these 5 most frequent diseases already point to cost-effectiveness of WES-based PCS. Considering that it is estimated that about 1-2 in 100 couples are at risk of having a child affected by any recessive genetic condition,\textsuperscript{18} in addition to the 37 couples from the calculation above, between 163 and 363 other carrier couples are expected to be
present in the total of 20,000 hypothetical couples. Evidently, the cost-effectiveness question is hereby in fact answered already.

The most important question in this context probably is whether WES-based PCS is more cost-effective compared to other PCS approaches. A limited panel may be less expensive but is also less universally applicable in our nowadays mostly multicultural communities. Panels need customization for specific populations, which necessitates investment of time and money as well. Despite the higher costs of WES, the obvious advantage is that carriership for more diseases can be detected, and in a universal way. Does the extra yield outweigh the extra costs? For this question to answer, one must quantify the extra yield. For one of the PCS panels currently available in the Netherlands (Groningen), consisting of ~70 genes causing ~50 serious autosomal recessive disorders, it was reported that the cumulative carrier couple frequency of the diseases included is 1 in 150 for the Dutch population\(^{19}\). When applying this number, in the 20,000 hypothetical couples the panel would identify ~133 carrier couples, and WES would potentially be able to identify 200-400 carrier couples. This difference seems to justify the use of WES. The WES-PCS strategy we developed could serve as a starting point to address this issue in a (cost-)effectiveness study. For this goal it will be necessary to perform WES-based PCS in a larger patient group, and compare the results to (hypothetical) results of targeted PCS based on limited gene panels in the same group. Consanguineous couples and couples opting for PGD could be the first candidates. Depending on these results, expanding PCS to a broader patient group or eventually the general population can be considered.

In the above-mentioned gross calculations, obviously several relevant factors have been left out. For example, whether or not a couple chooses to prevent the birth of an affected child, and the fact that not every carrier couple necessarily gets an affected child. The risk of the latter also depends on the total number of children a couple will have. We furthermore assumed that both the panel and WES would identify all carrier couples (in case of the panel only of the included genes of course), which in fact will not be the case. Also, for certain diseases a separate test will have to be added to the (whole exome) sequencing because otherwise they cannot be detected, and thus the PCS-test will likely be in fact a set of tests. Another factor is the variability of life-time costs of a disease, dependend on the severity in a given patient. However, such variables are in our opinion not expected to undermine the cost-effectiveness of (WES-based) PCS.

Apart from costs, and the willingness of for example health insurance companies to pay these, evidently other important factors determine whether or not PCS will eventually be applied in a population-wide manner. Examples are political opinions, societal acceptance, and awareness among the couples with a child wish. Thus, support needs
to be secured and knowledge spread among different layers of society. This is a task for the Dutch working group PCS, which was founded in 2014 as part of the “Vereniging Klinische Genetica Nederland (VKGN)” and the “Vereniging Klinisch Genetische Laboratoriumdiagnostiek (VKGL)” and contains representatives from all 8 Academic centers in the Netherlands, including me from Maastricht.

Concrete activities carried out to inform patients

Besides informing clinicians about our work it is important to reach patients, since they are the actual ‘target group’. The ‘modern patient’ is active and will approach health care professionals with requests if they are aware of certain opportunities. Therefore, our results and activities have not only been presented at scientific meetings, but were also reported in magazines from patient societies (e.g., magazine “Wisselstof” from “Volwassenen, Kinderen en Stofwisselingsziekten”, magazine “Oog” from “Oogvereniging Nederland”), and as poster and oral presentations at patient meetings (e.g., LHON meeting for couples with a child wish, organized by “Patiëntengroep LOA/LHON”, annual meeting for muscular disorders, organized by “Vereniging Spierziekten Nederland”). Also, there is close contact with for example “Stichting Metakids” and “Prinses Beatrix Spierfonds” which funded parts of our research. They receive reports of our findings and they are informed when the results are published in a scientific journal. Often they prepare, in collaboration with us, a notification/summary to publish on their websites. Furthermore, a press release is intended regarding the PCS paper. This thesis will be propagated as well and we will prepare a press release upon its publication.
References


