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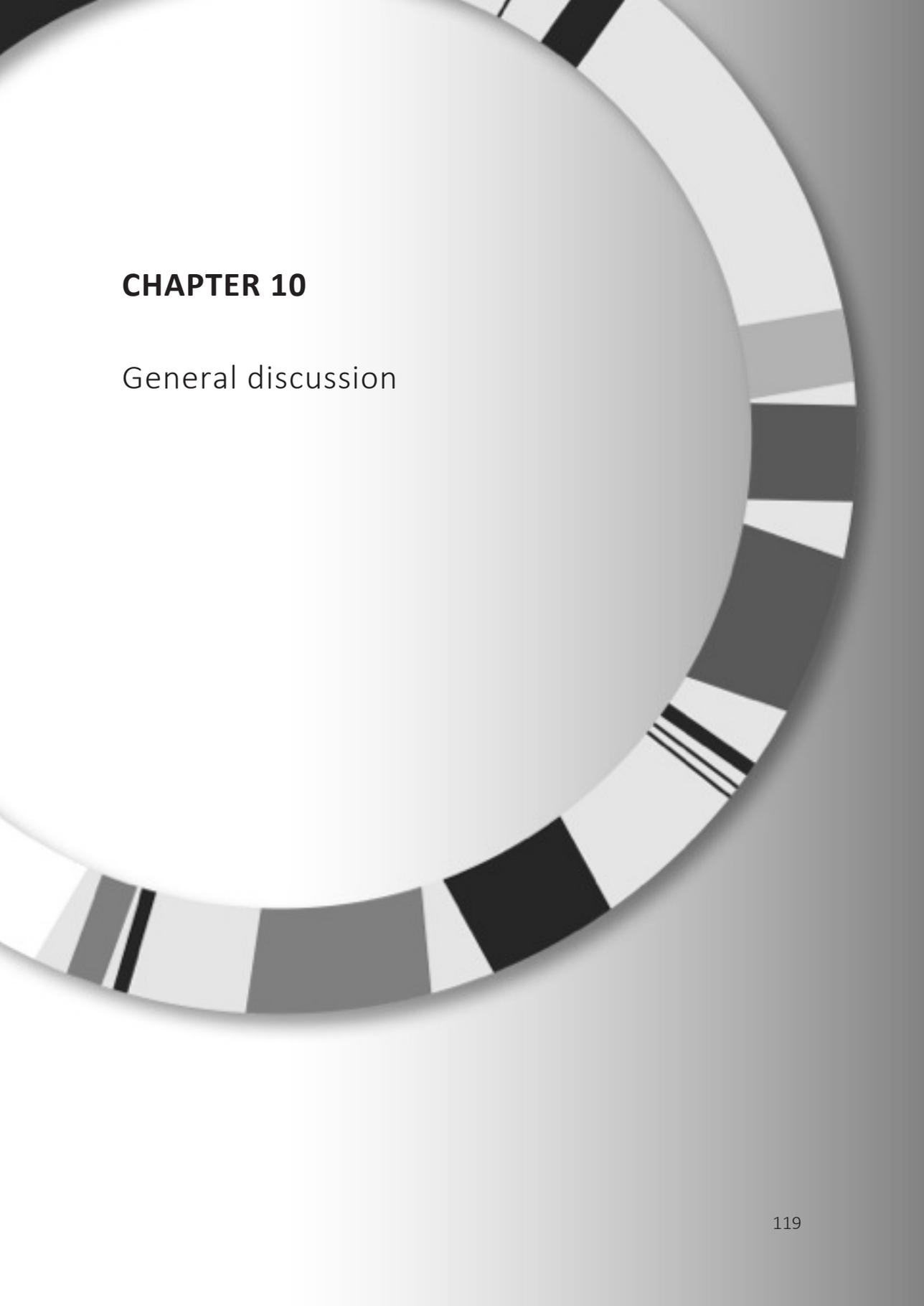
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CHAPTER 10

General discussion

INTRODUCTION

The reproductive risk associated with consanguinity, as well as the setting in which risk information and genetic counselling can be provided, are complex matters. It is often stated that consanguineous couples should be adequately informed about their risk of having an affected child, however, this implicitly involves various aspects: enquiring about marital status, providing reproductive risk information and assessing risk by using genetic tools. In genetic counselling, the risk for an individual consanguineous couple is currently assessed by using their family history and the average population risk. In clinical practice, it is hitherto not possible to make an assessment of the risk for an individual couple, nor does a clear consensus exist how to deal with these couples in health care. Also, the context in which the care for these couples should take place is complex. The influence of cultural and social aspects cannot be discarded, while in many Western countries, the attitude of the general public towards consanguinity is stigmatizing. The main objective of this thesis is to explore how the reproductive risk in consanguineous couples can be addressed in the future. In this thesis, we set out to take three different approaches, namely to study the clinical genetic and population genetic perspective, the perspective of the target population and the perspective of the (primary) health care provider. The latter two focused on the situation in the Netherlands.

MAIN FINDINGS

Clinical genetic and population genetic perspective

The first approach aimed at improving risk assessment for consanguineous couples by testing the clinical validity of a new test, i.e. looking at the amount of sharing of DNA identical-by-descent (IBD). Seventy-three case couples and 78 control couples were included from 10 different countries. After estimating the kinship coefficient for all couples by using three different methods, it was not found that a higher degree of genetic relatedness was associated with a higher likelihood for consanguineous parents to have an affected child (Chapter 3). The hypothesis that consanguineous parents with a child affected by an autosomal recessive disorder – and without a family history of an autosomal recessive (AR) disorder - have more DNA IBD than similarly related consanguineous parents with only healthy children was thus not confirmed by our results. A future project with ‘perfect’ selection of cases and controls and greater numbers, might give the study more power. However, even if a difference in DNA IBD between cases and controls would be found, then the effect size will be very limited as our point estimate was close to no effect. Given the promising recent advances in

sequencing technology (Chapter 4), it does not seem opportune to pursue the strategy of measuring the proportion of DNA IBD.

While collecting couples for the case control study, a relatively large proportion of compound heterozygotes was found among the patients. This led to the method of using mutational data to calculate the total frequency of pathogenic alleles. Further development of this methodology has resulted in a maximum likelihood method (MLM) that is able to estimate pathogenic allele frequency based on mutational data (Chapter 6). This had also led to a practical application of the method for familial Mediterranean fever (FMF). The MLM approach was used to calculate the pathogenic allele frequency for Tunisia and Morocco (Chapter 7).

Perspective of the target population

It was clear from the start that the development of a new genomic tool could not stand on its own. The second approach aimed to gain more insight into the attitudes of the target population towards consanguinity and their understanding of risk, as well as their attitudes regarding information about the reproductive risk. The attitudes of the population who will be targeted with information and/or a preconception test were found to be rather heterogeneous: Dutch Moroccan respondents had more favourable attitudes towards consanguinity than Dutch Turkish respondents and people in a consanguineous relationship were more positive than people with an unrelated partner. Overall, respondents were neither positive nor negative regarding seeking and providing information about reproductive risks. Most were in favour of the availability of information on reproductive risks associated with consanguinity, and in particular of providing information early, preferably even before marriage has taken place. These results can help in the design of implementing a new genetic risk tool, and have also led to the recommendation to shift the focus from targeting the reproductive risk information to couples already in a relationship, partly to providing more general information in an earlier stage, before their partner is chosen.

Perspective of the (primary) health care provider

The involvement of primary care in issues concerning the preconception phase is very important. Therefore, the third approach was to investigate the attitudes and beliefs of primary care professionals regarding their care for consanguineous couples. The interview study conducted among general practitioners and midwives has shown that they consider the providing of preconception risk information their task, however, several barriers are encountered, like professionals' beliefs about the religious and social values of their clients, the perceived limited options for referral and limited time for a consultation. These barriers seem to conflict with the professional norm to

address the topic of consanguinity. Feelings of embarrassment regarding addressing consanguinity did not seem to play a significant role (Chapter 9).

REFLECTION ON THE MAIN FINDINGS

The clinical genetic and population genetic perspective

Identifying consanguineous couples at high risk by using the amount of DNA IBD

In theory, the increase in risk of AR disorder in offspring of consanguineous partners is due to them having more DNA IBD than unrelated spouses. Moreover, the closer related the partners, the higher the risk. The average risk increase of 1.7-2.8% in first cousins is a general figure, and therefore not the actual risk in individual consanguineous couples, where it is either zero or much higher (Modell and Darr, 2002). Moreover, the average relatively small increase in risk has been forwarded as a reason not to provide genetic carrier testing for *all* consanguineous couples (Waelput and Achterberg, 2007). Since a percentage of 6.1-9.4% of first cousin couples are in fact at high risk for every pregnancy of 25% or higher (in case of carriership of more than one AR disorder), the identification of these couples preconceptionally seems justified. Therefore, a case-control study was set up to study the amount of DNA IBD (Chapter 2). This turned out not to discriminate between cases and controls and thus not to be clinically useful. The amount of DNA IBD was not associated with a higher risk of having affected children.

In some cases the genetic relationship, as measured by the three different estimators of relatedness used in our study (PLINK, King and IBDelphi), differed greatly from what was reported by the parents, possibly more than can be explained by stochastic variation or hidden consanguinity. Not counting the influence of possible errors resulting from sample swaps, several factors can explain the discrepancy between genomic relatedness and relatedness based on the reported pedigree. In population studies it was found that allegedly unrelated individuals showed significant relatedness when estimated by a genomic study (Stevens et al., 2012). Moreover, runs of homozygosity are often much larger than expected, even in outbred populations (Gibson et al., 2006). By solely focusing on the pedigree, which may not contain accurate information on relationships, combined with a family history that is often not known or inconclusive, the actual risk cannot be assessed adequately. Stochastic variation, hidden consanguineous loops and significant unannotated relatedness can greatly influence the actual amount of DNA IBD, and justifies the consideration to study the combination of the two genomes of the parents in order to assess their risk, as was done in the study focused on exome sequencing of consanguineous parents (Chapter 4).

Recruitment in case/control study

We experienced great difficulties in our attempt to include participants for our case/control study, especially in the Netherlands. The recruitment process of people from minority population often presents a great challenge (Mohammadi et al., 2008; Ibrahim and Sidani, 2013) and takes much time and effort. Moreover, recruitment of people for genetic research as well as for research that entails a subject that is considered more or less taboo in a society, is yet another challenge (James et al., 2008; Emami and Mazaheri, 2007). Although we could have anticipated this, the actual recruitment has turned out even more challenging than expected. Although we did not study the reasons of consanguineous couples for not wanting to participate, several factors stood out for us. Not counting all willing and helpful professionals and organisations, many health care professionals were reluctant to cooperate, mainly because they feared a negative response from their clients. Many of the invited couples refrained from participating and spontaneously reported that they did not have time as the care for their affected child(ren) was so time-consuming. Although this information was not systematically obtained, it can be helpful in future research. With help from collaborators in countries where consanguinity is more prevalent and from organisations focused on the emancipation of people from ethnic minorities in the Netherlands, we were finally able to achieve an appropriate sample size for this study, although somewhat lower numbers were included than initially aimed for. The point estimate (close to no effect, therefore no clinical utility) makes the inclusion of more couples redundant.

Next generation sequencing will lead to more accurate risk assessment

Over the last years, next generation sequencing (NGS), including whole genome and exome sequencing approaches have been developed and are now being widely used in research and clinical practice. The proof-of-principle study that is described in Chapter 7 involved exome sequencing in four consanguineous couples with an affected child due to an autosomal recessive disorder that was diagnosed at the molecular level. This method focused on over 500 genes and on known pathogenic mutations, similar in both partners. This approach is a first step to lower the *a posteriori* risk for consanguineous couples of having affected children, but there are still many challenges when applied in clinical practice. First of all, by focusing on known and previously reported mutations, unknown but possibly pathogenic variants are discarded. These will undoubtedly be present in consanguineous partners who belong to the same family and thus have a chance of carrying the same unique variant that has not been described before (Alkuraya, 2013; Ormond et al., 2010). Other challenges are similar to those in the preconceptional use of NGS in any future parent couple. In the changing landscape of genetic testing, carrier screening panels containing hundreds of genes possibly causing AR disorders are increasingly available to the general population, mostly offered by commercial companies (Levenson, 2010; Wienke et al., 2014). Issues concerning

decreased penetrance and variable expression leading to unclear clinical significance of discovered mutations and unsolicited findings apply to any couple undergoing preconceptional testing for carrier status of AR disorders (Bell et al., 2011; Wienke et al., 2014). Moreover, when restricting testing to similar mutations in both partners, a possible carrier status of only one of the parents cannot be reported, which might also have important consequences for other family members. Above all, the genetic counsellor who is in charge of informing the couple during pre- and post-test counselling that should be equipped for the task to counsel the parents regarding these uncertainties that the future parents have to consider.

Homozygotes and compound heterozygotes among affected children of consanguineous marriages

Not all children of consanguineous couples with an autosomal recessive disease are affected because of the consanguinity of the parents. This follows logically from the fact that the total risk for consanguineous couples consists of two parts: the affected IBD (calculated by Fq , the proportion of affected children resulting from the consanguinity of the parents) and the affected non-IBD (in a proportion of $(1-F)q^2$, where the consanguinity of the parents played no role). When an affected child is born to consanguineous parents, consanguinity is nevertheless often seen by both physicians and lay people as the causing factor, possibly leading to a feeling of guilt in the parents (Ten Kate et al., 1991). The more frequent the disease, the greater the proportion of children affected not-IBD, leading to a situation where consanguinity does not contribute substantially to the risk for example in a population with a high frequency of thalassaemia (Bittles, 2012).

Inferring total pathogenic allele frequency, even in case of partly uninformative data

Information on the consanguinity of parents and on mutation data of patients affected by an AR disorder in a population can be helpful for inferring the total frequency of pathogenic mutations in the implicated gene (q). We have shown that even in case of partly inconclusive data this can lead to a reasonable estimate of total pathogenic allele frequency. Whereas the earlier sketched scenario in which a whole genome sequencing approach is used for identifying carrier couples preconceptionally, this is – despite anticipated falling costs - still a rather costly scenario with several practical barriers to overcome (Kingsmore et al., 2012). Using mutational data of patients can, without much effort, give an insight into the total pathogenic allele frequencies of AR disorders, especially in populations with frequent consanguineous marriages. The method benefits greatly from an accurate estimate of the inbreeding coefficient. The case control study already showed that the real genetic relationship can be very different from the presumed genealogical relationship (Chapter 3). Therefore, if estimates are based on reported genealogical data, the accuracy of the estimation of q is also affected.

The perspective of the target population in the Netherlands

Awareness of risk

The survey among the population in which consanguinity is a common tradition tried to obtain some insight in the understanding and awareness of the risk involved in consanguinity (Chapter 8). Our target population was Dutch inhabitants of Turkish and Moroccan ancestry. The majority of participants were aware of the association of consanguinity with risk for offspring. Similar results were found in other studies in other countries that showed that people have heard of the link between consanguinity and risk for offspring (Shaw and Hurst, 2008; Darr et al., 2013). By recruiting participants through a snowball method and through forum sites focused on Dutch Moroccans and Turks, we have not taken into account other migrant groups and consanguineous couples of Dutch descent who might have a different perception of the matter. By restricting ourselves to a survey and not interviewing participants face-to-face, we were not able to obtain full understanding of how this risk was perceived. At the same time that our survey was conducted, qualitative research was done by the department of Anthropology at the VU University (Storms and Bartels, 2015). Focus groups as well as in-depth interviews with people from the target population were performed to study attitudes towards consanguinity, preconceptional genetic testing and reproductive options. This research showed that the respondents primarily value consanguineous marriage in the context of its social advantages as well as its social risk, more than a possible medical risk. Participants were familiar with the debate about the risks of having affected children, but many respondents considered the risk not applicable to them personally and had little understanding of the concept of heredity. Also, various respondents perceived the care for a child with a congenital disorder as a special task from a religious perspective and regarded it as a dedication. Taking responsibility for that care was seen as an important virtue in their perspective (Storms and Bartels, 2015).

Attitudes towards preconception risk information and testing

Most respondents to our own survey were rather positive towards the offer of preconception risk information focused on consanguineous couples, however, most favored the option that it should be given as early as possible, preferably premaritally. The fact that people already in a consanguineous relationship estimated the risk lower and valued preconception risk information less than those not in a consanguineous relationship, confirms that attention should be focused on the timing of providing information. The simultaneous qualitative focus group and interview study among Dutch Moroccan and Turkish women, showed similar results: the offer of preconception testing was valued positively by almost all participants, because they felt information on the topic is useful and can help to prepare themselves for a child with a disorder (Storms and Bartels, 2015). This is consistent with findings in the UK, where a study

showed that British Pakistanis were uniformly positive towards prenatal testing for serious health conditions, whereas they had on average less positive attitudes towards termination of pregnancy (Ahmed et al., 2006) and also with a Dutch study among Turkish Dutch women who were mostly favorable towards preconception carrier screening for hemoglobinopathies (van Elderen et al., 2010). Also, in our study, participants stated that testing before marriage might be a good option because, once married, they felt it is not possible, for example, to refrain from having children. Theologians, Muslim spiritual counsellors, and imams were also interviewed for a study among Islamic scholars in the Netherlands about the way they look upon preconception care and testing for consanguineous couples (Bartels and Loukili, 2012). They almost all considered preconception testing a positive development from an Islamic point of view for which they gave several arguments. Among those arguments were that Islam encourages people to pursue a good health status (both for themselves and their children), scientific information coming from physicians deserves respect, and expansion of knowledge must be pursued. The scholars did foresee ethical problems with regard to the reproductive options that are offered for couples who are found to have a high risk. Some of these reproductive options are controversial from an Islamic perspective, however, not always prohibited (Bartels and Loukili, 2012; Serour, 2008). A Dutch interview study among 10 Dutch Moroccan women nevertheless, found that religion was very important in reproductive decision-making and termination of pregnancy in case of an affected child was not an option for them because of religious beliefs (Gitsels-van der Wal et al., 2014a).

In this study we have taken several steps to investigate the attitudes towards consanguinity and risk information among the target population. It is important to keep in mind that subsequent steps from risk awareness to preconception testing and then to choosing a reproductive option, is not self-evident for all consanguineous couples. Although both the target population and Dutch Islamic scholars respond positively towards preconception testing, they view this technological possibility primarily as a means to increase knowledge about the risk for a child with a hereditary disease, but they foresee problems when it comes to the consequences of a 'positive' test. The couple will be confronted with choices that are difficult for any couple, but even more complicated in the light of religious beliefs. A factor complicating discussion of these issues in the Netherlands is that the Turks and Moroccans comprise minorities following different Islamic schools of law with different interpretations on such issues as preconception testing and the reproductive options associated with new reproductive technologies (Personal information, G. Loukili). The above mentioned Dutch study also stated that the participants had strong beliefs that termination of pregnancy is not allowed by Islam, whereas Islamic jurisprudence is available that allows termination of pregnancy in case of serious disabilities in the child, as long as this is done before 120 days of pregnancy (Gitsels-van der Wal et al., 2014a; Daar and al Khitamy, 2001). It

should also be recognised, however, that ethnicity is not a proxy for religious belief, and that people of a particular religious identity may make health-related decisions with reference to non-religious considerations (Ahmed et al., 2006; Atkin et al., 2008; Hewison et al., 2007).

The perspective of the (primary) health care provider in the Netherlands

The Health Council of the Netherlands advised the minister of Health, Well-being and Sports to implement a preconception care program. Preconception care is defined as “the entire range of measures to promote the health of the mother-to-be and her child” (Health Council of the Netherlands, 2007) and could very well serve as the context in which attention is given to the reproductive risk involved in consanguinity. Attention in the report was given to genetic factors that influence the health of the mother and child and apart from other issues a systematic examination of family history, ethnicity and parental consanguinity was recommended in the preconception phase. In spite of this advice, preconception care has not been embedded yet in regular health care nor has the initiative of consultations for people with a desire to have children taken off, although attempts are certainly made by professionals in the field (Van der Zee et al., 2011).

Primary care and consanguinity

Given the absent success of the implementation of preconception consultations for couples so far, it was not surprising that our study among primary care professionals showed that the subject of consanguinity was hardly touched upon in the preconception phase: in the case of midwives especially, simply because they do not see these women in their practice in the preconception phase. Most of the participating primary care professionals raised the subject during the consultations with their clients during the prenatal phase. Notwithstanding the sensitivity of the subject and despite findings in an Australian study (Bishop et al., 2008) primary health care providers in our study did not experience difficulty. It was evident, however, that there were barriers present that prevented them from extensively addressing the subject with their clients. A Dutch quantitative survey among 98 midwives studied the midwives’ belief to what extent they should take their clients’ religious background into account. The majority said to pay attention when counselling their clients about prenatal screening. However, most midwives had only limited knowledge about Islamic beliefs on prenatal screening for congenital anomalies.

It is conceivable that deficiencies in genetic knowledge can be overcome by offering training to professionals, and by implementing new tools in general care supported by a consensus of professionals in genetics. Primary care professionals have already expressed the wish for more knowledge and tools in case of consanguinity, Islamic beliefs on reproductive options and similar sensitive subjects (Houwink et al., 2011;

Gitsels-van der Wal et al., 2014b). Finally, our study was done by a qualitative approach, possibly with participants giving socially acceptable answers. The results should still be confirmed by a quantitative approach. This can also involve investigating the best method to offer training and tools regarding this subject in primary care.

Consanguinity and clinical genetic centres

Although the organisation of care for consanguineous couples in clinical genetic centres was not the focus of any of our studies, while searching for couples for the case-control study it became evident that there is no uniform approach towards consanguineous couples referred for or looking for preconception advice. Some geneticists follow the recommendation that no additional genetic testing should be offered in case of a negative family history (Bennett et al., 2002), others argue that the greater risk for consanguineous couples of being both carriers of a frequent disorder in the population is more than enough reason to offer carrier screening for disorder like hemoglobinopathies and cystic fibrosis. The fact that primary care professionals in our interview study expressed doubts and confusion about risk and referrals, and appeared interested in practical tools, could be seen as a message to clinical genetic centres that it is time to reach consensus.

PRACTICAL IMPLICATIONS²

This thesis has addressed not only the increased reproductive risk in case of consanguinity, but also explored the context in which the care for consanguineous couples is taking place. Despite the fact that the problem of consanguinity and risk is acknowledged and reports advice towards taking action, it seems that this challenge is not being met. It is urgent that the issues surrounding consanguinity and risk are faced with a uniform approach. This could be done by professional parties, for example primary care professionals or clinical geneticists, or even patient organizations. These parties have not yet shown collective interest in the subject, although individual initiatives are taken. For example the information brochure that was developed by Erfocentrum focused on providing accessible information on consanguinity and reproductive risk (www.erfelijkheid.nl/familiehuwelijken). The group of consanguineous couples entails mostly people from groups with a lower social economic status, and they form a heterogeneous group of people with a large variety of (possible) diseases. This makes the organization more challenging. A possibility may lie in the formation of a task group whose aim is to empower consanguineous couples. To unite all professionals, patients and parents with an interest in the subject and work on it

² Partly based on Teeuw ME, Borry P, Ten Kate LP. 2015. Preconception care for consanguineous couples in the Netherlands. In: Cousin marriages: Between tradition, genetic risk and cultural change. Edited by A. Shaw and A. Raz. Berghahn Books: Oxford and New York.

collectively may form a solution to the lack of action taken so far. The aim of the task group would in the first place be to provide information to both professionals and consanguineous couples and to other interested lay people. This could be done by the use of social media and, for example, small size meetings organized in cooperation with self organisations. Another goal could be to invest in the development of training and tools for professionals in primary care practice.

In the era of whole genome sequencing technology it is only a matter of time that a valid and useful 'risk tool' will become available for consanguineous couples which will allow genetic preconception counselling to be more focused, the couples to be better informed about their risk status and give them the time and possibility to make more informed decisions.

Possibilities to embed information about consanguinity in school education should be investigated. In the first place since the target population has expressed the wish to provide this type of information as early as possible, but secondly as a means to debunk the Western belief that consanguinity equals affected children.

In health care attention should be given to the fact that communication about this tool must be suitable for the target population. The experience from our studies confirm what was argued before, that a good opportunity and starting point is to first invest in a relationship of trust between health care provider and client. One way is to work in close liaison with the migrant organizations representing the target group and to disseminate information through them, and another is to engage the general practitioner in trying to identify these couples and referring them if desired.

An alternative family- and community-centred approach has also been suggested as a means to reach effective communication in close-knit societies (Darr et al., 2013; Modell and Darr, 2002). Communities with a tradition of consanguineous marriages and arranged and semi-arranged marriages, can offer a resource for sharing knowledge on genetic risk and mutual support and thus provide the conditions needed to approach future consanguineous parents (Darr et al., 2013). A pilot project "Family, Health and Genetics" was undertaken recently in the Netherlands with the aim of training community health workers to discuss cousin marriage and genetic risk with migrant women in the Netherlands. This community-oriented approach showed that local organizations in collaboration with experts from the field of genetics, were able to train community health workers, who all had a migrant background. However, health care professionals, genetic experts and community health workers had different views on how the information should best be offered to the migrant women (Ridder, 2014).

An important aspect to keep in mind is the fact that for the sake of simplicity, we often refer to Dutch Turks and Moroccans as 'the target population'. Reality, however, is much more complex. In addition to other groups from countries with a tradition of consanguinity, like Egypt, Iraq, Iran, Afghanistan, etc., there is also a small group of

native Dutch consanguineous couples, or couples with a high proportion of DNA IBD. Some belonging to small communities where people marry traditionally in the community and therefore have a high proportion of DNA IBD, more than their family relationship would suggest, others just because they happened to fall in love with a cousin. When offering a risk tool for consanguineous couples, it has to be self-evident that this involves *all* consanguineous couples who are interested. Also, it has to be clear for Dutch Turks and Moroccans that it is not meant to be directed at just them, with the risk of stigmatization.

Moreover, the offer of an improved risk tool for consanguineous couples might provide challenges to some core values that are prominent in genetic counselling (Biesecker, 1998; Mahowald et al., 1998). Firstly, in the tradition of clinical genetic counselling, respect for the autonomy of the person has been developed as a main principle. An individual has a fundamental right to freedom of choice, including control over his or her own life. This includes the right not to know and non-directive counselling. The notion of the 'right not to know' is increasingly accepted internationally. Article 5 of the Unesco Declaration on the Human Genome and Human Rights (Unesco, 1997) states that each individual has the right 'to decide whether or not to be informed of the results of genetic examination' and that the resulting consequences of this decision should be respected. This has also been recognized in the European Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine which states that 'Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed.' The counselling sessions should be oriented to empower individuals and families to make their own decisions: it should guide and help people to work more conclusively towards their own reproductive decisions (Biesecker, 1998). However, the discussion of the respect for autonomy of a patient in the context of a clinical encounter between a patient and a doctor may differ greatly from a discussion in the context of a public health programme where a preconception test would be offered to all couples or to all consanguineous couples wishing to become pregnant. In this latter case, special care should be taken to avoid applying societal pressure to perform a test and to preserve the voluntary character of testing. Currently, at the request of the Minister of Health, research is being done on ways to organize preconception and perinatal care, especially focusing on high-risk groups. It remains to be seen, however, how this will apply to consanguineous marriages and preconception genetic testing.

Secondly, the implementation of any consanguinity risk tool will inevitably be confronted with questions regarding the underlying values and norms that motivate the implementation of these technologies. It raises issues regarding the medicalization of normal life processes such as marriage and family planning. Similar to the first outlined

ethical issue regarding the respect for autonomy, much depends also in this discussion on the way the tool is presented and used in practice. Studies and recommendations that focus on the systematic offer of preconception genetic testing (Lakeman et al., 2008; De Wert et al., 2012; Human Genetics Commission, 2011) can be helpful to identify pitfalls and organize safeguard measures when implementing the consanguinity risk tool in practice.

Thirdly, the test offer will have to be acceptable to the target population and not have negative consequences for them. The target population of consanguineous couples is already vulnerable because its traditional marriage practice is controversial in the Netherlands, and because of their ethnicity and religion, therefore a risk of additional stigmatization exists (Fost, 1992; Markel, 1992). If one considers – because of possible stigmatization – adopting a less active strategy by only offering the test to people who find their own way to primary care and genetic centers with their request for counselling and testing, other rights are at stake. How is it possible to guarantee equity of access to such a resource when those who might most benefit from it do not know about the risk or the possible testing options? Because this is all taking place in a society with a political and public climate that is prejudiced against these types of marriages, the great challenge here is to balance these different rights and to aim for – first of all – an autonomous and informed decision of the couple to go or not go for genetic counselling. Moreover, after undergoing a test, a positive or negative test result should enable the couple to make an autonomous and informed decision for any of their reproductive options in a safe and non-directive atmosphere.

FURTHER RESEARCH

The approach where the potential of exome sequencing in prospective consanguineous parents was investigated, seems promising. Here, the analysis was restricted to identical, previously described or evidently pathogenic mutations in a limited number of genes known to cause severe recessive childhood disorders. Further research should focus on monitoring the outcomes of the prospective counselling of consanguineous couples. Attention should be given to several important aspects, like weighing pros and cons of adding genes to the list, the possibility of offering various options (e.g. a gene list containing ‘less severe’ disorders), and if adjusting the filter in accordance with the ethnic background of the couple is needed. Important lessons will come from evaluating psychological outcomes of the counselling of couples.

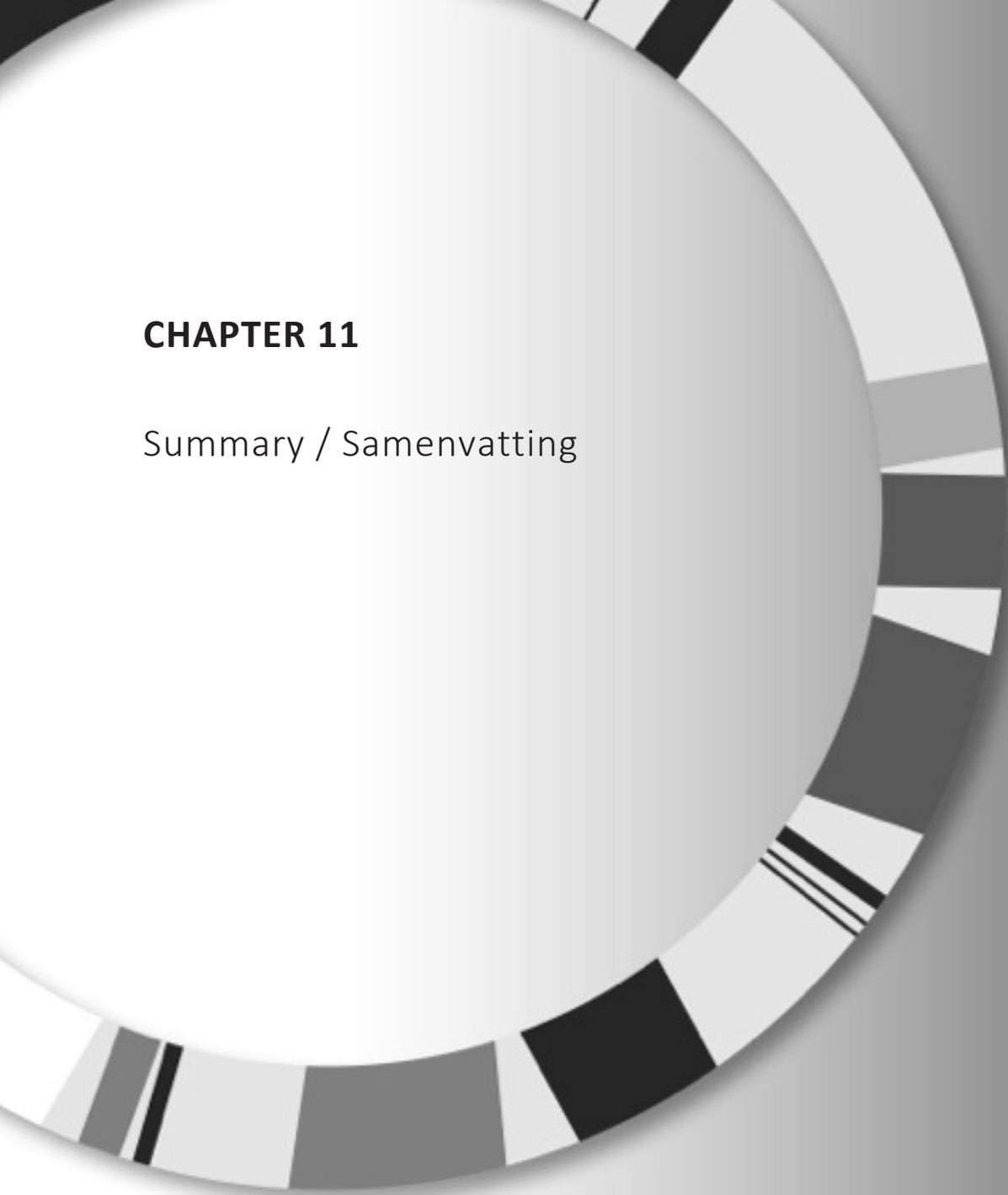
Study projects that focus on determining allele frequencies for AR disorder in population with a relatively high prevalence of consanguineous couples can make use of

the Maximum Likelihood method by collecting mutational data of patients, as well as their inbreeding coefficients.

In collaboration with migrant-organisations and other key persons belonging to the target population, research should be continued to work towards an offer of (preconception) genetic counselling and risk assessment for consanguinity that is sensitive towards the couples involved. Different approaches to reach couples should be investigated, like through primary care or through a community-oriented approach. Initiatives like the 'Family, Health & Genetics' programme should get a sequel to further investigate this joint effort of both health care professionals and people from the target population that can contribute to better informed decision-making of women from ethnic minorities.

Given the findings that people want to be informed as early as possible, collaboration can be sought with academic parties who work on school education concerning genetic subjects in order to investigate the possibility to integrate this subject into the school curriculum. Also, attention should be given to the possibility of reimbursement of the costs for genetic testing by health care insurance authority in the case of 'premarital' testing. Consanguineous couples who participate in a prospective exome sequencing study should also be asked to participate in a study that looks into the desirability and most appropriate design of this offer. In the further future, surveys investigating the attitudes towards consanguinity and risk can show whether these are changing when a genetic test is publicly available that addresses and possibly minimizes the risk. Another possible approach is the embedding of prospective sequencing of consanguineous couples within a broader context, such as targeted prospective carrier testing of future parents. Academic parties that study the offer of preconception care could make good collaborators regarding the embedding of consanguinity and risk in more general, possibly less stigmatizing, preconception information and care. Again, research into the attitudes of the couples involved, as well as the population, will have to show which approach is preferred.

The findings from our interview study among general practitioners and midwives can be generalized by applying a large quantitative approach involving more professionals in various areas in the Netherlands. Additionally, primary care professionals' perception can be investigated of the most feasible way to organize training on the subject. This could be embedded in the form of live training, or as online training modules which can be applied easily in practice. Clinical geneticists should be involved in the development of training for primary care, in order to reach alignment in the actions of all professionals involved.



CHAPTER 11

Summary / Samenvatting

