summary

Preconceptional carrier screening for cystic fibrosis and hemoglobinopathies. An ancestry-based offer in a multi-ethnic society.

Cystic fibrosis (CF) and hemoglobinopathies (HbPs), such as sickle cell disease and α- and β-thalassemia, are relatively common severe autosomal recessive disorders for which carrier screening tests have been developed. When both partners in a couple are heterozygous carriers, they face a 1-in-4 risk in each pregnancy of having an affected child. Without testing carriers are usually unaware of their carrier status and will only be informed about it after having an affected child. Preconceptional carrier screening enables future parents to make informed reproductive decisions before pregnancy at a time when all reproductive options are still open and there is no time-constraint. Compared to prenatal screening, the reproductive options include not only prenatal diagnosis followed (or not) by pregnancy termination in the case of an affected child, but also accepting the risk, deciding not to have (more) children, adoption, using donor sperm or eggs, or pre-implantation genetic diagnosis. In some culture related marriage practices it could possibly result in adapting the choice of a partner. In the Netherlands, as in many other European countries, preconceptional carrier couple screening for CF and HbPs is not current practice.

CF and HbPs have different prevalences among various groups, according to the ancestral origin. CF is the most common among Europeans and their descendants, with a carrier frequency of 1 in 20-30 individuals, resulting in 1 in 400-900 carrier couples and a CF birth prevalence of 1 in 1600-3600 births. A high prevalence of CF is also found in people with ancestors from North Africa, Turkey and the Middle East. HbPs are mainly found in people who have their origin or ancestry in (sub-)tropical regions where malaria is or was endemic (e.g. Africa, the Mediterranean area, the Middle East, parts of the Indian sub-continent, and South-East Asia), where carrier frequencies range from 5% to 40%. Therefore, the present multi-ethnicity in most (European) countries, including the Netherlands, results in sub-populations with markedly different CF and HbPs carrier frequencies. Therefore, carrier screening for both disorders in all prospective couples might not only be too expensive, but also unnecessary. One solution might be to offer all couples carrier screening, but in such a way that only couples who are at risk of having a CF-affected child, based on both partners' ancestry, will have the CF carrier testing, and only couples who are at risk of having an HbP-affected child will have the HbP carrier testing. However, offering preconceptional carrier

screening by selecting people beforehand on the basis of their ancestry may lead to stigmatisation and discrimination. An offer of *combined* preconceptional ancestry-based CF and HbPs carrier couple screening, though, may reduce this potential risk of stigmatisation or discrimination of sub-populations, because almost every couple, irrespective of ancestry, will be eligible for some form of carrier screening: for CF, HbPs or both disorders.

The main objective of this thesis was to evaluate the feasibility and desirability of preconceptional ancestry-based CF and HbPs carrier couple screening. Besides the evaluation of a screening study in which an offer of combined targeted ancestry-based preconceptional CF and HbPs carrier couple screening was actually made in a multi-ethnic population (Part I, Chapters 2, 3, 4 and 5), attention was given to other relevant aspects concerning the decision as to whether or not to implement this kind of screening (Part II). Ethical aspects of preconceptional carrier screening in general have been studied (Chapter 6), as well as sociotechnical aspects of the process of potential implementation of an ancestry-based CF and HbPs screening programme (Chapter 7). Finally, the test-sensitivity of the common commercially available *CFTR* mutation panels among Turkish and North African immigrants in Europe was studied (Chapter 8). At the time of the study there was no established general preconceptional health care setting either in which this kind of screening could easily be implemented.

The screening study

The feasibility and desirability of preconceptional ancestry-based CF and HbPs carrier couple screening was evaluated by a screening study which was carried out in 2005. In this study preconceptional ancestry-based CF and HbPs carrier couple screening was offered to 9453 individuals, including 50-60% non-Western immigrants, in Amsterdam, the capital of the Netherlands. Before the start of the study a decisional instrument was developed which could serve as a pre-screening tool to assess a couple's eligibility for the CF and/or HbPs carrier test(s), based on the ancestral origin of both partners. The instrument was found to have good validity (Chapter 2) and was used during the screening study to assess a couple's eligibility for the CF and/or HbPs carrier test(s).

During the screening study two different approaches of invitation were addressed: invitations were sent by either the general practitioner (GP) or by the Municipal Health Service (MHS). Invitees who had a partner with whom they were planning a pregnancy were defined as the target population. Those who were interested in participation in the carrier testing had to make an

appointment together with their partner for a pre-test consultation with their GP within one month. Test-participation was free of charge. Participation in the carrier testing was conditional on survey-participation. Data were gathered with four structured questionnaires, one of which was based on the Theory of Planned Behaviour. Participants in the testing were asked to complete questionnaires before and after pre-test consultation, and one week and three months after receiving the test-results. Invitees who belonged to the target population but who refrained from test-participation were asked to participate in the survey only, for which they were asked to complete only the first questionnaire. The size of the target group and response to the offer of CF and/or HbPs carrier screening were estimated based on a reply form and on a telephone survey among a sample of non-responders.

Of the 9453 individuals who received an invitation, 1365 responded by returning the reply form. Off all invitees, approximately 33% had a partner with whom they were planning a pregnancy. Of these, 3% participated together with their partner in the carrier testing (n=143). Non-Western invitees were under-represented (n=46). Invitations sent by the GPs compared to the MHS led to a higher uptake (Chapter 3).

Questionnaires were completed by 418 participants in the survey. Among these 418 survey-participants, 247 refrained from testing (offer-decliners) and 171 invitees intended to participate in the testing (offer-acceptors), but eventually 143 actually did. The large majority of survey-participants had a generally positive attitude towards participating in the screening: 98% of the invitees who accepted, and 83% the invitees who declined the current offer of preconceptional carrier screening. Of those who rejected the current offer of carrier screening, 68% intended to participate in testing in the future if the screening would be offered routinely. Their intention not to participate was mainly influenced by the fact that they perceived practical barriers in terms of the time (43%) and effort (38%) needed for participation. This applied to Western and non-Western study participants alike. Others, who declined the current offer of carrier screening stated that the results would not change their reproductive decisions. Moreover, among the test-participants no major adverse psychological outcomes were reported, and there were no major feelings of stigmatisation or discrimination. However, among a minority (14%) who thought that carriers might be discriminated, there were significantly more participants of non-Western than of Western origin (Chapter 4).

In general, those who participated in the carrier testing were satisfied, and none of them regretted participation. In total, three CF carriers and seven HbP carriers were identified, but no carrier couples. Three months after

receiving the test-results none of the carriers perceived themselves as being less healthy, six carriers felt relieved, and one carrier felt disappointed and worried. Four non-Western carriers were unaware of the residual risk of having an affected child. Five carriers shared their results with relatives (Chapter 5).

In general, the test-participants reported that they would draw reproductive consequences from the test-results if they had been identified as a carrier couple: 27% would consider not having (more) children, and, in case of a pregnancy, 89% would opt for prenatal diagnosis. Knowledge on autosomal recessive inheritance improved after the pre-test consultation but had decreased again to the pre-consultation level when assessed at the three-month follow-up. Of the participants, the majority (94%) were able to recall their test-results three months after receiving these results. Western compared to non-Western participants reported less anxiety, had higher knowledge scores, and were more often aware of the residual risk of having an affected child (Chapter 5).

Ethical aspects of preconceptional CF and HbPs carrier screening

In many European countries there has been discussion about whether or not preconceptional carrier screening for autosomal recessive disorders should be introduced, and if so, how. Social pressure threatening freedom of choice and medicalisation of the preconceptional period have been mentioned as unwanted potential consequences. During a workshop in Utrecht, the Netherlands in October 2003, the ethical tension between offering carrier couples the opportunity to make a free and informed reproductive choice and protecting individuals from unwanted side-effects, was investigated. Based on the debates of four experts who focused on the pros and cons of the two main ethical issues: 'freedom of choice' and 'medicalisation', it was concluded that a possible threat to freedom of choice and medicalisation of the preconceptional period can not be considered as convincing moral arguments against preconceptional carrier screening (Chapter 6). Absolute freedom of choice does not exist; choices are made in an environment that is co-determined by the choices of others. If preconceptional carrier screening is not available, then there is no freedom of choice at all. Nevertheless, a neutral wording of the offer and the information provided (neutrality of aim) is crucially important. Concerns underlying the objection to "medicalisation" can be addressed, firstly by ensuring that the test is made available in a way that takes informed decision making seriously, and secondly by continuous efforts to improve adequate societal provisions and care for the handicapped and their families. The discussion about autonomy and medicalisation should be redirected to address the way in which preconceptional carrier screening is made available (Chapter 6).

Sociotechnical aspects of preconceptional CF and HbPs carrier screening

To obtain more insight into the process of potential implementation of a programme for preconceptional CF and HbP carrier couple screening, a sociotechnical analysis was performed, based on a model of co-evolution between technology and society (Chapter 7). Furthermore, for comparison, the implementation processes of two already existing health care programmes with similar aspects to the screening programme at issue were studied (i.e. the program about the protective effect of folic acid in the prevention of foetal neural tube defects, and the cascade screening for familial hypercholesterolemia).

The fact that in the Netherlands the large majority of pregnancies are planned is an enabling factor in the implementation of preconceptional CF and HbPs carrier screening, but reaching couples who are planning a pregnancy is a major challenge in the absence of a consultancy setting for general preconception care. Factors important for success appeared to be the existence of sociotechnical *niches*, in which technological options can be developed and studied in an experimental setting; a structural approach of providing information to future parents; a party that can articulate demand; governmental involvement in the attunement between various stakeholders; and a screening infrastructure in which large-scale DNA diagnostic services are available. Successful implementation of preconceptional carrier screening for CF and HbPs will depend on changes at both *regime* and *landscape* level, including the establishment of a new preconceptional health care setting and a clearly visible public health authority which can co-ordinate, monitor and evaluate such an initiative in public health care (Chapter 7).

Test-sensitivity of CF screening tests among Turkish and North African people

To obtain more insight into the variability of the *CFTR* mutations found in immigrant CF-patients, who are living in Europe now and to estimate the test-sensitivity of different frequently used methods of DNA-analysis to detect CF-carriers or patients among these Turkish or North African immigrants, a survey was performed among 373 European CF-centers asking which *CFTR* mutations had been found in Turkish and North African CF-patients.

In Turkish and North African CF-patients who are living in Europe now, 31 and 26 different mutations were reported, identifying 64% (113/176) and 87% (118/135) alleles, respectively ($p<0.001$). The test-sensitivity of commonly available commercial *CFTR* mutation panels is 45% and 70% among Turkish and

North African people, respectively. If these panels will be expanded with 13 pathogenic mutations which have been found on two or more alleles among Turkish and North African CF patients in Europe, this would increase the test-sensitivity of these panels to 57% and 79% among Turkish and North African people, respectively. Therefore, the test-sensitivity of these panels is far from ideal for screening Turkish and North African people in Europe, even after expansion with frequent Turkish and North African mutations, because with a negative test-result there is still a considerable residual risk of being a carrier. Still it is recommended to make CF carrier screening generally available for couples at risk because of their ancestry, and to inform the Turkish and North African participants about the limitations of the DNA analysis. Meanwhile, further efforts should be made to identify the yet unknown pathogenic mutations among these populations, and the possibilities of screening the entire *CFTR* coding region for screening purposes should be investigated (Chapter 8).

Conclusions

The studies presented in this thesis have provided better insight into the feasibility and desirability of preconceptional ancestry-based CF and HbPs carrier screening. The feasibility of offering ancestry-based targeted screening was demonstrated: a decisional instrument is now available that can be used as a pre-screening tool to assess the eligibility of a couple for CF and/or HbP carrier couple screening, based on the ancestry of both partners. Furthermore, the feasibility of the invitation procedure for the carrier screening, the actual pre-test consultation and the carrier testing was demonstrated.

It was also demonstrated that preconceptional ancestry-based CF and HbPs carrier couple screening is desirable. Although, uptake in the CF and HbPs carrier testing was low in the present screening study, the general attitude towards participation in the screening was positive, even among non-participants. Practical barriers, such as the time and effort needed for participation, were important reasons for declining. Participants were satisfied and none of them regretted participation. The beneficial aspects outweigh the possible harmful effects, no convincing moral objections were identified, and no predominant feelings of stigmatisation and/or discrimination were reported. The results give rise to recommendations for the development of a more extensive screening study and/or an implementation study among prospective parents, to address the question of whether screening on a larger scale within a multi-ethnic society is also possible and desirable.

It is recommended to consider the performance of such an implementation programme within a general preconception care setting.