Preconceptional carrier couple screening for cystic fibrosis and hemoglobinopathies

An ancestry-based offer in a multi-ethnic society

Phillis Lakeman
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The study presented in this thesis was performed at the Department of Clinical Genetics within the EMGO institute of the VU University Medical Center in Amsterdam, the Netherlands. The EMGO institute participates in the Netherlands School of Primary Care Research (CaRe), which was re-acknowledged in 2006 by the Royal Netherlands Academy of Arts and Science (KNAW) for a second period of five years. The study was funded by grant 21.000.080 of the Netherlands Organisation for Health Research and Development (ZonMw). Financial support for the printing of this thesis has been kindly provided by the EMGO institute, the VU University, the Section Community Genetics of the Department of Clinical Genetics of the VU University Medical Center in Amsterdam, and by the J.E. Jurriaanse Stichting in Rotterdam, the Netherlands.

For reasons of consistency within this thesis, some terms have been standardised throughout the text. As a consequence the text may differ in this respect from the articles that have been published.

The letter of invitation to participate in the screening study, the information leaflet, the reply form, and the brochure for test-participants, as well as the questionnaires 1 to 4, and the questionnaire for those who refrained from test-participation can be found at www.emgo.nl/dissertations/Care/plakeman_dissertation.asp, or can be applied for at the author at p.lakeman@vumc.nl.
Preconceptional Carrier Couple Screening for Cystic Fibrosis and Hemoglobinopathies

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door

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Voor Tim en Pieter
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This thesis describes research that was carried out in the Netherlands to assess the feasibility and desirability of ancestry-based preconceptional cystic fibrosis (CF) and hemoglobinopathies (HbPs) carrier couple screening. As in many other European countries, preconceptional carrier screening for common autosomal recessive disorders is not current practice in the Netherlands, and at the time of the study there was no established general preconceptional health care setting in which this kind of preconception care could easily be implemented.

Preconception care

Increasing knowledge about ways in which to promote the health of prospective parents and their children has resulted in an increase in attention paid to preconception care in recent years. The aim of preconception care is twofold: on the one hand activities are aimed at promoting the health of mother and child, including for example advice regarding lifestyle (e.g. smoking, diet and alcohol), and on the other hand measures are being developed to promote informed reproductive decision making in a non-directive way, for example with regard to genetic testing.

Preconception care can provided in different organisational settings (Health Council of the Netherlands 2007) (see Table 1). Ideally, if specific risk factors are identified within a general preconception care setting, then referral for specialist preconception care should be considered. In the Netherlands there is no current consultancy setting for general preconception care, but several (experimental) initiatives have been taken to provide integrated general advice for individual prospective parents, for example preconception counselling in general practice, or provided by midwives, or the Internet (e.g. www.zwangerwijzer.nl). Moreover, several collective preconception care initiatives have been introduced in the past decade, for instance information campaigns on folic acid to prevent foetal neural tube defects, and non-smoking advertisements.

The Health Council of the Netherlands recently recommended to the Minister of Health, Welfare and Sports the implementation of a programme for preconception care, including the implementation of general preconception care for individual couples. In its report, the Health Council further recommended to pilot preconceptional carrier screening for autosomal recessive disorders, such as CF and HbPs within the general individual preconception care setting.
Table 1
Organisational settings in preconception care

<table>
<thead>
<tr>
<th>Setting</th>
<th>Target population</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Individual preconception care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) General preconception care (low risk)</td>
<td>All prospective parents</td>
<td>Advice to stop smoking; woman’s working environment, obstetric history, prescription history, medical and family history of both prospective parents, including genetic factors</td>
</tr>
<tr>
<td>b) Specialist preconception care (high risk)</td>
<td>- Prospective parents with an already known increased risk of an adverse pregnancy outcome</td>
<td>Specific factors relevant for that specialty; - risks related to epilepsy and use of anti-epileptic drugs in a neurologists consultancy - advice on diabetes care related to pregnancy - informed decision-making related to DNA tests for specific family risks in a clinical genetic setting</td>
</tr>
<tr>
<td>2. Collective measures</td>
<td>- All women (and men) - People of reproductive age</td>
<td>- Protection against radiation - Educational campaigns on the use of folic acid to reduce the risk of having a child with a neural tube defect</td>
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</table>


Aim of preconceptional carrier screening
When both partners of a couple are carriers of an autosomal recessive disorder, the couple faces a risk of 25% in each pregnancy of having an affected child. Without testing carriers are usually unaware of their carrier status. Preconceptional carrier screening would provide an opportunity to identify carrier couples, to inform them and to enable them to make informed reproductive decisions before pregnancy. Acquiring this information about carrier status before, instead of during pregnancy, has the advantage that there is less time constraint and a maximum of reproductive options. These options include not only prenatal diagnosis, followed (or not followed) by pregnancy termination in the case of an affected child, or accepting the risk, but also deciding not to have (more) children, adoption, to make use of donor sperm or eggs, and pre-implantation genetic diagnosis. In some culture related marriage practices it could possibly result in adapting the choice of a partner.16

Preconceptional carrier screening: why CF and HbPs?
CF and HbPs are relatively common, severe, incurable and life-shortening autosomal recessive disorders, which vary in prevalence among specific groups, according to ancestry.
**Cystic fibrosis**

CF is the most common autosomal recessive disorder 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. In the Netherlands approximately 35 to 45 new CF patients are born each year.

The clinical expression of CF varies, but classic CF is characterized by severe chronic respiratory infections and gastrointestinal problems, such as pancreatic exocrine insufficiency and meconium ileus, resulting from the production and accumulation of abnormally thick mucus. Other characteristics are growth problems, male infertility and elevated chloride concentrations in sweat. Although the medical care that is provided has greatly improved the life-expectancy and quality of life of patients with CF, the disease is still not curable. At present, the median life-expectancy of a newborn baby with CF is approximately 30-40 years.

CF results from mutations in a gene mapped to chromosome 7 (7q31) that encodes for a protein, the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which facilitates chloride transport. The gene was cloned in 1989, and since then more than 1400 mutations have been found. The key diagnostic test for CF is a sweat-test (chloride > 60 mmol/l), and further support for diagnosis is provided by the identification of two disease-causing mutations in the **CFTR** gene.

**Hemoglobinopathies**

HbPs, such as Sickle Cell Disease (SCD) and α and β thalassaemia, are hereditary blood disorders that cause severe anemia and variable, but often high morbidity. They are the world’s most common autosomal recessive disorders. As a result of heterozygote advantage against malaria, 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%. As a result of immigration into the Americas and Europe, SCDs and thalassemia have also spread to non-endemic countries. In the Netherlands it is estimated that at least 60 children are born each year affected with SCDs (~70%) or β-thalassaemia major (~30%).

HbPs are the consequence of molecular defects involving the hemoglobin molecule, a globular protein which is a tetramer consisting of two α and two β globin chains. The α-globin genes are duplicated and lie on chromosome 16.
The gene for the β-globin chains (HBB gene) is mapped on chromosome 11 (11p15.5). Some mutations in these genes will lead to structural defects of the globin chains, and others to expressional defects. Structural defects cause abnormal hemoglobin, such as HbS, which induce SCDs. Red cells with HbS assume a sickled configuration when blood is less oxygenated. As a result, patients with SCDs suffer from painful vaso-occlusive crises and irreversible organ and tissue damage, and are prone to infection in early childhood. Expressional defects are classified as α- and β- thalassemias, and are characterized by a lack of α or β globin expression, resulting in insufficient hemoglobin and decreased red blood cell counts. When the β gene is not expressed (β-thalassemia major), no adult haemoglobin (HbA) is formed, and although the clinical expression of β-thalassemia is heterogeneous, in the majority of cases, if there is no blood transfusion, death occurs in the first few years of life. The phenotype of the α-thalassemia syndromes depends on the degree of α-globin chain deficiency relative to β-globin production, varying from mild hypochromic anemia to HbH disease and stillbirth, due to Hb-Bart’s-hydrops fetalis. The phenotype of HbH disease also varies, but, in addition to anemia, the majority of individuals with HbH disease have a hepatosplenomegaly, mild jaundice, and sometimes thalassemia-like bone changes.

The present multi-ethnicity in most (European) countries results in sub-populations with markedly different CF and HbPs carrier frequencies. For example, in the Netherlands, the indigenous people have a higher risk of being CF carriers, and immigrants and their descendants from Surinam and the Netherlands Antilles have a higher risk of being HbP carriers. Turkish and Moroccan people have about an equal risk of being carriers for both disorders. Conclusively, CF and HbPs are both serious disorders, that are relatively common among various population groups in the Netherlands, and carrier testing for these disorders is technically possible. As such, studying an offer of preconceptional (ancestry-based) carrier screening for these disorders, may serve as a model for preconceptional carrier screening for other genetic disorders which are more or less common among different population groups. For example, Spinal Muscular Atrophy is also relatively common among Caucasians with an estimated carrier frequency of 1 in 45 to 50 individuals. In addition, individuals of Eastern European Jewish (Askenazi) descents are at increased risk for several recessively inherited disorders, like Tay-Sachs disease, CF, Canavan disease, Gaucher disease, and Familial Dysautonomia; and individuals who belong to the major immigrant groups in the Netherlands, are, among others, also at increased risk for Familial Mediterranean Fever, and glucose-6-phosphate
A genetic carrier screening programme for CF and HbPs seems to meet the general screening criteria, as outlined by the World Health Organisation (WHO), which include: 1) the disease is an important health problem, 2) there is an effective intervention or decision to be taken by the person screened, and 3) there is a suitable test with known predictive value. With regard to the third criterion, it was concluded by Henneman et al. that the methods that are currently used for DNA analysis have a test-sensitivity that is sufficient for CF carrier screening among Caucasians. However, the commercially available CF carrier screening panels include a limited number of mutations, leading to insufficient sensitivity (detection rate) for certain groups within ethnically diverse populations. In the United States, recommendations have therefore been made concerning the most appropriate CF mutation panel for screening purposes in different ethnic populations. However, their panels, which are based on ethnic compositions in the USA, might not be sufficiently sensitive for screening Turkish and North African people who have estimated carrier frequencies of at least 1 in 50 persons, and who represent the major immigrant groups in the Netherlands. The answer to the question whether this is indeed the case could be to investigate which CF mutations have been found in European CF patients with Turkish or North African ancestry.

Ancestry-based carrier couple screening

The ancestral origin of both partners in a couple determines a priori the disorder for which the couple is at greatest risk of having an affected child: for CF, for HbPs, for both disorders simultaneously, or for neither of these disorders. 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. Targeted carrier screening for autosomal recessive disorders, based on ancestral origin, has previously been advised, but not implemented in most countries.

Doubts have been raised about the offer of ancestry-based targeted screening in many countries including the Netherlands. These doubts are based on negative experiences, such as the discrimination and stigmatisation of carriers after the implementation of sickle cell screening in the USA in the early 1970s. Moreover, there are also practical barriers. A provider-driven ancestry-
based, targeted approach would require knowledge (from databanks, population registers) about the ancestral origin of a country’s inhabitants, in which mixed ancestral background should also be taken into account.

An offer of combined targeted CF and HbPs carrier couple screening could, however, reduce the 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. Furthermore, a consumer-driven approach, in which the participants decide which type of screening is appropriate in their specific situation, is more preferable than a provider-driven approach. Selection on the basis of physical appearance, nationality, or analysis of names by the care-provider or government has proven to be subjective, imprecise and unreliable. Consequently, for the implementation of an offer of combined targeted ancestry-based CF and HbPs carrier couple screening, a screening tool is warranted with which couples could self-assess eligibility for CF and/or HbPs carrier screening, based on both partners ancestry.

**Ethical issues regarding preconceptional carrier screening**

Objections have been made to reproductive screening programmes. For instance, some experts have mentioned medicalisation of the preconception period as a negative aspect of offering preconceptional carrier screening. Furthermore, it has been suggested that pressure from the social environment could threaten freedom of choice, and that such a programme might induce anxiety. These authors doubt that the offer of preconceptional carrier screening can be made in such a non-directive way that it will increase the couple’s reproductive autonomy, because the mere fact that the offer is made by a health care provider would itself imply that it would be a good decision to participate. Moreover, by offering preconceptional carrier screening, the provider overrules ‘the right not to know’ about the possible presence of a risk of having a child with a genetic disorder.

In conclusion, before any decision is made with regard to whether or not to implement preconceptional carrier screening in the Netherlands, there is a need to explore the ethical tension between maximising the reproductive options for carrier couples and protecting individuals from undesirable side-effects.

**Previous studies**

In most European countries there has been debate about whether or not preconceptional carrier screening for autosomal recessive disorders, such as CF, HbPs,
and Tay-Sachs disease (a severe neurodegenerative disorder relatively common among Ashkenazi Jews people), should be introduced, and if so, how. Despite the positive results of several pilot studies, preconceptional carrier screening for these disorders is still not current practice in those countries, and carrier testing is restricted to the families and partners of patients and carriers. Most carriers remain undiagnosed in this situation because they are healthy, and most of them often do not have any relatives with CF and/or HbPs. However, in some Mediterranean countries premarital HbP carrier screening programmes have been embedded in more extensive health care practices. In the USA it has already been recommended that genetic screening for CF should not be restricted to the families and partners of patients and carriers, but that it should also be offered to couples who are planning a pregnancy and to couples seeking prenatal care. Furthermore, various laboratory standards and guidelines have been published. With regard to HbPs and Tay-Sachs disease, it was advised that screening for these disorders should be offered before pregnancy to individuals and couples who are at high-risk, based on their ancestral origin.

In the Netherlands, the only recent experience of offering preconceptional carrier screening for CF was in a pilot study carried out by Henneman et al. Over 38,000 persons were invited by mail, either by the Municipal Health Service (MHS) or by their general practitioner (GP), to participate in a preconceptional CF carrier screening programme with their partner. Pre-test education was provided either during an educational session or during a GP consultation. Approximately 20% had a partner with whom they were planning a pregnancy. The uptake among couples who were planning a pregnancy ranged between 10% (educational session) and 25% (GP consultation). Ninety-five percent of the screened participants said that if they had to make the decision to be tested again, they would make the same decision, and 88% said that they would recommend testing to others. Furthermore, Poppelaars et al. found that, in general, recently married couples and care providers who might become involved in this kind of screening (i.e. GPs and MHS workers) had a positive attitude towards preconceptional CF carrier screening. Moreover, although cost-savings are not the primary goal of preconceptional carrier screening, it was concluded that preconceptional CF carrier screening, under certain circumstances, is cost-effective or that the costs incurred will be acceptable.

With regard to HbPs, elsewhere in Europe, apart from the above-mentioned premarital screening programmes in some Mediterranean countries, there has been experience with prenatal HbPs carrier screening, for example in the United Kingdom, Italy, Greece and Cyprus. In these countries the number of
affected children has subsequently fallen drastically. Outside Europe there has also been experience with HbPs carrier screening, for example, in combined Tay-Sachs disease and thalassemia screening among Ashkenazi-Jewish high school students in Montreal. As a result, the birth prevalence for these two disorders has fallen by 90%-95% in that region over a period of 20 years. Furthermore, it has been demonstrated that thalassemia screening programmes, prenatal diagnosis and termination of pregnancy were feasible and acceptable in Muslim-countries, such as Pakistan and Iran.

In the Netherlands, Giordano et al. carried out a pilot study in which, irrespective of ancestry, prenatal carrier screening for HbPs was offered to a sample of 139 early pregnant women, including 31% women of non-indigenous origin. In this study, 97.8% of the women agreed to participate in the testing. Giordano et al. furthermore reported a generally positive attitude among 328 immigrants in the Netherlands toward prenatal diagnosis and selective abortion in the case of an HbP-affected child. However, these studies focused on prenatal screening. There has, as yet, been no experience with preconceptional carrier screening for HbPs in the Netherlands.

Objectives and outlines of the thesis
The main objective of this research was to evaluate the feasibility and desirability of an offer of combined targeted ancestry-based preconceptional carrier couple screening for CF and HbPs. The offer of carrier screening was made during a screening study which was carried out in 2005 among nearly 10,000 individuals, including 50-60% non-Western immigrants, in Amsterdam, the capital of the Netherlands.

In Part I of this thesis, the screening study was evaluated (Chapters 2-5) and the following research questions were addressed:

1. Is it possible to develop and validate a decisional instrument for pre-conceptional ancestry-based carrier couple screening for CF and/or HbPs in the Netherlands, 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 both partners’ ancestry? (Chapter 2)

2. What is the response of couples planning a pregnancy to such an offer of ancestry-based preconceptional carrier couple screening, making use of the above-mentioned decisional instrument? And does an approach in which the general practitioner sends the invitations lead to a different response than an approach in which the invitations are sent by the Municipal Health Service? (Chapter 3)
3. What determines the intention to participate or not to participate in preconceptional ancestry-based CF and/or HbPs carrier couple screening among those who accepted and those who declined of such a screening offer? And is there a difference in these determinants between people of Western and non-Western origin?  
*(Chapter 4)*

4. What are the psychological consequences of test-participation, how is the understanding and satisfaction of the screening, what are the reproductive intentions, and do people share the test-results with their relatives? Are there differences between participants of Western and non-Western origin?  
*(Chapter 5)*

**Part II (Chapters 6-9)** of this thesis focuses on various other aspects that are also relevant in considering whether or not preconceptional ancestry-based CF and HbPs carrier couple screening should be implemented in the Netherlands: (1) ethical aspects of preconceptional carrier screening in general; (2) a socio-technical analysis to obtain more insight into the process of potential implementation of an ancestry-based CF and HbPs screening programme, and (3) analysis of the results of a European concerted action to register the identity and frequency of *CFTR* gene mutations among Turkish and North African CF patients in Europe.

The following research questions were addressed:

5. Can the possible threat to freedom of choice, and can medicalisation of the preconception period be considered as convincing moral objections to preconceptional carrier screening?  
*(Chapter 6)*

6. What are the constraining and enabling factors for the process of potential implementation of preconceptional CF and HbPs carrier screening in the current (Dutch) health care system? And what sociotechnical conditions at micro-, meso- and macro-level have to be created for a successful implementation?  
*(Chapter 7)*

7. Which *CFTR* mutations have been found in CF patients of Turkish or North African origin who are now living in Europe? Is it possible to formulate recommendations for the design of a *CFTR* mutation panel with a test-sensitivity that will also be suitable for CF (carrier) screening among Turkish and North African immigrants in Europe?  
*(Chapter 8)*
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part I

the screening study
two

developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society

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Abstract

Purpose: To develop a decisional instrument for ancestry-based cystic fibrosis (CF) and/or haemoglobinopathies (HbPs) carrier couple screening in The Netherlands.

Methods: A flow chart (instrument A) and a questionnaire with maps of geographical areas with originally high CF and HbP carrier frequencies (instrument B), were developed to support participants in self-assessing their eligibility as a couple for carrier screening for CF and/or HbPs. The outcome was compared to the self-reported origin of both partners’ ancestors during an in-depth interview. Furthermore, preference for instrument A or B was determined.

Results: Of the 112 participants, 88% (99/112, 95% CI 82-94%) (Instrument A) and 91% (102/112, 95% CI 86-96%) (Instrument B), respectively, arrived at a decision in accordance with their ancestral origin, and 57% (64/112, 95%CI 48-66%) preferred instrument B. A false negative proportion of 5.5% suggests that some carriers will exclude themselves from screening. Results might improve with minor changes in the instruments with regard to geographic specification, and availability of translated versions.

Conclusion: A decisional instrument to assess ancestry-based eligibility for CF and/or HbPs carrier screening, is now available and can with slight adaptations be used in other countries. The instrument also takes into account the possibility of mixed ancestry.
Cystic fibrosis (CF) and haemoglobinopathies (HbPs) are serious autosomal recessive disorders. CF is characterised by chronic lung disease and gastrointestinal problems. HbPs, including sickle cell disorders and α- and β-thalassaemia, are hereditary blood disorders with severe anaemia and variable, but often high, morbidity. Sickle cell disease is characterised by painful vaso-occlusive crises and infections. In the majority of cases of β-thalassaemia, without blood transfusion death occurs in the first few years of life.\textsuperscript{1-3}

Because of the recessive mode of inheritance there is a 25% risk in each pregnancy to have a child with a specific disorder only if both partners of a couple are heterozygous carriers of that disorder. Carrier screening permits couples that are at risk to make informed decisions with regard to available reproductive options, including prenatal diagnosis. However, in most European countries like the Netherlands, preconceptional or prenatal carrier screening for autosomal recessive disorders, like CF and HbPs, is not current practice. Carrier testing is restricted to the families of patients with CF or HbPs, and to the partners of patients and carriers. Most carriers remain undiagnosed in this situation because they are healthy and most often do not have any relatives with CF and/or HbPs.\textsuperscript{4} An important determinant of the risk of being a CF or HbP carrier is ethnicity. The highest population prevalences of CF are found in people with ancestors from Europe, North Africa, Turkey, and the Middle East,\textsuperscript{3,5-12} affecting 1 in 2500-4000 births, while CF is less frequent in people with ancestors from Africa and Asia, affecting 1 in 27,000 - 333,000 births.\textsuperscript{11,13} HbPs are mainly found in people with ancestors from 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%.\textsuperscript{14,15}

Targeted carrier screening based on ethnicity has been advised, but not implemented yet in most countries.\textsuperscript{9,11,16} The multi-ethnicity in most (European) countries though, results in sub-populations with higher CF and/or higher HbPs carrier frequencies. For example, in the Netherlands, indigenous people have a higher risk of being a CF carrier, and people from Surinam and the Netherlands Antilles have a higher risk of being a HbP carrier, while Turkish and Moroccan people are at about equal risk for both. At this moment hesitations have been posed by many countries including the Netherlands towards offering screening based on ethnicity. These hesitations are based on negative experiences, like discrimination and stigmatisation of people, after implementation of sickle cell screening in the USA in the early 1970s.\textsuperscript{17,18} A combined offer of targeted CF and HbPs carrier couple screening, however, could reduce the potential risk of
A decisional instrument for carrier screening based on ancestry

stigmatisation or discrimination of sub-populations, because almost everyone irrespective of one’s ancestry will be eligible for some form of carrier screening: for CF, HbPs or both disorders. Consequently, a screening tool or question to identify specific population groups eligible for CF and/or HbPs carrier screening is desired.

Aspinall et al.⁵ used self-reported ethnicity to identify individuals who are at risk for sickle cell disorders, because selection by physical appearance, nationality, or analysis of names is subjective, imprecise and unreliable.¹⁹,²⁰ Skol et al.²¹ also used self-reported ethnicity in an algorithm to construct genetically similar subsets of families and found excellent concordance with genetic data. However self-reported ethnicity does not take into account the possibility of mixed ancestry, which is especially frequent in Europe among immigrants from previous colonies. For instance, in the Netherlands many immigrants from Indonesia have one or more ancestors of European descent. If they report their ethnicity as Indonesian they will not be eligible for CF carrier screening irrespective of the partner’s ethnicity. If they report their ethnicity as Dutch the same will apply for HbPs carrier screening. One may therefore argue that targeted screening should be ancestry-based instead of ethnicity-based.

The aim of this study was to develop and optimise a decisional instrument that could serve as a pre-screening tool to assess a couple’s eligibility for CF and/or HbPs carrier when ancestry-based targeted CF and HbP carrier screening is piloted or implemented in the Netherlands. Such an instrument should be easy to use for a multi-ethnic lay target population and be useful as a decision aid in the pre-test counselling setting. To achieve this goal two different instruments were developed and pre-tested and the performance of these two pre-screening tests was evaluated. Finally, conditional on their performance the most suitable instrument will be used in a forthcoming pilot study on preconceptional CF and HbPs carrier screening for couples in Amsterdam, the Netherlands.

Methods

Design of the decisional instruments
An information leaflet and two decisional instruments were designed and pre-tested among 15 people (age 22–40 years) with different ethnic backgrounds and an expert panel of immigrants (9 people). Both instruments combined questions about ancestral background of both partners: (A) a flow chart (Figure 1), and (B) a questionnaire with maps of geographical areas with originally high prevalence of CF and HbPs (Figure 2).⁶,⁸-¹¹,¹³-¹⁵,²²,²³
Figure 1
Decisional Instrument A: A flowchart, combining question about both partners ancestors’ origin.
The outcome of the instrument is the couple’s eligibility for a carrier screening test for:
Cystic fibrosis (CF), hemoglobinopathies (HbPs), both disorders or none.

The risk areas for CF and HbPs were primarily defined based on the literature cited. However, based on the results of the pre-test, a balance between precision and practicability was needed and therefore, we decided to optimise the instruments for the Dutch population by making adaptations to the categories of countries and regions at higher risk for CF and HbPs, which have been
Figure 2

Decisional Instrument B: A questionnaire with pictures of original geographical areas at risk for Cystic Fibrosis (CF) and Hemoglobinopathies (HbPs). The outcome of the instrument is the couple’s eligibility for a carrier screening test for: Cystic fibrosis (CF), hemoglobinopathies (HbPs), both disorders or none.
mentioned in the text of Figure 2. During the pre-test, people from the Netherlands Antilles and Surinam often failed to mention that they had ancestors from Africa and/or Asia. Therefore, Surinam and the Netherlands Antilles were subsequently mentioned explicitly. In the instruction to the instruments it was explained that Surinamese people with European ancestors only, should not fill out that they originated from Surinam or the Netherlands Antilles. In addition, also with regard to the colouring of the CF and HbPs risk areas on the maps; for reasons of practicability, the focus was on colouring a (part of a) continent, instead of every individual country, taking into account the origin of the main immigrant groups in the Netherlands: people from Turkey, Morocco, Surinam and the Netherlands Antilles.19,24

Subjects
The criteria for the selection of participants were: having a partner, being of reproductive age and from various ethnic backgrounds, and being able to read Dutch. To test whether the instruments were suitable for the immigrant as well as the indigenous population, immigrants were deliberately over-represented, because they are more likely to have ancestors from different risk areas for CF and HbPs. Participants were recruited between February and November 2003: a) by mail: a selection of women with non-indigenous surnames who had an appointment to visit the antenatal clinic in the VU University Medical Center (VUMC) in Amsterdam (250 invited), and parents of children in three primary schools in suburbs of Amsterdam with a high percentage of immigrants (170 invited), and b) by pamphlets: high school students (age ≥ 18 years), women from Turkish and Moroccan social clubs and visitors of a multicultural summer festival. A minimum of 100 participants was considered to be necessary for an acceptable precision of proportions.

Procedure
All participants first read the information leaflet. Subsequently, with both instruments A and B, which were offered in random order, they arrived at a decision with regard to the disorder(s) for which they were eligible for screening: CF only, HbP only, both disorders, or none. In an additional questionnaire the participants were asked, whether they had at least one ancestor originating from a list of specific geographical areas. As the partners were not present, the participants were also asked whether their partner had at least one ancestor from these areas. An answer was required for each specific area (yes/no). Then, these answers were discussed with an interviewer (PL), and the par-
Participants were asked whether they were really sure that they did or did not have ancestors from any of these specific areas. If the participant then changed the answer (from no to yes, or vice versa), the answer after the in-depth questioning was considered to be the definitive answer. Finally, based on the additional questionnaire and the in-depth questioning, the interviewer determined whether or not the participant had arrived at a consistent decision by using instruments A and B. Incorrect decisions included all cases of self-assessed eligibility (for both, one, or none of the disorders) which were not in accordance with the self-reported origin of the participant’s own and their partners ancestors during the in-depth interview. Furthermore, the additional questionnaire contained questions about socio-demographic characteristics, preference for instrument A or B, and knowledge about CF, HbPs and carrier screening. Knowledge was assessed with seven multiple choice questions. The number of correct answers was calculated as a sum score (with a maximum of 7). No incentives were given, and the study protocol was approved by the Medical Ethics Committee of the VUMC, Amsterdam, The Netherlands.

Analysis
The chi-square test was used for the statistical comparison of proportions (McNemar when paired), and means were compared with the T-test. The 95% confidence intervals (CI) were also calculated, giving an impression of the precision of our estimates.

Results
Demographic characteristics
A total of 112 people participated: 67 people who attended the VUMC antenatal clinic, 18 parents of primary school children, 10 high school students, 11 women from social clubs and 6 visitors of a multicultural summer festival. The socio demographic characteristics of the participants are presented in Table 1.
Table 1
Socio demographic characteristics of the participants in the validation study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>31 (28)</td>
</tr>
<tr>
<td>Age men (mean (range))</td>
<td>37 (26–52)</td>
</tr>
<tr>
<td>Age women (mean (range))</td>
<td>31 (20–43)</td>
</tr>
<tr>
<td>Having children (% yes)</td>
<td>67</td>
</tr>
<tr>
<td>Planning a pregnancy (% yes)</td>
<td>80</td>
</tr>
<tr>
<td>Pregnant or partner pregnant (% yes)</td>
<td>47</td>
</tr>
<tr>
<td>First generation immigrants, n (%) a</td>
<td>71 (63)</td>
</tr>
<tr>
<td>Second generation immigrants, n (%) b</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Original background, n (%): c</td>
<td></td>
</tr>
<tr>
<td>The Netherlands (NL)</td>
<td>26 (23)</td>
</tr>
<tr>
<td>Europe (except NL)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Turkey</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Morocco</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Surinam (23) and Netherlands Antilles (3)</td>
<td>26 (23)</td>
</tr>
<tr>
<td>Asia (6) and Middle East (3)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Africa (incl. Ghana)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Mixed (NL/Curacao (1) or NL/Surinam (2) or NL/Indonesia (1))</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Level of education (%): d</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>22</td>
</tr>
<tr>
<td>Medium</td>
<td>35</td>
</tr>
<tr>
<td>High</td>
<td>38</td>
</tr>
</tbody>
</table>

a First generation immigrants: person was born in a foreign country; and at least one parent was born in a foreign country (definition from Statistics Netherlands: CBS).
b Second generation immigrants: person was born in the Netherlands; and at least one parent was born in a foreign country (definition from Statistics Netherlands: CBS).
c Original background, based on the additional questionnaire and in-depth interview.
d Low: primary school, lower level of secondary school or lower vocational training; Medium: higher level of secondary school or intermediate vocational training; High: higher vocational training or university.

Knowledge of diseases and carrier screening

The mean knowledge score was 5.5 (95% CI: 5.2-5.7). Non-immigrants scored higher than 1st or 2nd generation immigrants (6.5 versus 5.1 [range 4.6 – 6.2 among the different ethnic groups]; p < .0001). There was no significant difference between the knowledge scores according to gender or level of education.

Outcome of the decisional instruments

Table 2 shows that 84.8% (95/112, 95% CI 78.2-91.5%) of all participants arrived at a decision with both instruments in which the self-assessed eligibility was consistent with the eligibility based on the additional questionnaire and in-depth interview. The difference in proportions of consistent decisions resulting from the use of instrument A (88.4% [99/112, 95% CI 82.5-94.3%]) and B (91.1% [102/112, 95% CI 85.8-96.4%]) was not significant.
Table 2
Results of using both decisional instruments A and B

<table>
<thead>
<tr>
<th>Decision</th>
<th>Instrument B</th>
<th>Matches Interview</th>
<th>Inconsistent with interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instrument A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matches Interview</td>
<td></td>
<td>95 (84.8%)</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Inconsistent with interview</td>
<td></td>
<td>7 (6.3%)</td>
<td>6 (5.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102 (91.1%)</td>
<td>10 (8.9%)</td>
</tr>
</tbody>
</table>

Inconsistent decisions include all cases of self-assessed eligibility (for both, one, or none of the disorders) which were not in accordance with the self-reported origin of the participant’s own and their partners ancestors during the in-depth interview.

Table 3 shows for both instruments the self-assessed (participant-based) eligibility to be screened for CF, HbPs, both disorders or none, and the eligibility based on the additional questionnaire and the in-depth interview, which is considered as the gold standard. In total, 97.3% (109/112) participants were eligible for any carrier test (CF, or HbPs or both disorders). Of these people 5.5% (6/109, 95% CI 1.2-9.8%) incorrectly concluded that they were not eligible for any carrier screening, with no difference between the instruments.

Table 3
Self-assessed eligibility to be screened for CF, HbPs, either disorders or none, and the eligibility based on the in-depth interview

<table>
<thead>
<tr>
<th>Instrument A</th>
<th>Eligibility based on in-depth interview (gold standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CF</td>
</tr>
<tr>
<td>Self-assessed eligibility based on instrument A</td>
<td></td>
</tr>
<tr>
<td>CF</td>
<td>33</td>
</tr>
<tr>
<td>HbPs</td>
<td>-</td>
</tr>
<tr>
<td>CF and HbPs</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Total (N)</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Instrument B</th>
<th>Eligibility based on in-depth interview (gold standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CF</td>
</tr>
<tr>
<td>Self-assessed eligibility based on instrument B</td>
<td></td>
</tr>
<tr>
<td>CF</td>
<td>35</td>
</tr>
<tr>
<td>HbPs</td>
<td>-</td>
</tr>
<tr>
<td>CF and HbPs</td>
<td>-</td>
</tr>
<tr>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Total (N)</td>
<td>38</td>
</tr>
</tbody>
</table>

Instrument A is a flow chart (see Figure 1), and instrument B is a questionnaire with maps of geographical areas in which originally high CF and HbP carrier frequencies are found (see Figure 2). The numbers of participants who correctly assessed themselves for the carrier screening test for CF, HbPs, both or none of the disorders, are bolded.
Table 4
Screening test performance characteristics of instrument A and B

<table>
<thead>
<tr>
<th>Ability to differentiate between eligibility for:</th>
<th>Test characteristic (%)</th>
<th>Instrument A</th>
<th>Instrument B</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF carrier test and No CF carrier test</td>
<td>Sensitivity</td>
<td>93.2 (84.9-97.8)</td>
<td>93.2 (84.9-97.8)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>94.7 (82.2-99.4)</td>
<td>92.1 (78.6-98.3)</td>
</tr>
<tr>
<td>HbP carrier test and No HbP carrier test</td>
<td>Sensitivity</td>
<td>93.0 (84.3-97.7)</td>
<td>93.0 (84.3-97.7)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>95.1 (93.5-99.4)</td>
<td>100.0 (91.4-100.0)</td>
</tr>
</tbody>
</table>

In Table 4, screening test performance characteristics are shown.

There was no difference in the proportion of incorrect self-assessed eligibility according to gender, ethnic background, or order of the instruments, but there was a difference according to level of education and knowledge score (Table 5). The participants who arrived at an incorrect decision made a variety of mistakes, due to either inability to follow the instructions correctly (n=8), a false interpretation that “Europe” does not include the Netherlands as well (n=3), insufficient geographical knowledge (n=2), or difficulty with the Dutch language (n=2).

Table 5
Frequency of arriving at a decision matching the interview by gender, ethnicity, order of decisional instrument, level of education and knowledge score

<table>
<thead>
<tr>
<th></th>
<th>Both instruments matched the interview, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Men</td>
<td>26 (84)</td>
</tr>
<tr>
<td>Women</td>
<td>69 (85)</td>
</tr>
<tr>
<td>Dutch</td>
<td>23 (89)</td>
</tr>
<tr>
<td>Immigrants (1st and 2nd generation) b</td>
<td>72 (84)</td>
</tr>
<tr>
<td>Instrument A first c</td>
<td>48 (83)</td>
</tr>
<tr>
<td>Instrument B first</td>
<td>47 (87)</td>
</tr>
<tr>
<td>Level of education d</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>22 (73)</td>
</tr>
<tr>
<td>Medium</td>
<td>35 (80)</td>
</tr>
<tr>
<td>High</td>
<td>38 (100)</td>
</tr>
<tr>
<td>Knowledge score e</td>
<td>5.6</td>
</tr>
</tbody>
</table>

* The categories “Only instrument A matches with interview”, “Only instrument B matches with interview” and “Both instruments incorrect” were combined in the column “No”, because the number of cases in these categories were too small and there were no statistical differences found between these three categories.

b The original background of the participants is not further specified here, because there were no significant differences in proportion of decisions that did or did not match with the interview between the different ethnic groups.
c Instrument A and B were presented in random order to the participants.
d Significant difference between high level of education versus the other two levels of education (p=.004).
e Significant difference in mean knowledge score (p=.007).
Preference
More people preferred instrument B (57.1% [64/112, 95% CI 48.0-66.3%]) to instrument A (42.8%) (not significant). Gender, ethnicity, order of offering the instruments, level of education, and correctness of the decision showed no statistically significant association with preference for instrument A or B (data not shown).

Discussion
In this study two decisional instruments were developed for targeted ancestry-based CF and/or HbPs carrier couple screening. These instruments use self-reported information about ancestral origin to support participants in the self-assessment of their eligibility for carrier screening for both, one or none of these disorders, and to serve as a decision aid in the pre-test counseling setting. One instrument was a flow chart (instrument A) and the other was a questionnaire with maps of the originally high risk areas for CF and HbPs (instrument B).6;8-11;13-15;22;23

Although the originally high risk areas for CF and HbPs were primarily defined based on the literature cited, some additional remarks should be made here about the design of the instruments. It was clear after the pre-test that a balance between precision and practicability was needed. Therefore, we choose to focus on colouring an entire continent or large risk areas. As a consequence, on the one hand, not all countries that are coloured on the maps of the risk areas for CF and HbPs actually are at higher risk. In Finland, for example, a CF prevalence of 1 in 25,000 births has been described.6 However, there are hardly any immigrants from Finland in the Netherlands,24 so colouring Finland probably causes very few false positives. In addition, South-Africa was included on the map of the risk areas of HbPs, while on the maps of Weatherall et al.15 this region was excluded. However, they recommended carrier screening for HbPs to the entire continent of Africa and did not exclude South-Africa explicitly.22 Furthermore, HbPs have been described in the black population of South-Africa.25-26 On the other hand, the America's and Australia are not coloured, although CF and HbPs are prevalent on these continents today. However, due to the heterogeneous ancestral background of these populations, it is not correct to colour these continents as originally high risk areas for CF and/or HbPs, but immigrants from these areas should consider the provenance of their earlier ancestors: for example Europe, Africa or Asia. Furthermore, there are only a few immigrants from Australia in the Netherlands.24
Another consequence of the fact that we had to balance between precision and practicability was our choice not to use an actual cut-off percentage of carrier frequencies for CF and HbPs for the definition of high risk areas. Although it has been suggested by Haddow et al.\textsuperscript{11} that a carrier frequency of 1 in 35 is high enough to merit CF carrier screening, defining a cut-off value, in our opinion, is an arbitrary choice. Furthermore, if we exactly had formulated a cut-off point, we also should have looked at every single country, for example within Europe, and even within different regions of those countries, and include or exclude these smaller areas in our model on the basis of the CF or HbPs prevalence. Moreover, then we also should have taken the number of ancestors from these areas into account, as for instance two out of four grandparents from such an area might lead to a risk lower than 1 in 5000 while three grandparents would meet the criterion for eligibility. The instrument then would have been probably more precise than our instrument, but at the same time, would not be suitable for practical use anymore.

Our instrument was developed for the Dutch multi-ethnic society. Other countries may have to adapt the map and questionnaire to their ethnic subpopulations, taking into account the original high risk areas. The use of ancestry-based information can be easily generalized to specific groups of migrants and adopted globally.

Finally, regarding the definition of risk areas for CF and HbPs, it is important to realize that colouring risk areas for CF and HbPs does not mean that these disorders do not occur at all in the other countries or regions. Although uncommon, CF has been found among Africans and Asians, and HbPs have also been found among Europeans.\textsuperscript{27-30} Some carriers, therefore, will be falsely excluded from screening on the basis of ancestry. Bobadilla \textit{et al.}\textsuperscript{6} argued that disease-based data about CF prevalence in Africa may be artificial (because the condition is masked by non-survival based in other factors), and they also indicated that there has been very limited mutation testing, and that biased panels of tests may be used. In designing the instruments the current recommended areas for targeted screening have been used, but the instruments will need adaptations when new evidence becomes available.

Ancestry-based carrier screening (for couples) using self-reported information about ancestral origin obviously has its limitations. Additional remarks, therefore, can also be made about the goal, gold standard and the validity of instruments A and B. The primary goal was to design and optimise an instrument for selecting people at risk of being a carrier for CF and/or HbPs in order to define whether the man and woman together (the couple) have a substantial risk of offspring with CF and/or HbPs and whether they, consequently, are
eligible for CF and/or HbPs carrier screening. Eligibility for CF and/or HbPs carrier screening based on a questionnaire and an in-depth interview serves as the gold standard for the analysis of this study. Aspinall et al. already suggested using in-depth interviews in their study to design a pre-screening tool for ethnicity-based screening for sickle cell disorders. When actual carrier test results would have been chosen as gold standard, thousands of participants would have been needed for detecting enough CF and HbPs carriers to arrive at estimates with acceptable precision. Moreover, out of the thousands of participants only a minority will turn out to be CF and/or HbPs carriers. Consequently, the number of false positives will be extremely high when our instrument should serve as a screening tool to detect carriers in such a design. Moreover, the specificity of the instrument would have been extremely low in such a design. Therefore actual carrier test results were not chosen as our gold standard at this stage. Furthermore, it was not our goal to perform a perfect genealogical study, and therefore, self-reported ancestry was considered sufficient. Condit et al. reported that in the USA people are often unfamiliar with their ancestry, but in our study this did not seem to be a major problem. Finally, the participants also had to fill out the questions about their partners’ ancestors, which could lead to mistakes. Therefore, it is recommended that partners fill out the pre-screening instrument together, and serve as their own internal control, if ancestry-based targeted carrier screening for CF and HbPs would be implemented.

In a carrier screening program it is desirable to have high sensitivity of a potential pre-screening instrument (i.e. low false negative proportion), so that pre-test counselling will not be withheld to people who are eligible for screening. Both instruments reached a sensitivity of 93.2% and 93.0% to arrive at eligibility for a CF carrier test or a HbP carrier test, respectively. Unfortunately, 5.5% of the participants incorrectly arrived at ineligibility for any disorder. However, in our opinion, like the study of Aspinall et al., this participant-centred approach is still better than an approach where someone in the medical profession with no expertise on either geo-ancestry or the couple’s own ancestry makes a decision.

Furthermore, the mistakes that were made indicate that there is also room for improvement of the decisional instruments. The false interpretation that “Europe” was not meant to include the Netherlands can easily be solved by changing the answer category to “Europe (including the Netherlands)” or “the Netherlands and Europe”. Difficulties in following the instructions, due to insufficient knowledge of the Dutch language, can be overcome by offering translated versions.
Of course, because CF and HbPs are also found in lower risk areas, and because people need to know their ancestral origin and be able to use the instruments correctly, some carriers will be falsely excluded in this approach of CF and HbPs carrier screening. Offering screening to everyone, irrespective of the person’s ethnicity, is another option in which more carriers would be found. As costs are influenced by changes and innovations in the field of genetic carrier screening for CF and HbPs, this approach could become cost-effective in the future. However, offering carrier screening to all people, including those who do not have a substantial risk of having offspring with these disorders, has some important drawbacks, such as the potential for causing psychological distress. Only when in the future carrier screening for a larger number of disorders will be offered simultaneously, universal screening could be more practical and cost-effective than targeted screening based on ancestry.

Finally, in our study immigrants were deliberately over-represented, because we expected that our decisional instrument would be the most challenging for them, as they are more likely to have ancestors from different risk areas for CF and HbPs. However, in this small study no significant difference was found between Dutch and immigrant participants in arriving at the correct decision regarding eligibility.

The validity of the two instruments did not differ significantly (Table 4). Based on the lower failure rate (Table 2) and preference of the participants, although not statistically significant, instrument B was chosen as most suitable for our forthcoming pilot study, in which the self-assessed eligibility of participants will be checked by the general practitioner.

Although our decisional instrument was designed for the self-assessment of eligibility for carrier screening based on both partners’ ancestry, the specific questions about ancestral origin that are asked in this instrument are also very suitable for determining the individual risk of being a CF and/or HbP carrier. Furthermore, these questions can be considered as the further development and refinement of a pre-screening ethnic or ancestry question, as recommended by Aspinall et al. and Haddow et al.

An instrument which uses self-reported ancestry as a tool for the assessment of eligibility for CF and/or HbPs carrier screening in a multi-ethnic society is now available, and can theoretically be used in preconceptional, prenatal or neonatal screening programmes. In making a policy decision to implement this tool, it also would be desirable to conduct additional research, such as analysis of the incremental cost-effectiveness of this tool compared to other approaches (e.g., family-based screening, ethnicity-based screening, or universal population-based screening). Furthermore, it should taken into
account that the performance of such tools is expected to vary in different settings and societies depending upon the level of awareness or knowledge of ancestral countries of origin. Nevertheless, the cost aspects should never be the most important motive in the implementation of a carrier screening programme. The focus should be on offering those people who are at substantial risk of having offspring with CF and/or HbPs the opportunity to make informed reproductive choices by participating in a carrier screening programme, while avoiding unnecessary harm to people who are not eligible for screening as much as possible.

Reference list


three an offer of combined ancestry-based preconceptional carrier couple screening for cystic fibrosis and hemoglobinopathies: response in a multi-ethnic population

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Lidewij Henneman
Pieter D Bezemer
Johan JP Gille
Piero C Giordano
Rob van Zwieten
Martina C Cornel
Leo P ten Kate

Submitted
Abstract

Purpose: To study the response to an offer of combined preconceptional ancestry-based carrier couple screening for cystic fibrosis (CF) and hemoglobinopathies (HbPs), in a multi-ethnic population in the absence of a general preconceptional consultancy setting.

Methods: 9453 people (20-35 years), including 50-60% non-Western immigrants, were invited by their general practitioner (GP) (n=4720) or the Municipal Health Service (MHS) (n=4733) to visit their GP within one month with their partner for carrier testing, which was conditional on survey-participation. Invitees with a partner and planning a pregnancy were the target population. Eligibility for CF and/or HbPs carrier screening was determined with a validated ancestry-based decisional instrument.

Results: One third belonged to the target population of whom 3% participated in the testing with their partners, while 54-93% stated that they would participate in the screening if this became a standard offer. The majority (73%) favored offering these test(s) routinely to all couples planning a pregnancy. Non-Western immigrants were under-represented (31%) among the test-participants, but no feelings of discrimination and/or stigmatization were reported. “I’m too busy” (21%) was an important reason for non-participation.

Conclusion: There was a large difference in the proportion of study-participants who had a positive attitude towards the screening and the proportion who actually participated, suggesting limited facility for informed decision-making. In the implementation of preconceptional CF and/or HbPs carrier screening, identified barriers for test-participation should be removed: there should be no time limitation for making an appointment, translated copies should be available and test-participation should not be conditional on survey-participation.
Introduction

Couples in which both partners are heterozygous carriers of an autosomal recessive disorder face a 1-in-4 risk in each pregnancy of having an affected child. Carrier screening allows them to make informed reproductive decisions. Prenatal and preconceptional screening are options for targeting future parents. The advantages of preconceptional carrier screening, compared to prenatal screening, are the existence of a minimum of time constraint and a maximum of reproductive options, including not only prenatal diagnosis followed (or not) by pregnancy termination in the case of an affected child, or accepting the risk, but also deciding not to have (more) children, adoption, using donor sperm or eggs, pre-implantation genetic diagnosis, or eventually, in some customary marriage practices, adapting partner choice.

Nowadays, carrier screening is technically possible for an increasing number of disorders, for example cystic fibrosis (CF) and hemoglobinopathies (HbPs), including sickle cell disorders (SCD) and α and β thalassaemia, which are incurable, severe life-shortening, autosomal recessive disorders. Nevertheless, in most (Northern) European countries, preconceptional carrier screening for CF and HbPs is not current practice yet, despite positive results of several (pilot) studies. Programs of HbPs carrier screening were established in the UK, Italy, Greece and Cyprus in the late 1970s, and a high uptake of prenatal diagnosis was reported. In some Mediterranean countries premarital HbP carrier screening programs have been embedded in more extensive health care practices. Modell et al. calculated that, to date, more children affected with severe HbPs are born in Northern Europe than in Southern Europe.

An important determinant of the risk of being a carrier of CF and/or HbPs is ancestry. CF is most common among Europeans and their descendants, with a carrier frequency of 1 in 20-30 individuals, resulting in a 1 in 400-900 carrier couple frequency and a CF birth prevalence of 1 in 1600-3600. 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 with ancestors from 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%.

The present multi-ethnicity in most (European) countries results in sub-populations with markedly different CF and HbPs carrier frequencies. For example, in the Netherlands, indigenous people have a higher risk of being CF carriers, and immigrants from Surinam and the Netherlands Antilles have a higher risk of being HbP carriers, while Turkish and Moroccan people have
about an equal risk of being carriers for each disorder.

Previously, many countries, including the Netherlands, have been hesitant about offering screening based on ancestry. This hesitation is based on negative reports, for instance about the discrimination and stigmatization of Afro-American people after the implementation of sickle cell screening in the USA in the early 1970s.\textsuperscript{26,27} However, an offer of combined targeted ancestry-based CF and HbPs carrier couple screening could reduce the potential risk of stigmatization or discrimination of sub-populations, because almost everyone, irrespective of ancestry, will be eligible for some form of carrier screening: for CF, HbPs, or both disorders. In a previous study, we developed a decisional instrument which helps couples to self-assess their eligibility for CF and/or HbPs carrier screening.\textsuperscript{28} The instrument, a questionnaire with maps of geographical areas where, originally, there was a high prevalence of CF and HbPs, consists of questions about both partners’ ancestry.

The objective of the present study was to assess the response of couples planning a pregnancy to an offer of combined ancestry-based preconceptional carrier couple screening for CF and/or HbPs, making use of the above-mentioned decisional instrument. In general, in the Netherlands, 80-90\% of the pregnancies are planned.\textsuperscript{29} To our knowledge, there are no other studies in which a similar offer of combined targeted ancestry-based carrier screening has been made. In a previous study carried out by Henneman et al. in the Netherlands,\textsuperscript{30} in which CF carrier screening was offered to couples planning a pregnancy, 20\% had a partner with whom they were planning a pregnancy and an uptake of 25\% was found.

In 2005, when our offer was made, there was no general preconception care consultancy setting in the Netherlands. Therefore, we further studied whether invitations sent by the general practitioner (GP) (approach A) or by the Municipal Health Service (MHS) (approach B), led to a different response. We also studied the most important reasons for participation and non-participation in the testing.

**Methods**

Similar to the previous CF carrier screening study of Henneman et al, individuals were selected on the basis of age (20-35 years);\textsuperscript{30} the offer was made through personal invitations by either the GP or the MHS; and in all cases GPs provided the pre-test counselling. Therefore, it was necessary to recruit GPs and an MHS.
The study was carried out in Amsterdam in the Netherlands, a city with a high percentage of ethnic minorities (45%).\textsuperscript{31} The administration of the city of Amsterdam is subdivided into 15 districts. Districts in which participants were recruited (n=8), were selected on the basis of sufficiently high percentages of non-Western immigrant inhabitants (mean 51.4\% [range 32.6-86.0\%]),\textsuperscript{31} and willingness of the GPs to participate. In the Netherlands, in principle, all inhabitants are registered with a GP. The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam.

**Procedure**

**Invitations**

From January to December 2005, 9784 individuals were sent an invitation to participate in the carrier couple screening. The CF and the HbPs carrier screening tests were offered free of charge. Enclosed with the invitation were an information leaflet and the above-mentioned ancestry-based decisional instrument to assess eligibility for CF and/or HbPs carrier screening, which both had been pre-tested and validated,\textsuperscript{28} as well as a reply form and envelope. All documents were available in Dutch only. The information leaflet described the clinical and genetic aspects of the disorders, the carrier prevalence in different populations according to ancestry, the advantages and disadvantages of participation, the test procedure, and test-sensitivity.

**Recruitment of participants: two approaches**

In approach A invitations were sent by the GP, who selected the invitees’ names and addresses from the practice register. In this approach it was possible to ask the GPs to exclude patients with fertility problems or psychosocial problems from the mailing list beforehand, to avoid any emotional disturbance that might be caused by the invitation. In approach B the invitations were sent by the MHS. Names and addresses were selected from the population register by local authorities, with permission from the Registration Committee of the Municipality of Amsterdam.

**Recruitment of general practitioners**

In order to prevent an individual from receiving an invitation from both the GP and the MHS, approach A an B took place in separate districts. Approach B was complicated by the fact that the MHS could not select inhabitants based on registration with a particular GP, but was only able to provide the names and addresses of all 20- to 35 year-old inhabitants in one particular district.

To recruit GPs for approach B we contacted all GPs in several districts. If the
majority of the GPs in a district were willing to participate, then approach B could become operative in that district. If not, the minority of GPs in that district who were willing to participate in the study, were asked to participate in approach A. Parallel in time, individual GPs in other districts were also invited to participate in approach A. Eventually, all GPs (n=119) in eight districts were contacted before we reached a sufficient number of invitees for both approaches, as 20.2% (24/119; 95% CI 13.0-27.4) of the GPs agreed with participation. Twelve GPs located in six districts participated in approach A, and 12 GPs out of 15 practices (80%) located in two other districts participated in approach B.

Eligibility for participation in the study
Eligible for participation in the study were invitees who had a partner with whom they were considering a pregnancy, irrespective whether this would be in the near future or at a later date, further referred to as the “target population”. Exclusion criteria were pregnancy, inability to read and write Dutch, and a positive family history of CF and/or HbPs. In the latter situation, it was suggested that the couple should contact a clinical geneticist for counseling. The reply form was used, among other things (see below), to estimate the percentage of invitees belonging to the target population by asking them whether or not they had a partner with whom they were considering a pregnancy. If one (or more) of the exclusion criteria applied, the invitee was asked to state this on the reply form.

Options for study participation
On the reply form, eligible invitees were further asked whether they wanted to participate in: 1) the CF and/or HbPs carrier test(s), which was conditional on participation in a survey, or 2) the survey only. If they were not interested in participation at all, they were asked to give their reason(s) for non-participation. Invitees who did not return the reply form are further referred to as “non-respondents”.

Respondents who wished to participate in the survey only were sent two similar copies of a questionnaire, one for each partner of the couple. If necessary, reminders were provided after two and four weeks by post and telephone, respectively.

Procedure for test-participants
The eligible respondents who were interested in test-participation had to make an appointment with their GP within one month, together with their partner. Reminders by mail and a phone call were performed after four and six weeks,
respectively. They were reminded about the limited time-span of the study and the impossibility of testing after the time period of the study.

The partners in a couple did not necessarily need to be patients of the same GP. They could visit the GP of the partner who received the invitation, or choose one if both partners had received an invitation and both partners had a participating GP. Those invited by the MHS (approach B) received a list of participating GPs. It was possible that the invitee’s own GP had decided not to participate, or was not asked to participate in the study because the practice was located outside the boundaries of that district. Invitees were informed that an appointment with a GP in one of the other participating practices in their district could be arranged for such a couple.

Before the GP consultation, both partners had to complete a similar questionnaire in the waiting room. During the consultation the GP assessed the couple’s eligibility for the CF and/or HbPs test(s), based on the decisional instrument. Information about the advantages and disadvantages of carrier screening was repeated and the GP offered the couple the test(s). When the couple agreed, the samples for the test(s) were taken by the GP.

At the end of the GP consultation, the couple received a detailed brochure and an informed consent form. The actual testing in the laboratories did not start before the informed consent form was returned. If after two weeks the informed consent form was not returned, a phone call was made to find out whether this was on purpose or for instance the result of a postal failure.

**Questionnaires**

The questionnaire assessed, among other things, sociodemographic characteristics (gender, year of birth, marital status, level of education, number of children, native country, parental native country) and attitudes towards a standard offer of preconceptional ancestry-based carrier couple screening for CF and HbPs. The most important reason(s) for participation and non-participation were asked. Further, they were asked to use the decisional instrument to assess their eligibility for the CF and/or HbPs carrier test(s).

**The CF and HbPs carrier screening tests**

For the CF carrier test, both partners provided a mouthwash sample. The method of testing was stepwise, i.e. the sample of the second partner was only tested if the first one had a positive test result. The couple could indicate on the informed consent form which partner should be tested first, or could leave this choice to random assignment. For this study, we designed a CF transmembrane conductance regulator (*CFTR*) mutation panel, consisting of *CFTR* mutations.
that have been identified on at least two unrelated alleles in Dutch and Turkish people (see Table 1).\textsuperscript{18,32}

For the HbPs tests, venous blood samples from both partners were collected and both partners were tested. The samples were screened for abnormal hemoglobin (Hb) species by High Performance Liquid Chromatography (HPLC), for β-thalassemia by HbA\textsubscript{2} quantification (also by HPLC), and for β-thalassemia by DNA analysis (Southern blotting after restriction enzyme treatment, specific PCR amplification or by sequencing).

<table>
<thead>
<tr>
<th>Exon</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>E60X, K68N, G85E</td>
</tr>
<tr>
<td>4</td>
<td>E92K, E92X, A96E, D110H, R117H, M152V</td>
</tr>
<tr>
<td>Intron 4</td>
<td>621+1G&gt;T</td>
</tr>
<tr>
<td>Intron 5</td>
<td>711+1G&gt;T</td>
</tr>
<tr>
<td>7</td>
<td>R347H</td>
</tr>
<tr>
<td>9</td>
<td>A455E</td>
</tr>
<tr>
<td>Intron 9</td>
<td>1525-1G&gt;A</td>
</tr>
<tr>
<td>10</td>
<td>F508del, 1677delTA</td>
</tr>
<tr>
<td>Intron 10</td>
<td>1717-1G&gt;A</td>
</tr>
<tr>
<td>11</td>
<td>G542X, R553X</td>
</tr>
<tr>
<td>Intron 14b</td>
<td>2789+5 G&gt;A</td>
</tr>
<tr>
<td>17b</td>
<td>F1052V, R1066L, R1070Q</td>
</tr>
<tr>
<td>19</td>
<td>R1158X, R1162X</td>
</tr>
<tr>
<td>20</td>
<td>S1251N, W1282X</td>
</tr>
<tr>
<td>21</td>
<td>N1303K</td>
</tr>
</tbody>
</table>

Table 1
Panel of 33 CFTR mutations used in this study

- Panel consisting of CFTR mutations belonging to the oligonucleotide ligation assay (OLA, Celera Diagnostics) combined with mutations frequently identified in Turkish people (in Italics). CFTR = CF transmembrane conductance regulator.

Eligible non-respondents
Most of the invitees (>85%) did not return the reply form (see Results). To estimate the percentage of invitees who belonged to the target population among these non-respondents, a telephone survey was carried out in December 2005 and January 2006 among a random sample of 1,000 non-respondents. In 64.1% (641/1,000) of the cases, it was possible to find out the telephone number. They were phoned a maximum of three times at different times of the day and/or week. In total, 201 non-respondents were actually interviewed. This number is sufficient if random, to estimate how many belonged to the target population with a precision of approximately 6%. During the interview, the non-respondents were asked whether they could remember the invitation; whether they had a partner and were planning a pregnancy, and why they had not returned the reply form.

Determination of ancestry
To study whether or not the response to the screening offer was influenced by
ancestry, we collected data on ancestral origin. The method that could be used to identify or approximate the invitee’s ancestry depended on the approach (A or B) and whether or not the invitee participated in the survey. All survey participants, including those who had also the test(s) and irrespective of who had invited them (GP or MHS), were asked about their own and their parents’ native country. For those invited by the MHS (approach B), we obtained information about their own and their parents’ native country from the population register too. As the GPs did not register ethnicity, for those who had been invited by their GP (approach A), but who did not participate in the survey, we could only roughly estimate their ancestry at group level on the basis of data from the city’s Department for Research and Statistics, which registers the percentages of immigrant inhabitants in each district in Amsterdam.

Based on their ancestry, the participants were sub-divided into:
1) indigenous (Dutch) people and Western immigrants, because they were mainly eligible for CF carrier screening, and 2) non-Western immigrants, who are, in general, eligible for HbPs carrier screening. According to the definition of Statistics Netherlands, the indigenous people and Western immigrants have their ancestry in Europe, North-America, Australia, Japan and Indonesia. Unlike Statistics Netherlands, we classified Japanese and Indonesian invitees as non-Western immigrants, because of their eligibility, in general, for HbPs carrier screening instead of CF carrier screening. All other people were defined as non-Western immigrants, including people from Turkey, Surinam, Morocco and the Netherlands Antilles, which form the four largest immigrant groups in the Netherlands. In addition, to investigate whether or not the population register data would be sufficient to identify an individual’s risk of being a CF and/or HbP carrier, we compared data on the countries of birth of the invitees and the parents, with the risk assessment based on our decisional instrument.

Response and participation

To calculate the percentage of respondents, only individuals (not couples), were taken into consideration, since the invitations were sent to individuals. Some partners of respondents had also received a personal invitation, and were therefore original invitees too. The percentages of participating invitees in the testing and in the survey only, respectively, were calculated as the number of actual participants in the test(s) and in the survey only, divided by the number of invitees belonging to the target population. The percentage of people belonging to the target population was calculated as the sum of a) eligible invitees among the respondents, and b) an estimated number of eligible invitees among the non-respondents based on the telephone survey.
Data-analysis

Both partners in a couple were treated as independent subjects as earlier research showed that partners provide different information. The Chi-square test was used for the statistical comparison of percentages, and means were compared with the t-test. 95% confidence intervals (CI) were also calculated to indicate the precision of our estimates. All analyses were performed using SPSS 11.0 for Windows.

Results

Response, target population and participation

In total, 331 invitations were undeliverable. The remaining 9453 invitations were sent by either the GP (n=4720; approach A) or the MHS (n=4733; approach B) (see Figure 1). The GPs had only excluded 30 persons from their mailing lists beforehand. In total, 14.4% (1365/9453) of the invitees returned the reply form. Among these 1365 respondents, 490 (35.9%) belonged to the target population, which was not statistically different from the estimated percentage of 32.8% (66/201) who belonged to the target population among the non-respondents (p=.054). It was estimated, therefore, that 33.3% ([490+8088*66/201]/9453; 95% CI 30.4-36.1%) of all invitees belonged to the target population. More people invited by their GP than by the MHS responded: 16.0% (758/4733) versus 12.9% (607/4720) (p<0.001). Of the 1365 respondents, 47 were excluded from participation in the study because of pregnancy.

Reasons for not returning the reply form, mentioned during the telephone survey among 201 non-respondents by those who had belonged to the target population (n=66), were “they could not remember the invitation” (44% [29/66]), “lack of time” (21% [14/66]), “they did not feel like it” (12% [8/66]), and other reasons (23% [15/66]). Of the 135 non-respondents who did not belong to the target population, 6% (4/135) was pregnant when they received the invitation.

Intention to participate

In total, 33.9% (166/490) of the eligible respondents intended to participate in the testing, being 5.3% of all eligible invitees (166/[490+0.33*8088]). There was no significant difference in intention to test-participation between eligible respondents invited by the MHS (28.5% [57/200]) or the GP (37.6% [109/290]) (p=.088). Nineteen partners of these 166 respondents had received a personal invitation. So there were 147 couples who intended to participate in testing. Participation in the survey only was intended by 35.1% (172/490) of the eligible respondents.
(165 couples). The remaining 152 eligible respondents (141 couples) were not interested in participation at all, and the reasons were: “I don’t feel like it” (40.1%), “Lack of time” (22.4%), “I am going to move” (7.2%), “My Dutch language is not good enough” (5.9%), “I’m against carrier testing for these disorders” (5.3%), and other reasons.

**Figure 1**
Response to the invitation of preconceptional CF and/or HbPs carrier screening

GP = general practitioner; MHS = Municipal Health Service
Target population: invitees with a partner and who were considering a pregnancy with that partner.

* The percentage of respondents who belonged to the target population was 36% (490/1365; 95% CI 33-38%) and was almost statistically different from the proportion of 33% (66/201; 95% CI 26-39%) who belonged to the target population among the non-respondents (p = .054).

** One person was heterozygous for both sickle cell disease and α thalassemia.
Actual participation in the test(s)

Of the 166 respondents who intended to participate in the testing, 87 (52.4%; 95% CI 44.8-60.0%) actually had the test(s) done, representing 72 out of the 147 test-intending couples (49.0%; 95% CI 40.1-57.1%) (see Figure 1). The test-participation among eligible invitees was estimated to be 2.8% (87/[490+(0.33*8088)]; 95% CI 2.2-3.4%). A significantly higher percentage of couples in which both partners received a personal invitation, compared to the couples in which one partner was invited, actually had the test(s): 78.9% (n=15/19) versus 45.5% (n=57/128) (p=.006).

In total, 47, 6 and 19 couples, respectively, had a carrier test for CF, HbPs, and both disorders. Three CF carriers, seven HbP carriers and no carrier couples were identified. One person was heterozygous for both sickle cell disease and α-thalassemia. The CF carrier frequency among the 69 CF-tested participants (66 first tested participants and three subsequently tested partners), was 1 in 23 (95% CI 0.91-12.2%), and the HbP carrier frequency among the 50 HbPs-tested participants (25 couples in which both partners were tested), was 1 in 7 (95% CI 5.8-26.8%).

The remaining 79 out of these 166 test-intending respondents refrained from test-participation: 75 had made no appointment with the GP; and 4 no longer wanted the test(s) after visiting their GP. Of these four couples, two had to wait too long in the GP’s waiting room; one reported that their GP said that their risk to be a carrier couple was low (while they were eligible for testing according to the decisional instrument), and the other one was not eligible for any of the test(s) according to the decisional instrument. Reasons for the gap between intention to participate and actual participation were investigated by means of qualitative interviews and will be reported elsewhere (Plass et al. unpublished data).

Table 2
Mode of invitation versus ancestral origin among the 87 participants in preconceptional CF and/or HbPs carrier screening

<table>
<thead>
<tr>
<th>Mode of invitation</th>
<th>Indigenous (Dutch) people, n</th>
<th>Western immigrant, n a</th>
<th>Non-Western immigrant, n</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP (approach A) b</td>
<td>40</td>
<td>4</td>
<td>18</td>
<td>62 (71)</td>
</tr>
<tr>
<td>MHS (approach B) c</td>
<td>14</td>
<td>2</td>
<td>9</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>54 (62)</td>
<td>6 (7)</td>
<td>27 (31)</td>
<td>87 (100)</td>
</tr>
</tbody>
</table>

a Definition of Western and non-Western immigrants as defined by Statistics Netherlands, 37 except for Japanese and Indonesian immigrants who were included in the group of ‘non-Western immigrants’.
b Invitations were sent by the invitees’ own general practitioner (GP).
c Invitations were sent by the Municipal Health Service (MHS).
Table 2 shows that more test-participants had been invited by their GP than by the MHS: 71.3% (62/87) versus 28.7% (25/87). The test-participation among eligible invitees invited by the GP versus the MHS was therefore 3.9% \((62/[290+(0.33*3962)])\) versus 1.6% \([25/[200+(0.33*4126)])\), respectively \((p<.001)\). The majority of test-participants (62.0%) were of Dutch origin (54/87). There were significantly less non-Western immigrants among the participants than among the invitees: 31.0% (27/87) versus 51.4% (5029/9784) \((p=.001)\). There was no difference in the percentage of non-Western immigrants among those who intended to participate and those who actually did (data not shown).

**Sociodemographic characteristics**

In total, 72 couples participated in the testing and 128 couples participated in the survey only. They returned 143 and 247 questionnaires, respectively. Table 3 shows their socio-demographic characteristics. Test-participants were more likely to have no children \((p=.005)\), and to have a high or intermediate level of education \((p=.002)\), compared to the participants in the survey only.

**Table 3**

Socio-demographic characteristics of all participants in the carrier screening test(s) and in the survey

<table>
<thead>
<tr>
<th>Participants in:</th>
<th>Carrier screening test(s) and survey</th>
<th>Survey only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couples, n</td>
<td>72</td>
<td>128</td>
<td>390</td>
</tr>
<tr>
<td>Individuals, n</td>
<td>143</td>
<td>247</td>
<td>390</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>71 (50)</td>
<td>120 (49)</td>
<td>191 (49)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>72 (50)</td>
<td>127 (51)</td>
<td>199 (51)</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>32 (23-47)</td>
<td>32 (22-56)</td>
<td>32 (22-56)</td>
</tr>
<tr>
<td>Women</td>
<td>29 (19-41)</td>
<td>29 (20-42)</td>
<td>29 (19-42)</td>
</tr>
<tr>
<td>Married (% yes)</td>
<td>35.0</td>
<td>27.1</td>
<td>30.0</td>
</tr>
<tr>
<td>With children (% yes)</td>
<td>23.8</td>
<td>37.7 *</td>
<td>32.6</td>
</tr>
<tr>
<td>Level of education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>15 (11)</td>
<td>9 (4)</td>
<td>24 (6)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>63 (44)</td>
<td>89 (36)</td>
<td>152 (39)</td>
</tr>
<tr>
<td>High</td>
<td>65 (45)</td>
<td>149 (60) *</td>
<td>214 (55)</td>
</tr>
<tr>
<td>Ancestral origin, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indigenous (Dutch)</td>
<td>83 (58)</td>
<td>161 (65)</td>
<td>244 (63)</td>
</tr>
<tr>
<td>Western immigrant</td>
<td>14 (10)</td>
<td>18 (7)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Non-Western immigrant</td>
<td>46 (32)</td>
<td>68 (28)</td>
<td>114 (29)</td>
</tr>
</tbody>
</table>

* Of the 87 invitees who participated with their partner in the carrier screening test(s), fifteen partners also received a personal invitation. So there were 72 couples and 144 individuals participating in the carrier screening test(s). Of them, 143 individuals completed the questionnaire and thus also participated in the survey.

* There were 134 original invitees, forming 128 couples, who participated in the survey only. In 9 couples, only one partner returned the questionnaire.


* Definition of Western and non-Western immigrants as defined by Statistics Netherlands,31 except for Japanese and Indonesian immigrants who were included in the group of non-Western immigrants.

* Statistically significant difference between the participants in the carrier screening test(s) and the participants in the survey only \((p<0.05)\).
Reasons for participation and non-participation

Table 4 presents the most important reasons for participation in the screening. A total of 136 (out of 143) test-participants answered this question. A diversity of reasons for participation were mentioned by the indigenous (Dutch) and Western immigrant participants (n=95). Among the non-Western immigrants (n=41) the two main reasons for participation were “I want to have a healthy child” (26.8%), and “Participation gives me information and/or reassurance” (24.4%). “I want to have a healthy child” was mentioned significantly more often by the non-Western immigrants than by the other participants (p=.011).

Table 4
Main reason for participation in preconceptional CF and/or HbP carrier screening given by participants in the test(s)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Indigenous (Dutch) people and Western immigrants (n=95), n (%)</th>
<th>Non-Western immigrants (n=41), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gives me information / reassurance</td>
<td>15 (15.8)</td>
<td>10 (24.4)</td>
</tr>
<tr>
<td>I want to know if I am a carrier</td>
<td>15 (15.8)</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>I want to have a healthy child</td>
<td>9 (9.5)</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>I want to know the chance of having a child with CF and/or HbPs</td>
<td>12 (12.6)</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Being a carrier couple will influence my reproductive decisions</td>
<td>5 (5.3)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>To avoid having a child with CF and/or HbPs</td>
<td>5 (5.3)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>To help in scientific research</td>
<td>4 (4.2)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>5 (5.3)</td>
<td>6 (14.6)</td>
</tr>
</tbody>
</table>

* This was an open-ended question. Afterwards, the answers were categorized by one of the authors (PL) into eight categories.
* p=.011

Table 5 presents the most important reasons for non-participation in the screening among participants in the survey only. A total of 243 out of the 247 participants in the survey only answered this question (98.4%), and 243, 146 and 54 of them ticked one, two or three reasons, respectively, out of a list of eleven reasons. “I’m too busy” (21%) and “I’m not worried” (15%) were the two most important reasons for non-participation. Compared to the indigenous (Dutch) and Western immigrant participants, non-Western immigrants more frequently answered “I am too busy” (30.8% versus 16.9%) (p<.001), less frequently stated “I think that there is only a low risk that I will have a child with CF and/or HbPs” (1.7% versus 10.7%) (p=.001).
Table 5
Main reason for non-participation in preconceptional CF and/or HbP carrier screening given by participants in the survey only

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of times the reason was chosen, n (%)</th>
<th>Indigenous (Dutch) people and Western immigrants (n=176)</th>
<th>Non-Western immigrants (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of options ticked</td>
<td>326 (100.0)</td>
<td>117 (100.0)</td>
<td></td>
</tr>
<tr>
<td>I’m too busy</td>
<td>55 (16.9)</td>
<td>36 (30.8) **</td>
<td></td>
</tr>
<tr>
<td>I’m not worried</td>
<td>55 (16.9)</td>
<td>12 (10.3)</td>
<td></td>
</tr>
<tr>
<td>The results of the test(s) will not influence my reproductive decisions</td>
<td>40 (12.3)</td>
<td>16 (13.7)</td>
<td></td>
</tr>
<tr>
<td>I don’t think that I am a carrier</td>
<td>39 (12.0)</td>
<td>7 (6.0)</td>
<td></td>
</tr>
<tr>
<td>I think that there is only a low risk that I will have a child with CF and/or HbPs</td>
<td>35 (10.7)</td>
<td>2 (1.7) **</td>
<td></td>
</tr>
<tr>
<td>Participating would frighten me</td>
<td>21 (6.4)</td>
<td>8 (6.8)</td>
<td></td>
</tr>
<tr>
<td>I never heard about these disorders (cystic fibrosis, sickle cell disease and/or thalassemia)</td>
<td>15 (4.6)</td>
<td>8 (6.8)</td>
<td></td>
</tr>
<tr>
<td>I’m afraid that the results will be unfavorable</td>
<td>13 (4.0)</td>
<td>8 (6.8)</td>
<td></td>
</tr>
<tr>
<td>My partner thinks that we should not participate</td>
<td>11 (3.4)</td>
<td>4 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Other reason</td>
<td>42 (12.9)</td>
<td>16 (13.7)</td>
<td></td>
</tr>
</tbody>
</table>

*A total of 243 participants in the survey only answered this question, and 243, 146 and 54 of them ticked one, two or three reasons, respectively, out of a list of eleven reasons. The total number of times a particular reason was chosen is presented.

* p<.05: significant difference between the indigenous (Dutch) people and Western immigrants versus the non-Western immigrant participants.

** p<.005: statistically significant difference between the indigenous (Dutch) people and Western immigrants versus the non-Western immigrant participants.

Should carrier screening be offered to all couples planning a pregnancy?

A positive attitude towards a standard offer of preconceptional CF and HbP carrier screening in the Netherlands to all couples planning a pregnancy was reported by 77.8% (111/143) and 71.1% (175/246) of the test-participants and participants in the survey only, respectively. Moreover, 93.0% versus 53.7% of the test-participants and participants in the survey only, respectively (p<.001) would participate in such a screening if this became a standard offer.

Identifying the risk of being a CF and/or HbP carrier

For those invited by the MHS, a participant’s individual risk of being a CF and/or HbP carrier could be identified, either based on the population register (native country and parental native countries), or on the ancestry-based data from the decisional instrument.

In total, 250 out of 272 test-participants and participants in the survey only who had been invited by the MHS, completed the decisional instrument. Compared to the decisional instrument, the population register would lead to
an incorrect conclusion about the risk of being a CF and/or HbP carrier for 12.5% (9/72; 95% CI 5.9-22.4%) of the non-Western immigrants and for 3.4% (6/178; 95% CI 1.2-7.2%) of the indigenous (Dutch) and Western immigrant participants. For example, the instrument identified nine participants at risk of being a carrier of both disorders, while the population register would have identified them as being at risk for only CF (n=5) or only HbPs(n=4).

Discussion

In this study, an offer of combined ancestry-based preconceptional carrier couple screening for CF and/or HbPs was made to approximately 10,000 individuals, aged 20-35 years, in a multi-ethnic population in Amsterdam, the Netherlands. The target population was estimated to be 33.3% (95% CI 30.4-36.1%) of the invitees, which was higher than the 20.2% (95% CI 16.8-23.6) reported in the Henneman et al. study, in which CF carrier screening was offered in the mid-Western region of the Netherlands. This difference may be due to sociodemographic differences between the multi-ethnic, lower socio-economic population of the various districts in Amsterdam, and the mainly indigenous and more highly educated people in the mid-Western region of the Netherlands.

Participation

In the present study, only 2.8% of the target population participated in the testing. At the one side, this result is in accordance with other studies on preconceptional CF carrier screening in which a low uptake was reported. On the other side, the uptake in the present study is much lower than the uptake of 25% reported by Henneman et al. In our study 50-60% of the invitees were of non-Western origin, which could contribute to this difference, because in other screening studies a lower uptake among ethnic minority groups was reported, and the uptake among non-Western immigrants in our study was lower too.

However, the uptake found in the present study is in contrast with the positive attitude towards participation in the screening which was present among both the test-participants and the participants in the survey only: 77% and 71% of the test-participants and participants in the survey only, respectively, had a positive attitude towards this screening as a standard offer, and 93% and 54%, respectively, also stated that they would participate if it became a standard offer. These results are similar to previous studies in which positive attitudes towards preconceptional carrier screening were reported.
ed. For example, in a Dutch survey among 303 recently married couples, 73% had a positive attitude towards preconceptional CF carrier screening and 56% indicated that they would participate if the screening was offered routinely.\textsuperscript{41} With regard to HbP carrier screening, Giordano et al. also reported a generally positive attitude among 328 immigrants in the Netherlands toward prenatal screening and selective abortion in the case of an HbP-affected child.\textsuperscript{42} However, our study focused on preconceptional screening, and not on prenatal screening.

**Informed decision-making**

Achieving a high uptake is not the primary goal of a reproductive screening program; its aim is to enable couples to make informed reproductive decisions.\textsuperscript{43} The decision to participate or not in preconceptional ancestry-based CF and/or HbPs carrier couple screening, should be based on an informed choice, which is defined by Marteau et al. as ‘a choice that is based on relevant knowledge, consistent with the decision maker’s values and behaviorally implemented’.\textsuperscript{44} In other words, all people from the target population should be informed to gain relevant knowledge regarding the testing; and those with positive attitudes towards the testing should participate, and those with negative attitudes should not.

In the present study, there was a large difference in the proportion of study-participants who had a positive attitude towards the screening (54-93%) and the proportion who actually participated (3%). Therefore, among a large proportion of eligible invitees, it seemed that informed decision making was not achieved. The most important reason for their non-participation in the screening, was "I'm too busy", suggesting that practical reasons played an important role in the decision not to have the test(s) done, and not a negative attitude. Some of them stated that the results would not influence their reproductive behavior, suggesting that their decision not to participate was an informed choice. The results among the participants in the telephone survey also suggest that they generally valued the screening as positive. Unfortunately, we were not able to determine whether or not the majority of non-respondents had made informed decision not to participate in the screening, as they did not complete questionnaires.

In general, both participants and non-participants in the testing had a positive attitude towards participation in preconceptional ancestry-based carrier screening, and practical barriers in terms of time and effort needed for participation seemed an important reason for non-participation in the testing (Lakeman et al. unpublished data).
Barriers in informed decision-making

Several factors related to the study design could have resulted in a lower uptake and, as such, have resulted in limited informed decision-making in the present study. There was a short time period of only one month for making an appointment, and individual visits to the GP were not allowed. People might also have declined the offer because they were not interested in returning the reply form and/or completing the questionnaires. Moreover, in approach B it was possible that the GP of both partners of a couple was not participating in the study. Making a phone call to the researcher and having an appointment with an unfamiliar GP might have been a barrier. Furthermore, all the written material was only available in Dutch. Although the majority of the invitees of non-Western ancestry belonged to the second or third generation of immigrants in the Netherlands,33 and were expected to be able to read and write Dutch, a limited command of the Dutch language could still have contributed to the under-representation of non-Western immigrant people among the test-participants. It is not plausible that feelings of stigmatization or discrimination have resulted in a lower uptake among non-Western invitees, as none of the survey-participants expressed any feelings of this kind, nor did we receive any phone calls in which this kind of feelings were expressed.

People with a lower level of education were also under-represented among the test-participants (10%), a finding which is compatible with the possibility that making an offer in writing disadvantages those with less education.45 Although the information leaflet and the decisional instrument had been validated in a multi-ethnic population with a low level of education,28 these observations may indicate that ethnic minority groups and people with a lower level of education experience more barriers in participating in CF and/or HbPs carrier screening than the more highly educated indigenous people and Western immigrants.

Recommendations and challenges

The screening uptake in the present study of 2.8% might be interpreted as an indication that there was low interest among the invitees in this multi-ethnic population in preconceptional CF and/or HbPs carrier couple screening in general. Poor acceptance of general population screening has lead to the suggestion that such screening should not be implemented.46 However, as stated above, the low uptake in the present study first of all reflected people’s limited opportunities, and not just their preferences. The above-mentioned barriers may explain a substantial part of the gap between the general positive attitude towards the screening and the low actual uptake in the testing. A decision in favour of or
against implementation of this kind of preconceptional carrier screening, therefore, should not solely be based on the results about uptake in the present study.

As the majority of the study-participants had a positive attitude towards a standard offer of preconceptional ancestry-based CF and HbPs carrier screening and would participate in such a screening themselves, at this moment a more extensive pilot study is warranted. Couples who are interested in the screening should have access to it without investing too much time and effort. In such a study it should be investigated how thresholds could be lowered. Translations of the information leaflet and decisional instrument should be available; there should be more time for making an appointment, and test-participation should not be conditional on survey-participation. It should be pursued to invite both partners in a couple, because in our study a significantly higher percentage of couples in which both of the partners received an invitation actually had the test(s), compared to the couples in which only one partner was invited.

We found a higher uptake among those invited by the GP, which was in accordance with Tacken et al. who concluded that invitations and reminders sent by the GP enhanced the uptake of cervical cancer screening in the Netherlands. Henneman et al., however, reported no difference in uptake if the GP or the MHS was sending the invitations. One advantage of GPs sending the invitations is the possibility to exclude individuals for whom the invitation is considered to be inappropriate, or who are not or no longer (expected to be) contemplating a pregnancy. However, in a study carried out by Elsinga et al., in which preconceptional counseling was offered by the GP, who excluded women with adverse social circumstances, 33% of the pregnancies occurred in the group of women who had been excluded. Poppelaars et al. also reported that the target population preferred receiving an invitation from their own GP. However, they also found that 40% of the GPs did not consider the GP as the most appropriate person to provide such counseling. In our study, only 19% (23/119) of all the GPs who were invited were willing to participate in this screening study.

In deciding whether and where a standard offer of preconceptional CF and HbPs carrier screening should be implemented, the pros and cons of various approaches to carrier screening should be considered, including those in which the GPs or the MHS send the invitations. Other approaches include carrier detection in high schools, prenatal carrier screening, active cascade-testing, using the moment of contraceptive consultation, or the Internet to provide information and offer the carrier test(s).

Recently, the Health Council of the Netherlands recommended the implementation of a standard offer of preconception care, and initiatives are
being taken to develop a health care setting in which preconception care can be embedded. This care should consist of risk assessment, health promotion, and interventions to reduce adverse pregnancy outcomes. We recommend that the implementation of ancestry-based CF and HbP carrier screening in (future) preconception care should be considered, because it might fit well into this setting and reduce the time and effort that are needed to participate in the screening test(s) for couples who are interested. In addition, when ancestry-based preconceptional carrier screening for CF and HbPs is implemented, the ancestry-based decisional instrument should be used, because it proved to be a better tool with which to identify the risk of being a CF and/or HbPs carrier than the data that were obtained from the population register.

Moreover, irrespective of the setting in which the screening is implemented, it is necessary to educate GPs, midwives and gynecologists, as well as the target population, with regard to the screening procedure and inheritance patterns, and access to genetic counseling by expert geneticists should remain guaranteed.

Acknowledgements

We thank all survey-participants, the general practitioners and their personnel, the Municipal Health Service of Amsterdam, the Registration Committee of the Municipality of Amsterdam, the personnel of the Laboratory of Hemoglobinopathies and Red Cell Diagnostics at the Department of Human and Clinical Genetics of the Leiden University Medical Center, the personnel of the Department of Red Cell Diagnostics of Sanquin in Amsterdam, and the personnel of the Molecular Genetic Diagnostic Laboratory of the VU University Medical Center in Amsterdam for their co-operation. The study was funded by grant no. 2100.0080 from the Netherlands Organization for Health Research and Development (ZonMw). No conflicts of interest are present.

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Preconceptional CF and HbPs carrier couple screening
Preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies: determinants of the intention to participate or not to participate

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Lidewij Henneman
Pieter D Bezemer
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Leo P ten Kate

Submitted
Abstract

The present paper explores the determinants of the intention to participate or not in preconceptional ancestry-based carrier couple screening for cystic fibrosis (CF) and hemoglobinopathies (HbPs). Carrier-testing was offered to 9,453 individuals from a multi-ethnic population. Eligible for test-participation were invitees who were planning a pregnancy with their partner, and agreed to complete a questionnaire. The questionnaire, based on the Theory of Planned Behaviour, was completed by 418 survey-participants: 171 who intended to participate in the testing (“offer-acceptors”), and 247 who refrained from test-participation, but agreed to complete the questionnaire (“offer-decliners”). Both offer-acceptors and offer-decliners generally had a positive attitude towards test-participation, and perceived high behavioural control. This applied to Western and non-Western study-participants. Offer-decliners, however, had a less positive attitude, and perceived less control in terms of the time and effort needed for participation, than offer-acceptors. Still, 68% of offer-decliners intended to participate in the future if the screening would be offered routinely. Offer-acceptors more often would draw reproductive consequences from test-results, perceived a higher risk of being a carrier, perceived more benefits and less adverse psychological outcomes. The majority reported no predominant feelings of stigmatisation. A minority thought that there would be discrimination against carriers: among them were significantly more non-Western (23%) than Western participants (10%). Preconceptional ancestry-based CF and HbPs carrier screening was evaluated as positive and desirable among Western and non-Western participants. The effort and time needed for participation was an important reason for declining participation, which might be overcome by facilitating access to the screening.
Introduction

Cystic fibrosis (CF) and hemoglobinopathies (HbPs), including sickle cell disorders and thalassaemia, are serious autosomal recessive disorders. CF is found predominantly among people who originate from Europe, North Africa, Turkey, the Middle East, and the former Soviet Union.\(^1\)\(^2\) HbPs are mainly found in people with ancestors from Africa, the Mediterranean area, the Middle East, parts of the Indian sub-continent and South-East Asia.\(^3\)\(^4\) As a result of the autosomal recessive inheritance pattern, most of these patients are born with no family history of the disorder, and heterozygous carriers are usually unaware of their carrier status. Therefore, couples in which both partners are carriers, generally do not know that they face a risk of 25% in each pregnancy of having an affected child.

Carrier couple screening aims to inform prospective parents about their risks, and enables them to make informed reproductive decisions. If offered preconceptionally, the reproductive options do not solely include prenatal diagnosis followed (or not followed) by termination of the pregnancy or accepting the risk, but also the decision not to have (more) children, adoption, the use of donor sperm or eggs, and pre-implantation genetic diagnosis. In some culture-related marriage practices it could possibly involve adapting the choice of a partner.

In the Netherlands, as in other countries, there has been debate about whether or not preconceptional CF and/or HbPs carrier screening should be introduced and, if so, how, because there is no consultancy setting for general preconception care.\(^5\)\(^8\) Since the risk of being a CF or HbP-carrier depends on ancestry, targeted ancestry-based carrier screening for these disorders has been advised.\(^9\)\(^11\) At the same time doubts about ancestry-based screening have been expressed, based on negative experiences, such as discrimination and stigmatisation, after the implementation of sickle cell screening in the USA in the early 1970s.\(^12\)

The present study is part of a project in which a unique offer of combined ancestry-based preconceptional CF and/or HbPs carrier couple screening was made in a multi-ethnic population in the Netherlands. Such a combined offer could reduce the suggested risk of stigmatisation or discrimination of sub-populations, because almost every couple, irrespective of their ancestry, will be eligible for some kind of carrier screening; for CF, HbPs or both disorders. A validated decisional instrument was used to assess eligibility for CF and/or HbPs carrier screening, based on both partners’ ancestry.\(^13\) In our project the test-uptake among invitees who had a partner and were planning
a pregnancy was 3%, and non-Western immigrants and invitees with a low level of education were under-represented among the respondents (Lakeman et al. unpublished data). The under-representation of non-Western invitees might reflect a difference in attitude or a failure to facilitate informed decisions.\textsuperscript{14,15} The uptake of 3% was not in accordance with the reported uptake of 25% in a previous preconceptional CF carrier couple screening study in the Netherlands.\textsuperscript{6} It was also not in accordance with the findings in this study that the majority of test-participants (78%) and non-participants (71%) favoured a routine offer of preconceptional couple screening (as has been reported previously \textsuperscript{16,17}) and that 93% and 54% of them, respectively, intended to participate in the future if the screening would be offered routinely. These results gave rise to questions about how invitees perceived the offer and what determined their decision to accept or decline participation in the testing.

Factors affecting the decision to accept or decline carrier screening for CF have been reviewed by Chen et al.\textsuperscript{18} Important acceptance factors included: ‘higher perceived benefits’ (e.g. not having an affected child, knowing one’s carrier status), ‘weaker perceptions of barriers’ (e.g. social stigma, psychological harm), and ‘having fewer or no children’. Acceptance factors reported elsewhere were: lower perceived negative consequences of test results,\textsuperscript{17} more knowledge,\textsuperscript{17,19,20} strong perception of the severity of the disease,\textsuperscript{16,18,21} high perceived susceptibility,\textsuperscript{18,22,23} and higher socio-economic status, female gender, and age.\textsuperscript{18} Important factors for declining, reported by Chen et al.\textsuperscript{18} included: perceived barriers to obtain the screening, parity, lack of knowledge, and weaker perceptions of benefits. Other factors for declining mentioned elsewhere were: attitudes towards abortion, perceived severity of carrier status, low perceived susceptibility, and ethnicity.\textsuperscript{14,15,18,20,21,24} Furthermore, Chen et al.\textsuperscript{18} noticed a lack of theoretical frameworks in studies investigating the determinants of participation in carrier screening.

The aim of the present study was to explore the intention to participate in combined ancestry-based preconceptional CF and/or HbPs carrier couple screening in a multi-ethnic population. The Theory of Planned Behaviour (TPB) will be applied (see Figure 1),\textsuperscript{25} as it has proven to offer a useful framework in explaining and predicting behaviour.\textsuperscript{26} According to the TPB, behaviour (here test-participation) is explained by intention, which in turn is explained by attitude, social influence and perceived behavioural control.\textsuperscript{25} The latter is also a direct determinant of behaviour.

The following research questions were addressed: 1) What are the determinants of intention to participate in the screening among those who accepted and those who declined the offer? 2) What determined actual participation
among of those who accepted the offer (i.e. those who intended to participate)?
3) What determined the intention to participate in future screening of this kind, if this became possible, among those who declined the current offer?
4) Do these determinants differ between participants of Western and non-Western origin?

Figure 1
The Theory of Planned Behaviour

Methods

Design
From January to December 2005, 9,453 individuals (20-35 years) in Amsterdam, the Netherlands, including 50-60% non-Western immigrants, received an invitation to participate in preconceptional CF and/or HbPs carrier testing and a questionnaire survey. Invitees with a partner and who were planning a pregnancy were defined as the target population. Participation in the testing was conditional on completing the questionnaire. Invitees who declined the current offer of carrier testing were invited to participate in the survey only. A validated ancestry-based decisional instrument was enclosed to assess the couple’s eligibility for CF and/or HbP test(s), together with an information leaflet and a reply form. All the study materials were only available in the Dutch language. The information leaflet described clinical and genetic aspects of the disorders, the carrier prevalence in different populations according to ancestry, the pros and cons of participation, the test procedure, and the test-sensitivity.
Data from the reply form were used to estimate the proportion of invitees who belonged to the target population, because the invitees were asked to state whether or not they had a partner with whom they were planning a pregnancy. If so, they were also asked whether or not they were willing to participate in the survey and whether or not they also wished to participate in the carrier testing. Thus, data from the reply form were also used to indicate the respondents’ intention to participate or not to participate in the current preconceptional CF and/or HbPs carrier testing. The tests were offered free of charge to the participants in the study. Exclusion criteria for survey and test-participation were pregnancy, inability to read and write Dutch, and a positive family history of CF and/or HbPs, in which case the individual was referred to a clinical genetics centre. The invitees were informed beforehand that participants in the survey only would be asked to complete one questionnaire (see below), and that participants in the testing would be asked to complete three additional questionnaires at different moments during the screening study. Only data from the first questionnaires, completed by both groups, are reported here.

Those who wished to participate in the carrier testing had to visit their GP within one month, together with their partner, for pre-test consultation and subsequent sampling for the test(s). The GP checked the correct use of the decisional instrument as a pre-screening tool to determine eligibility of the couple for the CF and/or HbP test(s). The actual testing in the laboratory did not start before a signed informed consent form had been received. The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam.

**Respondents**

The invitees who returned the reply form are further referred as *respondents* and those who did not as *non-respondents* (see Figure 2). The respondents who belonged to the target population and who stated that they were willing to participate in the survey and the carrier testing are further referred to as *offer-acceptors* (i.e. test-intenders), and respondents who were willing to participate in the survey only, but who declined test-participation are further referred to as *offer-decliners* (i.e. test non-intenders). Finally, not all offer-acceptors actually took part in the test(s); those who did are further referred as *test-participants*, and those who did not as *test-intending non-participants*.

**The survey procedure**

A structured questionnaire was developed to address the research questions. Each partner in a couple was asked to complete the whole questionnaire
without conferring with their partner. The test-participants completed their questionnaires in the GP’s waiting room before the consultation. The offer-decliners received two copies of the questionnaire by mail at home. The test-intending non-participants were contacted by telephone, if possible, or by mail. After reminding them that test-participation was no longer possible because of the limited time-span of the study, they were asked if they were still willing to complete the questionnaire, since they had initially agreed to participate in the survey. Two copies of the questionnaire were then sent to them by mail. In general, if the questionnaires were not returned, a reminder was sent after two weeks and a phone call was made one month later.

Questionnaire
The questionnaire was mainly based on the TPB, in addition of other variables that were expected to explain intention (Table 1). All variables that were included in the questionnaire and investigated among both the offer-acceptors and offer-decliners are presented in Table 1, as well as their corresponding items, and the answer format.

For each scale, factor analysis with direct oblimin rotation was performed to investigate whether items loaded on one or more component(s). Reliability analysis was applied to each scale to determine whether the set of items was homogeneous (Cronbach’s α ≥ .50, see Table 1). Unless stated otherwise, the individual items were measured on a 5-point Likert scale, and were recoded if necessary: a score of 1 indicated a negative / unfavourable score and a score of 5 indicated a positive / favourable score, except for ‘psychological impact’, ‘stigmatisation’ and ‘feelings of eugenics’ (see Table 1). For these three variables a score of 1 indicated a positive / favourable score, representing the absence of negative psychological impact, stigmatisation and feelings of eugenics, and a score of 5 corresponded with a negative / unfavourable score, representing the presence of negative psychological impact, stigmatisation and feelings of eugenics.

Future intention among decliners of current offer
Those who declined the current offer indicated on the reply form that they did not intend to accept the current offer of carrier testing. They were then asked in the questionnaire whether or not they would participate in preconceptional CF and/or HbPs carrier screening in the future if this became possible. An intention-scale representing this ‘future intention’ to participate in the screening was constructed, based on three items: 1) “Would you consider having a carrier test in the future if the preconceptional CF and HbPs carrier screening became a standard offer to all couples planning a pregnancy?”
Table 1
Construct of the questionnaire: scales with corresponding items and single items

<table>
<thead>
<tr>
<th>Variables / scales</th>
<th>Crohnbach’s α</th>
<th>Statements / Items</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Theory of Planned Behaviour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attitude</td>
<td>0.85</td>
<td>I think that participating in carrier screening for cystic fibrosis, sickle cell disease and/or thalassemia before pregnancy, if my partner and I are eligible for screening, is…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… good – bad</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… important – unimportant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… alarming – reassuring (emotional)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… sensible – unwise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… undesirable - desirable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… pleasant - unpleasant (emotional)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… discriminatory – a privilege</td>
</tr>
<tr>
<td></td>
<td></td>
<td>… harmful - beneficial</td>
</tr>
<tr>
<td>Social influence</td>
<td>0.84</td>
<td>- I think that … my partner… thinks that we should participate in the screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- … my family…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- … my friends …</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- … my neighbours…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I am afraid that people will look differently at me if I had a child with CF, sickle cell disease and/or thalassemia</td>
</tr>
<tr>
<td>Perceived behavioural control</td>
<td>0.73</td>
<td>- I am not capable of participating in carrier screening if blood needs to be taken from me with a needle (external control)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I am not capable of participating in carrier screening if I need to wash out my mouth with salt water (external control)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- It costs me too much effort to participate in the carrier screening (internal control)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- It costs me too much time to participate in the carrier screening (internal control)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I am reluctant to participate in the carrier screening (internal control)</td>
</tr>
<tr>
<td>Additional variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived benefits</td>
<td>0.63</td>
<td>- I would want to prevent the birth of a child with CF, sickle cell disease and/or thalassemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I want to get more reassurance about my chance of having a child with CF, sickle cell disease and/or thalassemia</td>
</tr>
<tr>
<td>Reproductive consequences of test-results</td>
<td>0.79</td>
<td>- I am against the abortion of a child with CF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I am against the abortion of a child with sickle cell disease or thalassemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The test-results will not influence my reproductive behaviour</td>
</tr>
<tr>
<td>Severity of the disorders</td>
<td>0.93</td>
<td>- CF is a severe disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Sickle cell disease and thalassemia are severe disorders</td>
</tr>
<tr>
<td>Perceived susceptibility (risk perception)</td>
<td>0.83</td>
<td>- At this moment I am feeling worried about being a carrier of CF sicle cell disease and/or thalassemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- At this moment I am feeling worried about having a child with CF, sickle cell disease and/or thalassemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I think there is a high chance that I am a carrier of CF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I think there is a high chance that I am a carrier of sickle cell disease and/or thalassemia</td>
</tr>
</tbody>
</table>
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Variables / scales</th>
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<td><strong>Additional variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological impact</td>
<td>0.69</td>
<td>- I think that offering these carrier test(s) will cause anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I think that by offering these carrier test(s) people will be burdened with unwanted information</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I think it is annoying that I am expected to think about these carrier test(s) before a pregnancy</td>
</tr>
<tr>
<td>Stigmatisation</td>
<td>0.73</td>
<td>- I would feel less healthy if I was a carrier</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I think people will see me in a different light if I was a carrier</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I think I would be subject to discrimination if I was a carrier</td>
</tr>
<tr>
<td>Feelings of eugenics</td>
<td>0.60</td>
<td>- The carrier tests create too high expectations about the birth of a healthy child</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- I am afraid that the carrier tests will contribute to the development of the perfect human being</td>
</tr>
<tr>
<td>Knowledge about inheritance</td>
<td></td>
<td>- A carrier of CF can also have CF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Yes, I agree / No, I do not agree / I don’t know)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- A carrier of sickle cell disease or thalassemia, can also have these disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Yes, I agree / No, I do not agree / I don’t know)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- It is possible to be a carrier of CF or HbPs when these disorders are not present in your family</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Yes, I agree / No, I do not agree / I don’t know)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- In which situation do parents have a high risk of having a child with CF or HbPs?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(If both partners are carriers / If just one partner is a carrier / I don’t know)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- What is the chance of having a child with CF or HbPs when both partners are carriers?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(100% / 50% / 25% / I don’t know)</td>
</tr>
<tr>
<td><strong>Other questions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familiarity with the disorders with CF?</td>
<td></td>
<td>- Have you ever heard of CF or do you know someone (Yes / No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Have you ever heard of sickle cell disease or thalassemia or do you know someone with (one of) these disorders? (Yes / No)</td>
</tr>
<tr>
<td>Familiarity with carrier tests</td>
<td></td>
<td>- Have you ever heard of a carrier screening test for CF? the (Yes / No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Have you ever heard of a carrier screening test for sickle cell disease or thalassemia? (Yes / No)</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td>- Did your religion influence your decision to participate or not to participate? (Yes / No / I have no religion)</td>
</tr>
</tbody>
</table>

* Attitude was constructed from two components: one with an emotional (two items) and another with an instrumental/cognitive quality (six items).

b Perceived Behavioural Control was constructed from two components: external control (two items) and internal control (three items).

For the other variables measured by means of a scale, the items were loaded on one factor (component) and were constructing one component.
Intention to participate in ancestry-based carrier screening

(Activity format no/ probably not/ not sure / probably / yes); and the two items of the variable ‘perceived benefits’: 2) “I would want to prevent the birth of a child with CF, sickle cell disease and/or thalassemia” and 3) “I want to get more reassurance about my chance of having a child with CF, sickle cell disease and/or thalassemia”. These three all loaded on one factor, and Cronbach’s α was 0.71.

Ancestry

Based on their own and parental native countries we distinguished participants of: 1) Western origin, who have their ancestry in Europe (including the Netherlands), North-America, and Australia, and who are mainly eligible for CF carrier screening, and 2) non-Western origin, including people from Turkey, Surinam, Morocco and the Netherlands Antilles, who form the four largest immigrant groups in the Netherlands, and who are eligible for HbPs carrier screening. Couples from Turkey and Morocco were eligible for both the CF and HbPs carrier screening tests. These categories Western and non-Western origin corresponded to the way Statistics Netherlands classified ethnic groups. The validated decisional instrument developed for this study would categorize third and higher generation descendants of migrants differently.

Data-analysis

Both partners in a couple were treated as independent subjects, because earlier research showed that individual partners provide different information. Independent sample T-tests were used to compare the mean scores between groups. Offer-acceptors were compared with offer-decliners, test-participants with test-intending non-participants, and non-Western with Western survey-participants. In addition, for each variable we calculated the proportion of survey-participants who had a score below and /or above 3 (the neutral point). The Chi-square test was used for the statistical comparison of proportions. All analyses were performed in SPSS 14.0 for Windows, and p-values below 0.05 were considered to be significant.

Among all participants in the survey, hierarchical linear regression analysis was applied stepwise to investigate which variables determined the intention to participate in the current preconceptional carrier testing. The predictive power of the TPB determinants (step 1), the other variables mentioned in Table 1 (step 2), and the sociodemographic variables (step 3) was investigated. Additionally, among the offer-decliners, hierarchical linear regression analysis was performed stepwise to investigate which variables determined their future intention to participate in the testing. Finally, among the offer-acceptors, hierarchical linear regression analysis was performed stepwise to investigate which variables determined actual test-participation.
Results

Response

Figure 2 presents a flow-chart of the response to the original invitation, as well as the proportion of respondents who belonged to the target population (i.e. invitees who had a partner and who were planning a pregnancy) and the number of couples included in the survey. Fourteen percent (1365/9453) of the invitees returned the reply form, 490 of whom belonged to the target population (36%). There were 166 offer-acceptors, representing 147 couples (in 19 couples both partners had received the invitation). Of these 147 couples, 72 participated in the testing. We were able to send questionnaires to 62 of the remaining 79 test-intending non-participants. Of the 324 respondents who declined the offer, 134 (representing 128 couples) were willing to participate in the survey only.

A total of 262 couples (72+62+128, Figure 2) were included in the survey. All couples received two identical copies of the questionnaire (one for the original invitee and one for the partner), 80% (418/524) of which were returned: 99% (143/144) of the test-participants, 23% (28/124) of the test-intending non-participants, and 96% (247/256) of the offer-decliners returned the questionnaires.

Figure 2
Response to the offer of preconceptional CF and/or HbPs carrier screening
Intention to participate in ancestry-based carrier screening

Table 2 presents the sociodemographic characteristics of these 418 survey-participants. As there were no significant differences in characteristics between the 143 test-participants and the 28 test-intending non-participants, the data of all offer-acceptors are combined and presented in one column. Offer-decliners more often had children and a higher level of education than offer-acceptors (see Table 2).

<table>
<thead>
<tr>
<th></th>
<th>Offer-acceptors</th>
<th>Offer-decliners</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(test-intenders)</td>
<td>(test non-intenders)</td>
</tr>
<tr>
<td>Number</td>
<td>171</td>
<td>247</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>85 (50)</td>
<td>120 (49)</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>32 (23-47)</td>
<td>32 (22-56)</td>
</tr>
<tr>
<td>Women</td>
<td>30 (19-44)</td>
<td>29 (20-42)</td>
</tr>
<tr>
<td>Married, n (%) yes</td>
<td>57 (33)</td>
<td>67 (27)</td>
</tr>
<tr>
<td>With children, n (%) yes</td>
<td>40 (23)</td>
<td>93 (38) **</td>
</tr>
<tr>
<td>Level of education, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>17 (10)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>75 (44)</td>
<td>89 (36)</td>
</tr>
<tr>
<td>High</td>
<td>79 (46)</td>
<td>149 (60) *</td>
</tr>
<tr>
<td>Ancestry, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western origin</td>
<td>117 (68)</td>
<td>179 (72)</td>
</tr>
<tr>
<td>Non-Western immigrant</td>
<td>54 (32)</td>
<td>68 (28)</td>
</tr>
</tbody>
</table>

There were no significant differences in these characteristics between the 143 test-participants and the 28 test-intending non-participants. Therefore the data of the offer-acceptors are presented in one column.


*p<.01; **p<.001

Mean scores for the variables that determine intention

The mean scores for the determinants of intention to participate in the current preconceptional carrier testing among both the offer-acceptors and offer-decliners corresponded with positive / favourable scores (see Table 3).

The survey-participants, acceptors and decliners, generally had a positive attitude towards participation (M= 3.8), they perceived a low level of social influence (M= 2.5), and a high level of behavioural control (M= 4.0). They generally perceived benefits (M= 3.9) from test-participation, and would draw reproductive consequences from the test-results (M= 3.2), but perceived low susceptibility of being a carrier or having an affected child (M= 1.8). The majority did not expect a negative impact of the offer (M= 2.2), or feel that it would lead to stigmatisation or discrimination (M= 2.1) or feelings of eugenics (M= 2.5). The disorders were perceived as serious (M= 4.4). The mean knowledge score was 2.6, but there was a large variation in the sum-scores: 20% (82/418) had the minimum score of 0; 51% (212/418) had a score of 3 or higher, and 25% (103/418) had the maximum score of 5.
### Table 3
Mean scores and proportion of participants in the survey who had a score above or below 3 (the neutral point) for determinants of the intention to participate or not to participate in the screening

<table>
<thead>
<tr>
<th>Variables/scales</th>
<th>All (n=418) Mean</th>
<th>Offer-acceptors (n=171) Mean</th>
<th>Offer-decliners (n=247) Mean</th>
<th>n (% ≥ 3)</th>
<th>n (% ≥ 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Theory of Planned Behaviour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Attitude</td>
<td>3.8</td>
<td>4.1</td>
<td>3.5 ***</td>
<td>206 (83)***</td>
<td>168 (98)</td>
</tr>
<tr>
<td>- Social influence</td>
<td>2.5</td>
<td>3.1</td>
<td>2.2 ***</td>
<td>42 (17)***</td>
<td>83 (49)</td>
</tr>
<tr>
<td>- Perceived behavioural control</td>
<td>4.2</td>
<td>4.5</td>
<td>4.0 ***</td>
<td>227 (92)***</td>
<td>165 (96)</td>
</tr>
<tr>
<td><strong>Other variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Perceived benefits</td>
<td>3.9</td>
<td>4.3</td>
<td>3.6 ***</td>
<td>198 (80)***</td>
<td>158 (92)</td>
</tr>
<tr>
<td>- Perceived consequences of test-results</td>
<td>3.2</td>
<td>3.4</td>
<td>3.1 ***</td>
<td>158 (64)***</td>
<td>132 (77)</td>
</tr>
<tr>
<td>- Severity of disorders</td>
<td>4.4</td>
<td>4.3</td>
<td>4.4</td>
<td>239 (97) *</td>
<td>158 (92)</td>
</tr>
<tr>
<td>- Perceived susceptibility</td>
<td>1.8</td>
<td>2.0</td>
<td>1.7 ***</td>
<td>42 (17)</td>
<td>32 (19)</td>
</tr>
<tr>
<td>- Knowledge about inheritance</td>
<td>2.6</td>
<td>2.5</td>
<td>2.6</td>
<td>125 (51)</td>
<td>87 (51)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n (%≤ 3)</th>
<th>n (%≤ 3)</th>
<th>n (%≤ 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Impact of the offer</td>
<td>2.2</td>
<td>1.9</td>
<td>2.4 ***</td>
</tr>
<tr>
<td>- Stigmatisation</td>
<td>2.1</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>- Feeling of eugenics</td>
<td>2.5</td>
<td>2.2</td>
<td>2.6*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n (% yes)</th>
<th>n (% yes)</th>
<th>n (% yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Familiarity with disorders</td>
<td>241 (58)</td>
<td>94 (55)</td>
<td>147 (60)</td>
</tr>
<tr>
<td>- Familiarity with carrier test(s)</td>
<td>64 (15)</td>
<td>21 (12)</td>
<td>43 (17)</td>
</tr>
<tr>
<td>- Religion</td>
<td>16 (4)</td>
<td>7 (4)</td>
<td>9 (4)</td>
</tr>
</tbody>
</table>

*Mean scores were based on a 5-point Likert scale. Except for ‘impact of the offer’, ‘stigmatisation’, and ‘feelings of eugenics’, (1) represents a negative/unfavourable score and (5) a positive/favourable score.

**Knowledge about inheritance was calculated as a sum-score, with a minimum of 0 and a maximum of 5.

*p<.05; **p<.01; *** p<.001. Offer-acceptors were compared to offer-decliners on mean scores and on proportion of people with a score of 3 or above.

---

### Differences between offer-acceptors and offer-decliners

In general, offer-decliners, although positive, had less positive / favourable mean scores on the above-mentioned variables than offer-acceptors (see Table 3). Offer-decliners had a less positive attitude towards participation in the current carrier testing than offer-acceptors, mainly due to their negative score on the item ‘pleasant/unpleasant’ (mean score 2.86), and they perceived less behavioural control, because they more often stated that participation would cost them too much ‘effort’ and ‘time’. The slightly positive mean score for social influence among the offer-acceptors was mainly due to the social influence they experienced from their partner (mean score on this single statement was 3.8). Offer-acceptors perceived more benefits of participation and more consequences of the test-results than offer-decliners. However, four offer-acceptors who had a
negative score (below 3) for these variables did participate in the testing. Their partners had a positive score for these variables. Furthermore, offer-acceptors perceived a lower psychological impact of the offer and feelings of eugenics, and offer-decliners perceived themselves less susceptible to be a carrier than the offer-acceptors. The majority of the survey-participants (86%; n = 359) reported no feelings of stigmatisation (score ≤ 3), with no difference between offer-acceptors and offer-decliners.

**Explaining intention to participate in the screening**

Among all survey-participants, whether they accepted or declined the offer, 29% of the variance in intention to participate in the current preconceptional CF and/or HbPs carrier testing, as a results of stepwise hierarchical linear regression, was explained by ‘attitude’ (19%), ‘perceived behavioural control’ (4%), and ‘social influence’ (7%) in the first step (see Table 4a). Including ‘perceived severity of the disorders’, ‘perceived benefits’ and ‘perceived feelings of eugenics’ in the second step, explained another 3.3% of the variance. None of the sociodemographic variables in the third step explained any additional variance in intention. The total predictive value of the equation (steps 1-3) was 33% (p<.001).

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>R² change</th>
<th>β1</th>
<th>β2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Attitude</td>
<td>.187</td>
<td>.24 ***</td>
<td>.15 **</td>
</tr>
<tr>
<td></td>
<td>Perceived behavioural control</td>
<td>.037</td>
<td>.21 ***</td>
<td>.23 ***</td>
</tr>
<tr>
<td></td>
<td>Social influence</td>
<td>.069</td>
<td>.31 ***</td>
<td>.29 ***</td>
</tr>
<tr>
<td>2.</td>
<td>Perceived severity of disease</td>
<td>.014</td>
<td>-.16 ***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perceived benefits</td>
<td>.011</td>
<td>.12 *</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perceived feelings of eugenics</td>
<td>.008</td>
<td>-.10 *</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>R²</td>
<td>.29</td>
<td>.33 ***</td>
<td></td>
</tr>
<tr>
<td>ΔR²</td>
<td></td>
<td></td>
<td>.4 *</td>
<td></td>
</tr>
</tbody>
</table>

N=418. Variables are explained in Tables 1 and 2.

* None of the sociodemographic variables in the third step explained any additional variance in intention.

**Differences between test-participants and test-intending non-participants**

As stated above, not all offer-acceptors actually took part in the test(s) (see Figure 2). The test-participants (n=143) perceived more behavioural control over participation in the current carrier screening, compared to the test-intending non-participants who completed the questionnaire (n=28): mean score 4.6 versus...
4.3 (p=.024), which was mainly due to the fact that the latter more often stated that participation would cost them too much effort and time. Furthermore, test-participants were less familiar with the tests: 9% (13/143) versus 30% (8/27) (p<.01); and they were also younger: mean age 30.5 versus 32.8 years (p=.026).

**Explaining actual test-participation among offer-acceptors**
In the regression analysis the determinants of actual test-participation among the 171 offer-acceptors were: less familiarity with the carrier test(s) and younger age, which together had a predictive power of 31% (p<.001) (data not shown).

**Future intention among decliners of the current offer**
The majority of offer-decliners (n = 247) had a positive intention to participate in the future in a preconceptional CF and/or HbPs carrier screening programme if this became possible (M = 3.5); 68% (167/247) had a positive score (score > 3) on the future intention scale. Offer-decliners who did not have children more often had a positive future intention than those who already had children: 74% (114/154) versus 57% (53/93) (p = .004). The offer-decliners who were intending to participate in this kind of screening in the future if it became possible (n = 167; score > 3) had a significantly more positive attitude towards participation in the current screening (M = 3.7 versus 3.2 (p < .001)); they perceived significantly more social influence (M = 2.3 versus 1.8 (p < .001)); perceived more benefits from the screening: (M = 4.1 versus 2.5 (p < .001)); would more often draw consequences from the test-results: (M = 3.3 versus 2.6 (p < .001)); perceived less negative psychological impact: (M = 2.3 versus 2.7 (p = .004)); perceived less negative feelings of eugenics: (M = 2.5 versus 2.9 (p = .005)), and had a lower score for knowledge: mean scores 2.39 versus 3.03 (p = .012), compared to those who were not intending to participate in such a screening if it became possible in the future (n = 80; score ≤ 3). Offer-decliners perceived a low risk of being a carrier (M = 1.7), with no difference between those having a positive and negative intention to participate in the future in this kind of screening. However, those offer-decliners who had a negative future intention and already had one or more children, perceived a significantly lower susceptibility than those offer-decliners who had with a negative future intention, but who had no children: M = 1.5 versus 1.9 (p =.02).

**Explaining intention to participate in the future**
Among the offer-decliners, the TPB determinants explained 36% of the variance in intention to participate in future preconceptional CF and/or HbPs carrier screening if this became possible (see Table 4b) in the first step of the hierarchical linear regression analysis. Attitude was again the most impor-
tant explanatory factor, explaining 30% of the variance (p < .001), followed by 'perceived behavioural control' (4.0%) and 'social influence' (2.5%) in the first step. Including 'perceived test consequences' and 'knowledge about inheritance' explained another 10% of the variance in the second step. 'Ancestry' and 'having children', explained another 4% in the third step of the hierarchical regression analysis, resulting in a total predictive value of the equation (steps 1-3) of 50% (p < .01).

Table 4b
Regression analysis: determinants of intention to participate in the future in preconceptional CF and/or HbPs carrier screening among decliners of the current offer

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>R² change</th>
<th>β1</th>
<th>β2</th>
<th>β3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Attitude</td>
<td>.296</td>
<td>.53***</td>
<td>.46**</td>
<td>.45***</td>
</tr>
<tr>
<td></td>
<td>Perceived behavioural control</td>
<td>.04</td>
<td>-.18**</td>
<td>-.16**</td>
<td>-.11*</td>
</tr>
<tr>
<td></td>
<td>Social influence</td>
<td>.025</td>
<td>.17*</td>
<td>.17**</td>
<td>.12*</td>
</tr>
<tr>
<td>2.</td>
<td>Perceived test consequences</td>
<td>.082</td>
<td>.31***</td>
<td>.32***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Knowledge about inheritance</td>
<td>.018</td>
<td>-.14**</td>
<td>-.12*</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Ancestry</td>
<td>.019</td>
<td></td>
<td>.19***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Having children or not</td>
<td>.021</td>
<td></td>
<td>.15**</td>
<td></td>
</tr>
</tbody>
</table>

R² | .36  | .46*** | .50** |
ΔR² | .10** | .04** |

N=247. Variables are explained in Tables 1 and 2. *** p≤0.001; ** 0.001<p≤0.01; * 0.01<p≤0.05

Differences between Western and non-Western participants

There was no statistically significant difference in ancestry among the offer-acceptors (test-participants and test-intending non-participants) and offer-decliners: 32% (54/171) and 28% (68/247) were of non-Western origin, respectively. Table 5 presents the mean scores for the variables for Western and non-Western survey-participants, irrespective of their intention to participate or not to participate in the current screening. Compared to the Western survey-participants, the non-Western participants had less positive or less favourable scores, except for attitude towards participation in the screening and level of perceived benefits, for which there were no significant differences. The non-Western survey-participants had a higher score for stigmatisation, representing a less favourable score. This was due to the fact that non-Western participants more often expected that people would see them in a different light and that they would be the subject of discrimination if they turned out to be a carrier (score > 3); 23% (28/122) versus 10% (31/296) (p = .001).

Non-Western people who declined the offer compared to Western offer-decliners had a significantly higher mean score on the future intention scale: M = 3.8 versus 3.4 (p = .011), and 75% (51/68) and 65% (116/179), respectively, intended to participate in future screening if this became possible (p = .08).
Table 5
Mean scores for determinants of intention to participate or not to participate in the current screening among Western and non-Western participants in the survey

<table>
<thead>
<tr>
<th>Variables/scales *</th>
<th>Western origin (n=296)</th>
<th>Non-Western origin (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Theory of Planned Behaviour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Attitude</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>- Social influence</td>
<td>2.3</td>
<td>3.0 ***</td>
</tr>
<tr>
<td>- Perceived behavioural control</td>
<td>4.4</td>
<td>3.9 ***</td>
</tr>
<tr>
<td><strong>Other variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Perceived benefits</td>
<td>3.8</td>
<td>4.0</td>
</tr>
<tr>
<td>- Perceived consequences of test-results</td>
<td>3.3</td>
<td>2.9 ***</td>
</tr>
<tr>
<td>- Severity of disorders</td>
<td>4.5</td>
<td>4.0 ***</td>
</tr>
<tr>
<td>- Perceived susceptibility</td>
<td>1.6</td>
<td>2.2 ***</td>
</tr>
<tr>
<td>- Knowledge about inheritance b</td>
<td>2.9</td>
<td>1.7</td>
</tr>
<tr>
<td>- Impact of the offer</td>
<td>2.1</td>
<td>2.4 *</td>
</tr>
<tr>
<td>- Stigmatization</td>
<td>2.1</td>
<td>2.3 **</td>
</tr>
<tr>
<td>- Feeling of eugenics</td>
<td>2.3</td>
<td>2.9 ***</td>
</tr>
<tr>
<td><strong>n (% yes)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Familiarity with disorders</td>
<td>182 (61)</td>
<td>58 (48) *</td>
</tr>
<tr>
<td>- Familiarity with carrier test(s)</td>
<td>49 (17)</td>
<td>15 (12)</td>
</tr>
<tr>
<td>- Religion</td>
<td>9 (3)</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

a Mean scores were based on a 5-point Likert scale. Except for ‘impact of the offer’, ‘stigmatization’, and ‘feelings of eugenics’, (1) represents a negative or unfavourable and (5) a positive or favourable score.
b Knowledge on inheritance was calculated as a sum score, with minimum of 0 and maximum of 5.
* p<.05; ** p<.01; *** p<.001. Western participants in the survey were compared to non-Western participants.

Discussion

Intention and its determinants

In general, we found that most of the survey-participants had positive / favourable mean scores for the determinants associated with intention to participate in the current screening, implying that the large majority of both those who accepted and those who declined the offer were in favour of participation in preconceptional CF and HbPs carrier screening. This conclusion was further supported by the fact that the majority (68%) of the decliners of the current offer had a positive intention to participate in future preconceptional CF and/or HbPs carrier screening if it became possible.

Most offer-acceptors and decliners had a positive attitude towards participation in the current carrier testing, and perceived a high feeling of personal control over their behaviour (participation in carrier testing). However, the offer-decliners were significantly less positive with regard to these issues than the offer-acceptors. They more often perceived testing as unpleasant, and more often stated that participation would cost them too much effort and time. In addition, the test-intending non-participants (i.e. those who accepted the offer, but eventually did not participate in the testing) who completed the ques-
tionnaire also more often stated that participation would cost them too much effort and time. This finding is in accordance with the model of the Theory of Planned Behaviour (TPB) in which ‘perceived behavioural control’ in itself also determines behaviour (see Figure 1). In the present study the TPB, which has already been used successfully in cervical cancer and cholesterol screening studies, was found to offer a useful framework for exploring the determinants of participation in preconceptional CF and/or HbPs carrier couple screening. The TPB determinants explained a considerable amount of the total variance: a) in the intention to participate in the current carrier testing (29%), and b) in the intention to participate in the future in such a screening programme (36%) among the decliners of the current offer.

Compared to the findings of previous (preconceptional) carrier screening studies, no major differences were found in the determinants that were associated with accepting or declining the current offer of carrier screening (see Table 4a). Factors influencing acceptance in the present study were: a more positive attitude, perceiving more behavioural control, perceiving some social influence, and perceiving more benefits. The disorders were perceived as severe. A strong perception of severity was found to be a declining factor in the present study, while there was no significant difference between offer-acceptors and offer-decliners. Previously, a strong perception of severity has been described not only as a declining factor, but also as a factor for acceptance, which poses questions about its value as a determinant of intention to participate. Very few of the offer-acceptors as offer-decliners perceived any feelings of eugenics, but offer-decliners perceived more feelings of eugenics, which in the present study appeared to be a small declining factor. Furthermore, although there was a large variation, the survey-participants generally had a low mean level of knowledge about inheritance, which has previously been reported as a reason for declining. Fear for needles appeared to be the most important reason for declining to participate in a Tay-Sachs screening programme among school-aged Ashkenazi Jews, but it was of no importance in our study.

Of the offer-acceptors, 8% stated that they perceived limited benefits from participation, and 23% reported that they would draw no reproductive consequences from the test-results, a finding also reported by Poppelaars et al. The fact that they nevertheless accepted the offer of screening might be due to social pressure from the partner, because offer-acceptors did perceive more social influence from their partners in the present study, and/or it might be just because they wanted to know their carrier status, as reported by Ahmed et al.

Decliners of the current offer of screening, who had a negative intention to participate in the future in this kind of screening too, in general would
draw no consequences or less consequences from the test-results. Their attitudes towards abortion and the fact that the test-results would not influence their reproductive behaviour might have been their reason for declining.\textsuperscript{19} In addition, they more often already had children. Having children had previously also been found to be a reason to decline participation in CF carrier screening.\textsuperscript{18;22;33;34} However, the offer-decliners in the present study had not regarded their family as complete, because they had stated on the reply form that they were planning another pregnancy. Perhaps people who already have unaffected offspring are less inclined to perceive their future children at risk for CF and/or HbPs.\textsuperscript{33} In the present study the offer-decliners who had no intention to participate in the future, and who already had children, did indeed perceive less susceptibility to being a carrier than those who had no children.

Feelings of stigmatisation or discrimination have been mentioned and feared as undesirable side-effects of genetic screening.\textsuperscript{10;35} However, in the present study, no predominant feelings of stigmatisation or discrimination were reported, and the absence of such feelings has been reported as a reason for acceptance in previous studies.\textsuperscript{17;18}

**Differences between Western and non-Western participants**

More Western than non-Western invitees participated in the survey: 71% versus 29% respectively, with no difference between offer-acceptors and offer-decliners. Among the invitees, 50-60% were of non-Western origin.

Both Western and non-Western participants in the survey had a positive attitude towards participation in the screening, but Western participants perceived a higher level of behavioural control. The lower uptake in the survey and the subsequent lower participation in the screening among the non-Western invitees might therefore not (only) be attributed to negative attitudes towards the testing in itself.\textsuperscript{15} A general failure to facilitate informed choices among ethnic minority groups, as suggested by Dormandy et al.,\textsuperscript{14} may have resulted in a lower uptake among non-Western immigrants as well. The fact that all the written study material was only available in Dutch, could have resulted in hesitations or limited opportunities to participate in the survey and subsequent testing among non-Western invitees who would have been interested in testing, but who did not respond because of their limited command of the Dutch language.

Although, in general, offer-acceptors and offer-decliners perceived low impact barriers with regard to ‘stigmatisation’ and ‘eugenics’, non-Western survey-participants had more concerns, which might also have been present among the non-respondent non-Western immigrant invitees, resulting in their non-response.
The non-Western immigrants less often answered that they would draw consequences from the test-results. This finding was in accordance with the above-mentioned Ahmed et al. study, in which participants in prenatal β-thalassemia screening mostly opted for prenatal diagnosis, because they just ‘wanted to know’ and not because they would have wanted to prevent the birth of a child with the disorder by opting for termination of the pregnancy. However, it has been demonstrated that pregnancy termination was accepted by a major proportion of non-Western populations as an option in prenatal screening for HbPs.

**Limitations**

This study has some limitations, one of which is the limited response: of the invitees, 33% of whom were estimated to belong to the target population, more than 85% did not return the reply form. We have no information about these non-respondents as they did not complete questionnaires. However, in a telephone survey among a sample of non-respondents (n = 201), there was no difference in the proportion of invitees who belonged to the target population between the respondents and non-respondents (data not shown).

Furthermore, of those who originally intended, but eventually declined test-participation, only a small proportion completed the questionnaires (23%). The results are therefore based on 418 invitees who were willing to participate in the survey, and thus might not be generalizable to the entire target population or to other parts of the Netherlands, other countries, other cultures and/or other religions.

There were also practical limitations related to the study design. Although the intention was positive, the limited period of time that was available for making an appointment with the GP, the fact that the partner also had to be present at this GP consultation, and the fact that test-participation was not possible without survey-participation, might all have resulted in non-participation in the testing. Furthermore, the written study material was only available in Dutch.

**Conclusion and implications**

In the present study, the offer of combined ancestry-based preconceptional CF and/or HbPs carrier couple screening was, in general, valued as positive and desirable among people of Western and non-Western origin, and among those who accepted and those who declined the current offer of carrier testing. A large proportion of those who declined to participate in the current testing intended to participate in the future if it became possible. The amount of effort and time needed for participation was an important reason for declining actual test-participation, and the fact that test-participation was conditional on survey-
participation must also have resulted in a lower uptake.

The results of the present study are similar to the results reported in previous studies of factors influencing decisions to accept or decline preconceptional carrier screening in and outside the Netherlands. The results of the present study contribute to the identification of factors that influence the decision to accept or decline preconceptional carrier screening, and indicate that there must be less barriers if we are to promote reproductive decision-making, especially among prospective parents who are of non-Western origin.

The results of the survey, notwithstanding the low response and the study limitations, favour the implementation of ancestry-based preconceptional CF and HbPs carrier screening. A more extensive pilot study should be carried out to determine whether implementation on a larger scale is possible. In such an extensive pilot study participation should be facilitated for those with a positive intention to participate in the screening: translated copies of all written study materials should be available, test-participation should not be conditional on survey-participation, and more time should be allowed for making an appointment for the testing.

Acknowledgements
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Reference list


Intention to participate in ancestry-based carrier screening
five

three-month follow-up of western and non-western participants in preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies

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Lidewij Henneman
Pieter D Bezemer
Martina C Cornel
Leo P ten Kate

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Abstract

Objective: To study psychological outcomes, knowledge, recall of, understanding of and sharing of test-results, satisfaction and reproductive intentions among 97 Western and 46 non-Western participants in a preconceptional ancestry-based carrier couple screening study in the Netherlands.

Methods: Eligibility for cystic fibrosis (CF) and/or hemoglobinopathies (HbPs) testing was based on both partners’ ancestry. Participants completed questionnaires before (n=143) and after pre-test consultation (n=139), and one week (n=116) and three months (n=120) after receiving the test-results. Three Western CF carriers and seven non-Western HbP carriers were identified, but no carrier couples.

Results: Overall, anxiety levels were low, knowledge improved after pre-test consultation but decreased after three months. The majority (94%) was able to recall their test-results. Western participants reported less anxiety than non-Western participants, had higher knowledge scores, and were more often aware of the residual risk of having an affected child. None of the carriers felt less healthy, six felt relieved, and one felt disappointed. Four non-Western carriers were unaware of the residual risk of having an affected child. Five carriers shared their results with relatives. In general participants intended to draw reproductive decisions from test-results, were satisfied, and none of them regretted participation.

Conclusions: The participants in the testing reported no adverse psychological outcomes and intended to draw reproductive decisions from test-results. Understanding the test-results and sharing test-results with relatives needs further attention in future implementation. Recognizing the small differences between Western and non-Western participants could lead to recommendations for implementation of the screening.
Introduction

Cystic fibrosis (CF) and hemoglobinopathies (HbPs), like sickle cell disease and thalassemia, are both common serious autosomal recessive disorders, for which the risk of being a carrier depends on a person’s ancestry. CF is most common among Europeans and their descendants, and HbPs are mainly found in people with ancestors from Africa, the Mediterranean area, the Middle East, parts of the Indian sub-continent and South-East Asia. As a result of the autosomal recessive inheritance pattern, most patients lack a family history of the disorder, and healthy carriers are usually unaware of their carrier status. Therefore, couples in which both partners are carriers (i.e. carrier couples) generally do not know that they face a risk of 25% in each pregnancy of having an affected child.

Preconceptional carrier couple screening is assumed to benefit prospective parents because it enables them to make an informed reproductive decision before a pregnancy, without the emotion and pressure associated with prenatal screening, and with the availability of a maximum of reproductive options. These options not only include prenatal diagnosis followed (or not followed) by abortion or accepting the risk, but also deciding to refrain from (further) having children, adoption, using donor sperm or eggs, and pre-implantation genetic diagnosis, or possibly, in some customary marriage practices, adapting the choice of a partner.

Potential harmful effects of (preconceptional) carrier screening, such as negative psychological outcomes (e.g. stress, anxiety, excessive worrying) and misunderstanding of the test-results should be avoided, as well as adverse social consequences, such as the stigmatisation and discrimination of carriers. Multiple studies have demonstrated that both carriers and non-carriers may experience some negative feelings, such as anxiety and worry, when participating in genetic screening, but anxiety levels often decrease after a few months. Some CF carriers perceived themselves as less healthy after having received the test-results, Moreover, in several studies it was found that some carriers falsely believed that they were only likely to be carriers, instead of certainly, while many couples in which only one partner had been identified as a carrier were unaware of their residual risk of having an affected child, - a risk due to the limited sensitivity of the DNA testing. Correspondingly, it was found among those who tested negative, that they falsely believed that they were definitely not carriers, although they had been informed that the test had a sensitivity of less than 100%.
In most (Northern) European countries, including the Netherlands, preconceptional screening for CF and HbPs is not current practice, despite the positive results of several (pilot) studies. Targeted ancestry-based carrier screening for each of these disorders has been advised, but at the same time concern has been expressed about the potential harm of ancestry-based screening because of negative experiences, such as the discrimination and stigmatisation that occurred after the implementation of sickle cell screening in the USA in the early 1970s. In considering whether or not to implement routine preconceptional carrier screening based on ancestry for these disorders in general health care, it must first be clear whether or not the benefits outweigh the potential harms for both Western and non-Western prospective parents.

The present study is part of a larger project in which a unique offer of combined ancestry-based preconceptional CF and/or HbPs carrier couple screening was actually made in a multi-ethnic population in Amsterdam. A validated decisional instrument was used to assess eligibility for CF and/or HbPs carrier screening, based on both partners’ ancestry. With such a combined offer the assumed risk of stigmatisation or discrimination of sub-populations could be reduced, because almost every couple, irrespective of their ancestry, will be eligible for some kind of carrier screening: for CF, HbPs or both disorders.

The aim of the present study was to investigate how the participants in this preconceptional ancestry-based carrier couple screening for CF and HbPs study had experienced their participation in the screening. The following research questions were addressed: 1) How do participants in a study on preconceptional ancestry-based carrier screening for CF and HbPs experience their participation in terms of psychological outcomes? What is the extent of their knowledge and recall, and to what extent do they understand the test-results? What are their reproductive intentions? Do they share their results with relatives? Were they satisfied with their test-participation? 2) Are there differences on these issues between Western and non-Western participants?

Materials and methods

Participants and procedure
Details of the above-mentioned project, in which preconceptional CF and HbPs carrier couple screening was offered, have been described elsewhere (Lakeman et al. unpublished data). Screening was offered to 9,453 individuals (20-35 years),
including 50-60% non-Western immigrants, in eight districts of Amsterdam from January to December 2005. Those who had a partner with whom they were planning a pregnancy were eligible for participation, and were defined as the target population. It was estimated that 33% of the 9,453 individuals belonged to the target population. In total, 87 of the original invitees actually participated in the testing, forming a total of 72 couples (there were 15 couples in which both partners had received a personal invitation).

The participants had to visit their general practitioner (GP), together with their partner, for pre-test consultation and sampling of both partners for the carrier tests (all free of charge during the study period). A total of 47 couples were eligible for screening for CF only, 6 for HbPs only, and 19 for both disorders, based on assessment with the validated decisional instrument. In addition to the pre-test consultation, the couples were also provided with information about clinical and genetic aspects of the disorders, advantages and disadvantages of participation, the test procedure, and test-sensitivity, by means of a leaflet which was enclosed with the invitational letter, and a detailed brochure that was given to the couple after the pre-test consultation, together with an informed consent form. Testing took place after receiving a signed informed consent form, which had to be returned to the researcher (PL) within one week after sampling. All written material was available in Dutch only.

It was explicitly explained that a positive test-result definitely means that a person is a carrier, but that a negative result does not definitely exclude the possibility of being a carrier.

The CF carrier testing was carried out step-wise: one partner was tested first, and the second partner was tested only if the test-result of the first partner was positive. On the informed consent form the couples could indicate who should be tested first. For the HbPs carrier testing, both partners were tested. Three CF carriers of Western origin and seven HbP carriers of non-Western origin were identified, but no carrier couples.

All test-results were sent together by mail in a letter addressed to the couple, and the GP received a copy. Couples in which one partner was identified as a carrier, and the other tested negative, were informed about the residual risk of having an affected child. It was emphasized to people with a negative test-result that there still might be a small risk of being a carrier and a (small) residual risk of having an affected child. People with a positive test-result were told that this result was definite, and that they should advise family members to have themselves tested, since they also had an increased risk of being a carrier. None of the carriers contacted the researcher for further information. Carrier couples, if identified, would have been invited for counselling at a Clinical
Genetic Service. The study protocol of the project was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam.

**Questionnaires**
The participants were asked to complete individually a structured questionnaire at four different measurement moments during the study: 30 minutes before the pre-test consultation (Q1), within one week after the consultation (Q2, and this questionnaire should be returned together with the informed consent form), and one week (Q3) and three months (Q4) after receiving the test-results. Of the 72 participating couples, the male partner in one couple was not willing to complete the questionnaires, so we report here only on 143 test-participants.

**Outcome measures**

1. **Psychological outcomes**
   
   (A) Anxiety (Q1-Q4) was assessed on a 4-point scale with the 6-item short form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). A mean score of 1 indicates a low level of anxiety, and a mean score of 4 indicates a high level of anxiety.

   (B) Other emotional outcomes. The participants were asked to indicate whether or not they had been worried while waiting for the test-results (Q3). They were also asked whether or not: 1) they were worried after receiving the test-results, 2) they perceived themselves as being less healthy, 3) they felt relieved, or 4) they felt disappointed after receiving the test-results (Q3-Q4). All items were measured on a 5-point Likert-scale ranging from fully disagree (1) to fully agree (5).

2. **Knowledge**

   Knowledge was assessed with the following five multiple choice questions about knowledge of the health implications for carriers and the risk for a carrier couple of having an affected child (Q1-Q3): 1) 'A carrier of CF can also get the disease', 2) 'A carrier of sickle cell disease or thalassemia, can also get these disorders', 3) 'It is possible to be a carrier of CF or HbPs when these disorders are not present in your family', 4) 'If only one partner in a couple is identified by the test as being a carrier, it is impossible for that couple to have an affected child’ (answer format 'yes', 'no' and 'I don’t know'), and 5) ‘What is the risk of having a child with CF or HbPs when both partners are carriers?’ (answer format ‘100%’, ‘50%’, ‘25%’, and ‘I don’t know’). The number of correct answers was calculated as a sum-score, with a maximum of 5.
(3) Recall of the test-results

In Q3 and Q4, the participants were first asked to indicate the carrier test(s) for which they were eligible: CF, HbPs or both disorders; and secondly, what the test-results had been. Those who had been tested for CF were asked to tick one option out of the following: ‘I was not identified as a CF carrier, and my partner has not been tested’, ‘My partner was not identified as a CF carrier, and I have not been tested’, ‘I am a CF carrier, but my partner is probably not’, ‘My partner is a CF carrier, but I am probably not’, ‘We are both CF carriers’, and ‘I don’t know’. Those who had been tested for HbPs were asked to tick one or more options out of the following: ‘I am a carrier of sickle cell disease’, ‘My partner is a carrier of sickle cell disease’, ‘I am a carrier of thalassemia’, ‘My partner is a carrier of thalassemia’, ‘Neither of us is a carrier of sickle cell disease’, ‘None of us is a carrier of thalassemia’, and ‘I don’t know’. Subsequently, one of the researchers (PL) scored the answers as correct or incorrect by comparing them with the actual test-results and letter.

(4) Understanding of the test-results

A) Understanding of test-validity was assessed after the pre-test consultation (Q2) and one week after receiving the test-results (Q3) with the following two statements: ‘A person with a positive test-result is definitely a carrier’ and ‘A person with a negative test-result is definitely not a carrier’ (answer format ‘yes’, ‘no’ and ‘I don’t know’).

B) Understanding of the consequences of the test-results was determined by understanding of the residual risk of having an affected child, and assessed by means of a multiple choice question ‘If you and your partner are planning to have children together in the future, what is, with your test-result, the risk of having a child with CF/sickle cell disease/thalassemia?’ (Q3-Q4). (Answer format ‘Very high risk’, ‘High risk’, ‘Not a high risk, but also not a low risk’, ‘Low risk’, ‘Very low risk’, ‘No risk of having an affected child’ and ‘I don’t know’). These answers were subsequently scored as correct or incorrect by comparing them with the actual test-results. As there were no carrier couples, the answers ‘Low risk’ and ‘Very low risk’ were assessed as the correct answers.

(5) Reproductive intentions

After the pre-test consultation with the GP, but before receiving the test-results, the participants were asked (Q2) about their expected reproductive intentions in the hypothetical situation that they would turn out to be a carrier couple, with the following three statements: ‘I would not have (anymore) children if my partner and I were both carriers’, and in case of a pregnancy ‘I would opt for
prenatal diagnosis if my partner and I were both carriers’, and ‘I would consider termination of the pregnancy if the unborn child was affected’. All items were measured on a 5-point Likert scale ranging from fully disagree (1) to fully agree (5).

In Q4, the participants were asked whether or not the test-results had changed their ideas about having children (answer format ‘yes’, ‘probably’, ‘no’ and ‘I don’t know’). If so, the participants were asked to indicate in what way their ideas had changed, by choosing one of the following options: ‘I am more sure about having children’, ‘I now have doubts about having (anymore) children’, ‘I want more children than I did before the carrier testing’, ‘I want less children than I did before the carrier testing’, ‘I now definitely don’t want children (anymore)’, and ‘My ideas have changed in other ways’.

(6) Sharing the test-results
In Q4 the participants were asked whether or not they had shared their test-results with other people. If so, they were asked to choose one or more of the following options: I told ‘my parents’, ‘my siblings’, ‘my children’, ‘other members of the family’, ‘my friends’, and/or ‘someone else’.

(7) Satisfaction
In Q3 and Q4 the participants were asked to indicate the extent to which they agreed with the following three statements: 1) ‘If I had to decide again, I would participate again’, 2) ‘I would recommend the screening to other couples if this was a possibility’, and 3) ‘I regret the fact that I participated in the screening’. All items were measured on a 5-point Likert scale ranging from fully disagree (1) to fully agree (5).

(8) Sociodemographic characteristics and ancestry
In Q1 sociodemographic variables (gender, age, marital status, level of education, number of children, native country, and parental native country) were assessed.

Based on their own and their parental native countries, we distinguished: 1) participants of Western origin, who have their ancestry in Europe (including the Netherlands), North-America, and Australia, and who are mainly eligible for CF carrier screening, and 2) participants of non-Western origin, including people from Turkey, Surinam, Morocco and the Netherlands Antilles, who form the four largest immigrant groups in the Netherlands, and who are eligible for HbPs carrier screening. Couples from Turkey and Morocco were eligible for both the CF and the HbPs carrier screening tests.
Data-analyses
In general, both partners in a couple were treated as independent subjects, because earlier research showed that individual partners provide different information. We compared participants of non-Western origin with those of Western origin. As only seven carriers completed all the questionnaires (Q1-Q4), we performed no statistical comparison of carriers and non-carriers. Independent sample T-tests or ANOVA analyses were performed to compare the mean scores for the variables between groups at the same measurement moment. For each measurement moment, the total number of participants who completed that specific questionnaire were included in the analysis: Q1 (n=143), Q2 (n=139), Q3 (n=116) and Q4 (n=120).

For longitudinal comparison of the mean scores for the variables in one group at different measurement moments, we used dependent sample T-test(s) and General Linear Model-analysis for repeated measurements (MANOVA). In the analysis of these measurements, we included the total number of participants who completed all the questionnaires in which questions were asked about that specific variable. Not all variables were included in each questionnaire (see ‘Questionnaires’). Therefore, for each variable there was different total number of participants who could be included in the analyses for repeated measurements.

In addition, for each variable we calculated the proportion of Western and non-Western participants who had a score below and/or above 3 (the neutral point). The Chi-square test was used for the statistical comparison of proportions. All analyses were performed in SPSS 14.0 for Windows, and p-values below 0.05 were considered to be significant.

Results
Response
Q1 was returned by 100% of the participants (n=143), Q2 by 97% (139/143), Q3 by 81% (116/143) including 7 out of the 10 carriers, and Q4 was returned by 84% (120/143), including 9 carriers. In total, 110 participants completed all questionnaires (Q1-Q4), resulting in a response of 77% (103/133) among the non-carriers, and 70% (7/10; 3 CF and 4 HbP carriers) among the carriers. In total, 68% (97/143) of the participants were of Western origin: indigenous Dutch (n=83) and other European origin (n=14); 32% (46/143) were of non-Western origin: from Southeast Asia (n=15), Turkey (n=14), Morocco (n=5), other North African Countries (n=7), Surinam (n=3), the Middle East (n=1) and South America (n=1).
The sociodemographic characteristics of the 143 participants are presented in Table 1. Compared to the Western participants, the non-Western participants had a significantly lower level of education; and significantly more of them were married and already had children (see Table 1).

Table 1
Socio-demographic characteristics of Western and non-Western participants in the screening test(s)

<table>
<thead>
<tr>
<th>Participants</th>
<th>Western origin</th>
<th>Non-Western origin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals, n</td>
<td>97</td>
<td>46</td>
<td>143</td>
</tr>
<tr>
<td>- Men, n (%)</td>
<td>46</td>
<td>25</td>
<td>71</td>
</tr>
<tr>
<td>- Women, n (%)</td>
<td>51</td>
<td>21</td>
<td>72</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>32 (23-47)</td>
<td>31 (23-47)</td>
<td>32 (23-47)</td>
</tr>
<tr>
<td>- Men</td>
<td>30 (19-41)</td>
<td>27 (20-35) *</td>
<td>29 (19-41)</td>
</tr>
<tr>
<td>- Women</td>
<td>20 (21)</td>
<td>30 (65) ***</td>
<td>50 (35)</td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>15 (16)</td>
<td>19 (41) ***</td>
<td>34 (24)</td>
</tr>
<tr>
<td>With children, n (%)</td>
<td>4(4)</td>
<td>11 (24) ***</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Level of education, n (%)</td>
<td>37 (38)</td>
<td>25 (54) *</td>
<td>62 (43)</td>
</tr>
<tr>
<td>- Low</td>
<td>56 (58)</td>
<td>10 (22) ***</td>
<td>66 (46)</td>
</tr>
</tbody>
</table>

a Definition of Western origin, including the indigenous Dutch people (n=83), and of non-Western origin as defined by Statistics Netherlands.  
* p < .05; ** p < .01; *** p < .001. Difference between Western and non-Western participants.

Psychological outcomes

The participants (n=110) reported low levels of anxiety (general mean score on the STAI was M= 1.5): the level of anxiety was low at the start and decreased further during the study (p=.001) (see Figure 1). Among the carriers, two felt anxious one week after receiving the test-results (Q3), and one of these two was still anxious at the three-month follow-up (Q4). The majority of participants (73%; 85/116) reported that they had not been worried (score ≤ 3) while waiting for their test-results (M= 2.1). At the three-month follow-up, two participants were worried, including one CF carrier.

None of the participants, including the carriers, perceived themselves as being less healthy one week after receiving the results (Q3) or at the three-month follow-up (Q4). Further, 68% (79/116) felt relieved (score >3) at Q3 (M= 3.6) and 62% (74/120) felt relieved at Q4 (M= 3.5), including, respectively, seven and six carriers. Among those who did not feel relieved, there were six and seven partners of carriers, respectively, at Q3 and Q4. Feelings of disappointment (score >3) were rarely reported: four participants, including two carriers, were disappointed one week after receiving the results, but none of them were disappointed at the three-month follow-up. However, four other participants reported feelings of disappointment at the three-month follow-up, including
both partners in a couple in which one partner was a CF carrier and the other tested negative.

**Western versus non-Western participants**

Compared to non-Western participants, the Western participants generally reported lower levels of anxiety (see Figure 1). Non-Western participants were almost significantly more often worried while waiting for the test-results: 38% (13/34) and 22% (18/82) had a mean score above 3 (p=.06). There were no differences in the frequency of feelings of relief or disappointment between the Western and non-Western participants.

![Figure 1](image)

**Figure 1**

Level of anxiety* during the study among 110 test-participants who completed all questionnaires (Q1-Q4)*

Anxiety was assessed on a 4-point scale using the 6-item short form of the state scale of the Spielberger Stait-Trait Anxiety Inventory (STAI).

*Participants were asked to complete individually a structured questionnaire at four different moments in the study: 30 minutes before the pre-test consultation (Q1), within one week after the pre-test consultation (Q2), and one week (Q3) and three months (Q4) after receiving the test-results.

**Knowledge**

Table 2 shows the proportion of participants with a high level of knowledge (sum-score > 2.5) and the mean knowledge scores of the participants who completed Q1-Q3 (n=116). In general, in these 116 participants there was a significant increase in the knowledge score from before (Q1) to after the pre-test consultation (Q2), but also a significant decrease when measured one week after receiving the test-results (Q3) (p<.001). Among those with a high level of knowledge at Q3, there were two carriers (out of seven who completed Q3) and three partners who tested negative.
Western versus non-Western participants
The non-Western participants had significantly lower mean knowledge scores than the Western participants before the pre-test consultation (Q1) and one week after receiving the test-results (Q3) (p<.05), but the scores were similar at Q2 (see Table 2).

Table 2
Proportion of Western and non-Western participants (n=116) with high knowledge sum-scores (>2.5) at different assessment moments during the study (Q1-Q3)

<table>
<thead>
<tr>
<th>Participants’ origin:</th>
<th>Knowledge sum-score &gt; 2.5*</th>
<th>n (%)</th>
<th>mean</th>
<th>n (%)</th>
<th>mean</th>
<th>n (%)</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western (n=82)</td>
<td>52 (68)</td>
<td>3.1</td>
<td>15 (44)*</td>
<td>2.4</td>
<td>67 (58)</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Non-Western (n=34)</td>
<td>23 (68)</td>
<td>3.4</td>
<td>89 (77)</td>
<td>3.7***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=116)</td>
<td>54 (66)</td>
<td>2.9</td>
<td>15 (44)*</td>
<td>2.5</td>
<td>69 (59)</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

* Knowledge about inheritance of the disorders was calculated as a sum-score, with a minimum of 0 and a maximum of 5.
* p<.05: difference between Western and non-Western participants.
*** p<.001: difference between Q1 and Q2 representing a significant increase, and difference between Q2 and Q3 representing a significant decrease.

Recall of test-results
In total, 93% (108/116) and 94% (113/120) of the participants were able to recall their test-results one week (Q3) and three months after receiving them (Q4). At the three-month follow-up, seven participants, including two HbP carriers and their partners, did not remember their test-results.

Western versus non-Western participants
Significantly more non-Western than Western participants did not recall their test-results at the three-month follow-up: 18% (6/34) versus 1% (1/86) (p=.002).

Understanding of test-results
Tables 3a and 3b present the understanding of test-results based on: a) understanding of test-validity in general (assessed at Q2 and Q3) (Table 3a), and b) understanding of the consequences of their own test-results (assessed at Q3 and Q4) (Table 3b).
In general, with regard to test-validity, the meaning of a positive test-result (i.e., the person who tested positive is definitely a carrier) was better understood than the meaning of a negative test-result (i.e., the person who tested negative has a residual risk of being a carrier): these questions were answered correctly 66% (153/232; 95% CI 60-72%) of the times versus 41% (95/232; 95% CI 35-47%) of the times, respectively (p<.001) (Table 3a). In the comparison of understanding test-validity at Q2 and Q3, the meaning of a positive test-result was better understood after the pre-test consultation (p=.03), and the meaning of a negative test-result was better understood one week after receiving the results (p<.001). In addition, three carriers did not understand the meaning of a positive test-result: they thought that a person who tested positive was definitely not a carrier, or stated ‘I don’t know’. Four partners who tested negative did not understand the meaning of a negative test-result incorrectly: they thought that a person who tested negative had no residual risk of being a carrier, or stated ‘I don’t know’.

With regard to understanding their own test-results, the proportion of participants who correctly understood their residual risk of having an affected child decreased significantly from the measurement one week after receiving the test-results (Q3) compared to the measurement at the three-month follow-up (Q4): 53% versus 39%, respectively (p<.001) (see Table 3b). Among those who misunderstood their residual risk were the seven participants who also failed to recall their test-results. Four carriers and five partners who tested negative thought that there was no residual risk of having an affected child.

Western versus non-Western participants
Compared to non-Western participants, the Western participants had a better understanding of the test-validity, but only with regard to the meaning of a positive test-result directly after the pre-test consultation (Q2) was the difference significant (p=.044) (see Table 3a). Furthermore, Western participants more frequently understood correctly their residual risk of having an affected child, which was significant at Q4: 42% versus 26% (p<.001). Both the Western and the non-Western participants showed a significant decrease between Q3 and Q4 in understanding the consequences of their own test-results.
Table 3a
Understanding of test-validity after consultation (Q2) and one week after receipt of the test-results (Q3) among Western and non-Western participants

<table>
<thead>
<tr>
<th>Correct understanding of positive (unfavourable) test-result:</th>
<th>Western (n=82)</th>
<th>Non-Western (n=34)</th>
<th>All (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>after consultation – Q2</td>
<td>63 (77)</td>
<td>20 (59)*</td>
<td>83 (72)</td>
</tr>
<tr>
<td>one week after test-results – Q3</td>
<td>52 (63)</td>
<td>18 (53)</td>
<td>70 (60)**</td>
</tr>
</tbody>
</table>

Table 3b
Correct understanding of consequences of own test-results one week after receiving the test-results (Q3) and at the three-month follow-up (Q4) among Western and non-Western participants

<table>
<thead>
<tr>
<th>Correct understanding of own test-results:</th>
<th>Western (n=82)</th>
<th>Non-Western (n=34)</th>
<th>All (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>one week after receiving the test-results – Q3</td>
<td>47 (55)</td>
<td>14 (41)</td>
<td>61 (53)</td>
</tr>
<tr>
<td>at the three-month follow-up – Q4</td>
<td>36 (42)</td>
<td>9 (26)*</td>
<td>45 (39)***</td>
</tr>
</tbody>
</table>

Reproductive intentions
In total, if the couple turned out to be a carrier couple, 27% (37/139) of all participants reported that they would consider not having (more) children. In case of a pregnancy, 89% (124/139) would opt for prenatal diagnosis, and 68% (84/124) reported that they would consider an abortion if they were expecting an affected child. At the three-month follow-up, 93% (112/120) of all participants, including all carriers, stated that the test-results had not changed their ideas about having children, and 26% (19/72) of the couples reported a pregnancy.

Western versus non-Western participants
A significantly lower proportion of non-Western, compared to Western participants (mean score 3.89), reported that they would consider an abortion if the foetus was affected: 49% (22/45) versus 66% (62/94) (p=.041).
Sharing the test-results
In general, 59% (71/120) of the participants shared their test-results with others. Among them were five out of the nine carriers who completed Q4 (56%). They told their friends (n=3), parents (n=4), siblings (n=3), a relative (n=1), and someone else (n=1). We are not aware of any request for testing from relatives so far. The four carriers who had not shared their results were all non-Western males; two of them were also not able to recall their test-results. In general, there was no significant difference between the proportion of Western (64%; 55/86) and non-Western participants (47%; 16/34) who shared their test-results with others (p=.069).

Satisfaction
The extent to which the participants reported that they were satisfied about their participation did not differ between the measurement moment (Q3 or Q4). Therefore, we only present the results at the three-month follow-up (Q4).

In general, the participants were satisfied with their participation (see Table 4): most of them agreed or fully agreed with the statements ‘If I had to decide again, I would participate again’ (91%), ‘I would recommend the screening to other couples if this was a possibility’ (75%), and all of them disagreed or fully disagreed with the statement ‘I regret having participated in the screening’. The four participants who felt worried at the three-month follow-up (see ‘Psychological outcomes’) and eight of the nine carriers stated that they would participate again and did not regret their participation.

Western versus non-Western participants
There were no differences in satisfaction between Western and non-Western participants: they were equally satisfied.

Table 4
Satisfaction with participation in the screening at the three-month follow-up (Q4)

<table>
<thead>
<tr>
<th>Statements</th>
<th>Western (n=86)</th>
<th>Non-Western (n=34)</th>
<th>All (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I would participate again</td>
<td>80 (93)</td>
<td>29 (85)</td>
<td>109 (91)</td>
</tr>
<tr>
<td>I would recommend testing to others</td>
<td>64 (74)</td>
<td>26 (77)</td>
<td>90 (75)</td>
</tr>
<tr>
<td>I regret having participated</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Statements were measured on a 5-point Likert scale. Presented are the numbers and proportion of participants who had a score > 3 for these items, as well as the mean scores.
* p<.05: difference between Western and non-Western participants.
Discussion

Psychological outcomes, knowledge, recall, understanding and sharing of test-results, satisfaction and reproductive intentions were studied among 97 Western and 46 non-Western participants in a unique preconceptional ancestry-based carrier couple screening study in a multi-ethnic population in the Netherlands.

Similar to the findings of other studies, we found no major adverse psychological effects among the participants. Overall, levels of anxiety were low, the majority of the participants had not been worried while waiting for the test-results, and only two remained worried after receiving the test-results. Furthermore, as reported before, none of the participants, and none of the carriers, perceived themselves as less healthy after receiving the test-results. In other studies, however, it was found that carriers had a poorer perception of their health than non-carriers. There was no difference though in the way of asking whether or not they perceived themselves as less healthy after receiving the test-results between the present and the Henneman et al. study. Our study lacked power to solve this question. Some studies reported an increase in anxiety after receipt of the test-results. The absence of such an increase in anxiety in the present study might be due to the fact that both partners in a couple received their results simultaneously, and all partners of carriers tested negative, or it could simply be due to the relatively low number of participants. Striking, though, is the result that not the identified carriers personally, but their partners (respectively 6/7 at Q3, and 7/10 at Q4) responded that that felt not relieved after receipt of the results. Nevertheless, we conclude that this offer of combined ancestry-based preconceptional carrier couple screening for CF and HbPs meets one of the genetic screening criteria, i.e. that psychological harm caused by the offer and/or participation must negligible.

With regard to knowledge and understanding of the test-results, the results of the present study showed no major difference from those of previous studies. Knowledge improved significantly from before to just after the pre-test consultation. However, this increase in knowledge was not sustained, a finding that also was reported previously, although others reported no (major) decline in knowledge. Furthermore, similar to the results of other studies, the large majority of the participants could recall their test-results. With regard to understanding the test-results, almost half of the participants in the present study were unaware that a negative test-result does not definitely exclude the possibility that is the person can still be a carrier, and almost half...
of the carriers thought that there was no residual risk of having an affected child. These results are similar to those of previous studies, in which people who tested negative erroneously believed that they were certainly no carriers, and in which proven carriers believed that their result meant that they were only likely to be carriers. Not being aware of the limitations of DNA testing might confront some carriers who tested negative with the consequences of false reassurance, because carriers still have a small risk of having an affected child. However, the risk is considerably smaller than if they had not participated in the screening.

Similar to the results reported by Henneman et al., the participants in the present study were satisfied with their participation: the large majority would participate again if they had to decide again, and would recommend the screening to others if it was routinely. None of the participants regretted their participation, but this finding might have been different if one or more carrier couples had been identified. Furthermore, in addition to the fact that the participants reported that they were satisfied, they also reported that they would draw reproductive consequences from the test-results if they turned out to be a carrier couple, which was also found in other studies. Twenty-seven percent would refrain from having more children, in the case of pregnancy, 89% would opt for prenatal diagnosis, and 68% of them reported that they would consider an abortion if expecting an affected child. Therefore, this preconceptional screening program for CF and HbPs meets its general aim of facilitating informed reproductive decision-making among the participants.

Although termination of a pregnancy was acceptable for many participants in the present study, both for CF and HbPs, knowledge about carrier status in general also seemed to limit plans to have more children. However, Poppelaars et al. reported that 21% of 380 recently married participants in a survey focusing on preconceptional CF carrier screening did not intend to change their reproductive plans, and that 54% were against the abortion of a child with CF. Married couples, however, may not be representative of all couples who are planning to have children in the Netherlands.

In contrast to the findings of other studies, we found that only five out of nine carriers shared their results with parents and siblings, although we explicitly had stated in the letter with test-results that they were advised to inform their relatives as they have an increased risk of being a carrier too. This finding might be due to the reported difficulties in understanding the test-results (see Table 3b), or difficulties in disclosing the results to relatives, because of geographical separation and/or irregular contact, or the wish that relatives should not be tested. Otherwise, we investigated sharing three months after
receipt of the results, and it is imaginable that the carriers had planned to tell their relatives, but just not had done this yet.

Western versus non-Western participants
In the present study, despite the limited number of participants, it was possible to focus on both Western and non-Western participants. In general, Western and non-Western participants reported no adverse psychological outcomes, were satisfied with the screening, and intended to draw reproductive decisions from test-results. No feelings of stigmatisation or discrimination were reported (Lakeman et al., unpublished data), suggesting that a combined ancestry-based offer to the whole population might be a solution to exclude or diminish feelings of this kind. There were (small) differences, though, that need further investigation and could lead to recommendations for implementation.

Non-Western participants had low, but higher levels of anxiety than the Western participants. We did not investigate whether or not the degree of anxiety that was experienced had anything to do with participation in the screening or with other worries. They might have felt that they were more at risk, resulting in a slightly higher level of anxiety, because most non-Western participants were eligible for carrier screening for two disorders (CF and HbPs), while the Western participants were eligible for screening for ‘only’ one disorder. It is also possible that the non-Western participants had a different interpretation of the six items of the short form of the STAI, which has not been validated among a large group of non-Western people. However, the reliability analysis that we performed showed Cronbach’s alpha’s of above 0.7.

Furthermore, non-Western participants, including four carriers, were more often unaware of the residual risk of having an affected child, and these carriers did not share their test-results with relatives. These findings might be due to misunderstandings about inheritance of the disorders, since the non-Western participants had a significantly lower knowledge score. This lower knowledge score might, in turn, be related to the fact that the non-Western participants had a lower level of education than the Western participants, and/or a limited command of the Dutch language (the leaflet and brochure were available only in Dutch).

Compared to the Western participants, the non-Western participants were less likely to consider the abortion of an affected foetus. However, with regard to HbP carrier screening, Giordano et al. reported a generally positive attitude among 328 pregnant immigrants in the Netherlands toward prenatal diagnosis and selective abortion in the case of an HbP-affected child, a finding that has also been reported by others outside the Netherlands.
Limitations of the study

The present study has some limitations. The study was conducted in the Netherlands in a specific multi-ethnic sub-population in Amsterdam, and the results may therefore not be generalizable to other parts of the Netherlands and/or to other countries. Furthermore, only a small number out of almost 10,000 invitees actually participated in the testing and were willing to complete the questionnaires. Non-Western participants and people with a lower level of education were under-represented, and the non-Western participants were a heterogeneous sub-group with regard to ancestry. Moreover, in the present study all participants had adequate command of the Dutch language, because translated copies of the leaflet, brochure and questionnaires were not available.

Before the start of the project one of the authors (PL) visited each participating GP, explained the project in detail, and provided educational information about the disorders and their inheritance. However, we had no control over the quality of the actual information the GPs gave to the participants. Finally, only nine carriers and no carrier couples were identified.

Recommendations

In the present study, we did not investigate how tests could be offered in order to maximize the meaning of the test-results, as reported by Marteau. Nevertheless, based on the results of the present study the following recommendations can be made to improve understanding of test-results. First of all, providing the results and offering the possibility of counselling by letter only may be insufficient. Carriers could also be proactively contacted with the offer of post-test consultations, in which the results can be repeated and the consequences for the carriers as well as for their relatives can be more clearly explained. However, Gordon et al. found that the degree of understanding of the test-results in the longer term did not differ significantly between those who accepted an offer for post-test consultation and those who did not. Nevertheless, if counselling is offered, it should be available in the participants’ own language. Secondly, copies of a letter to the family should be provided, explaining to the relatives their risk of being a carrier, and the participants should be encouraged to give these letters to their relatives. Thirdly, translated copies of the information leaflet, the decisional instrument and family letters should be made available.

Although the large majority of participants were able to recall their test-results, 6% could not remember them, including two carriers. Storing test-results should be considered, for example in the GP’s medical filing system or in patient files in a future general preconception consultancy setting.
The findings of the present study indicate the importance of education. Due to insufficient knowledge about genetics in the general population, genetic screening programmes must include educational and counselling components. Furthermore, not only the target population, but also the general population should receive information about genetic risks and genetic tests (school education programmes, leaflets, mass media campaigns, the Internet). This education will be important in increasing public knowledge and in shaping attitudes towards genetic testing to avoid stigmatisation. Moreover, it is not only necessary to educate the target population, but also GPs, obstetricians and gynaecologists with regard to the screening procedure and inheritance patterns.

If preconceptional ancestry-based CF and/or HbPs carrier couple screening is implemented, these issues must receive ample attention. However, prior to nationwide implementation of the screening program in the Dutch health care system an extensive pilot study should be carried out, for example within the context of a general preconception care setting, as recently suggested by the Health Council of the Netherlands.

Conclusion

Although the approach and setting in the present study differed considerably from that of previous studies on preconceptional carrier screening, the findings of the present study are similar to those of previous studies, and generally demonstrate that there were no major adverse psychological effects among the participants, that the participants were satisfied with the screening, and that they would base reproductive decision on the test-results. Less positive results were found among the non-Western participants, but the differences in this Dutch setting between non-Western and Western participants were small. The recognition of these (small) differences between Western and non-Western participants provides the opportunity for optimizing a future screening offer. In our opinion, therefore, the results of the present study provide no arguments for rejecting an offer of preconceptional ancestry-based CF and HbPs carrier couple screening. An extensive pilot study should be carried out to investigate whether or not this type of screening should be implemented on a large scale in the Netherlands.
Reference list


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other aspects relevant for implementation
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preconceptional carrier screening: will the offer impair freedom of choice and lead to medicalisation?

Phillis Lakeman
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Martina C Cornel

Submitted
Abstract

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 consequences. We studied preconceptional cystic fibrosis carrier screening, as an example, to investigate the ethical tension between offering carrier couples the opportunity to make a free and informed reproductive choice and protecting individuals from unwanted side-effects. During a workshop on this topic in the Netherlands in October 2003, four experts focussed on the pros and cons of the two main ethical issues: ‘freedom of choice’ and ‘medicalisation’. Based on their debates, we conclude that: 1) 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, there is no freedom of choice. A neutral wording of the offer and the information provided (neutrality of aim) is crucially important; 2) 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.
Introduction

In most European countries there has been discussion about whether or not preconceptional carrier screening for autosomal recessive disorders, such as cystic fibrosis (CF), Tay-Sachs disease and hemoglobinopathies (HbPs), should be introduced, and if so, how.¹⁻⁴ In the USA, a Consensus Development Conference convened by the National Institute of Health recommended that genetic screening for CF should not be restricted to the families and partners of patients and carriers, but should also be offered to couples who are planning a pregnancy and to couples seeking prenatal care.⁵ Laboratory standards and guidelines for population-based CF carrier screening have been published.⁶ Furthermore, the Committee on Genetics of the American College of Obstetricians and Gynaecologists stated that screening for Tay-Sachs disease and HbPs should be offered before pregnancy to individuals and couples at high-risk, based on their ancestral origin.⁷⁻⁸ In most (northern) European countries preconceptional CF and HbPs carrier screening is not current practice, except for some Mediterranean countries where premarital HbP carrier screening programmes have been embedded in more extensive health care practices.⁹⁻¹¹

Preconceptional carrier screening

Preconceptional carrier screening for autosomal recessive disorders would provide an opportunity to identify carrier couples and to inform these couples about the 25% (1-in-4) risk in every pregnancy of having an affected child, at a moment when all possible options with regard to procreation are still open. The availability of a maximum number of reproductive options and a minimum of (time-) constraint favours preconceptional screening over prenatal screening.¹²⁻¹³ In contrast to most non-genetic screening programmes, where the primary goal is prevention and therefore a high uptake is pursued,¹⁴ preconceptional carrier screening aims to inform prospective parents and enable informed reproductive decision making before pregnancy.¹⁵ Reproductive options include not only prenatal diagnosis followed (or followed not) by abortion in the case of an affected child or accepting the risk, but also deciding not to procreate, adoption, using donor sperm or eggs, and pre-implantation genetic diagnosis. The identification of carriers can theoretically take place among school-age children, couples planning a pregnancy (preconceptional screening), pregnant women and their partners (prenatal screening), and among newborns (neonatal carrier screening).
Ethical issues regarding preconceptional carrier screening

During a workshop on the feasibility of preconceptional CF carrier screening that was held in Amsterdam, the Netherlands, on the 27th of September 2002, some experts mentioned medicalisation of the preconceptional period and following pregnancy as a negative aspect of offering preconceptional carrier screening. Furthermore, they also mentioned that pressure from social environment might threaten freedom of choice, and the potential anxiety that might be caused by the offer of screening. In the literature, similar objections have been made to other reproductive screening programmes. Thus, there is a need to investigate this ethical tension between maximising reproductive options for carrier couples and protecting individuals from the unwanted side-effects. In this paper we focus on two main ethical issues: ‘freedom of choice’ and ‘medicalisation’, which have been mentioned previously by addressing the following general questions:

1. Is the possible threat to freedom of choice a convincing moral objection to preconceptional carrier screening?
2. Can medicalisation of the preconceptional period be considered as a convincing moral objection to preconceptional carrier screening?

We addressed these questions from the perspective of CF preconceptional carrier screening, but the same questions are equally relevant for other (autosomal recessive) disorders.

Investigation of preconceptional CF carrier screening

CF is the most common severe autosomal recessive disorder in Caucasians, affecting approximately 1 in 1,600-3,600 live births. The clinical expression varies, but the disease in its classic form remains one of chronic pulmonary disease and pancreatic insufficiency, and is associated with high morbidity resulting in a current median life-expectancy of 35-40 years. In Europe, CF carrier testing is currently restricted to the families and partners of CF patients and carriers of CF. However, most patients are born without a family history of this autosomal recessive disorder. To increase the CF carrier detection rate, population-based carrier screening has been proposed. In the Netherlands, the preconceptional approach seems to be the most appropriate because of the high percentage (85%) of planned pregnancies as well as the late presentation of some pregnancies to a health care worker. One barrier, however, in realizing this approach, is the absence in most countries of an appropriate preconceptional health care setting, which implies that considerable effort is needed to reach the target population. Therefore, most carrier screening studies and practices focus on prenatal care settings, in which it is much easier to implement.
During a pilot-study in the Netherlands to assess the desirability and feasibility of preconceptional CF carrier screening, the uptake was 25%. Ninety-five percent of the screened participants said that they would decide to have the test if they had to decide again, and 88% would recommend testing to others. Furthermore, Poppelaars et al. concluded that the offer of routine preconceptional CF carrier screening would lead to substantial acceptance among couples planning a pregnancy, as long as freedom of choice can be guaranteed. Furthermore, care providers who might become involved in a preconceptional CF carrier screening programme in the Netherlands, i.e. general practitioners (GPs) and Municipal Health Service (MHS) workers, generally had a positive attitude towards the implementation of such a programme. Therefore, it was concluded that preconceptional CF carrier screening is feasible and, under certain circumstances, it is cost-effective or will incur acceptable costs. Of course, the primary goal is not to achieve economic savings, but to enable participants to make an autonomous informed decision about reproductive options. The positive results of various pilot studies in and outside the Netherlands support the implementation of preconceptional CF carrier screening. Furthermore, preconceptional carrier screening for CF meets the requirements for genetic screening.

Workshop on ethical issues regarding preconceptional CF carrier screening
To investigate the ethical issues of ‘freedom of choice’ and ‘medicalisation’ regarding preconceptional CF carrier screening, four experts presented opposite opinions during a workshop about the benefits and disadvantages of this kind of screening. This workshop was held in Utrecht, the Netherlands, on the 8th of October 2003, and was organized as a follow-up to the above-mentioned workshop that was held in 2002. The workshop was visited by 36 people representing the fields of medical genetics, general practice, public health, obstetrics, paediatrics, medical research, patient organisations, and a number of other fields. During this workshop Tymstra and Den Hartogh presented opposite views about the question of whether or not the threat to freedom of choice represents a convincing moral objection to preconceptional CF screening, and Verweij and Dondorp discussed the question of whether or not medicalisation of the preconceptional period should be considered as a convincing moral objection to preconceptional CF screening. This is the first of a series of five papers on this ethical investigation of ‘freedom of choice’ and ‘medicalisation’ regarding preconceptional (CF) carrier screening.
The points of view of the experts are presented in the four papers which have been added as appendices to this thesis.\textsuperscript{31-34}

Discussion

Here, we briefly summarise the papers \textsuperscript{31-34} and comment the experts’ arguments, as well as their contribution to the debate about whether or not, and if so, how to implement a preconceptional CF carrier screening programme.

**Freedom of choice (Tymstra vs. Den Hartogh)**

Tymstra stated in his paper that he does not believe in absolute freedom of choice, and that belief in the capacity of people to make rational and autonomous decisions is questionable.\textsuperscript{33} He argued that the offer of CF carrier screening does not necessarily contribute to freedom of choice. Psychological factors, such as anticipated decision regret and difficulty in dealing with risk information (the tendency to think binary), as well as environmental factors, such as the normative expectations of one’s culture, hinder a truly free decision.\textsuperscript{35,36} Tymstra paid attention to the problem that the very fact that the subject is raised by a health worker conveys the message that it is a good idea to participate, otherwise the screening would not have been offered. He focused on the problem that even when a person makes a truly free decision to participate, the test results are also of importance for the members of participant’s family, which implies an additional responsibility. Tymstra therefore concluded that CF carrier screening has consequences which people are hardly able to oversee beforehand - then a truly free decision does not exist. He recognized, however, that if a screening procedure is withheld from people, they are also deprived of the freedom to make their own decisions about it.

Den Hartogh examined and dismissed the validity of the following argument: “The aim of preconceptional screening for cystic fibrosis is to increase the freedom of choice of individuals. For that it is crucial that the decision whether or not to accept the offer of screening is made in complete freedom. However, it is impossible to make the offer in such a way that the decision is made in complete freedom. That is why the offer should not be made.”\textsuperscript{31}

First, he discussed factors that could possibly undermine the complete freedom that is involved in the decision as to whether or not to accept the offer: A) a totally neutral wording of the offer is not possible, because it will always be coloured by the attitude of the one who makes the offer; B) even if the offer is made in a totally neutral form, the sheer fact that it is made is important;
C) a spiralling effect occurs as soon as a substantial number of people take up the offer, which in turn increases the pressure on the next person who has to make a decision; D) people might process information in the wrong way, especially over a longer period of time.

Den Hartogh concluded that the above-mentioned argument is invalid, because every free choice has to be made in an environment that is co-determined by the free choices of others. That is not an impairment of freedom, but that is freedom. A choice that is totally uninfluenced would not be a free choice, but merely a random choice. On the other hand, Den Hartogh could well imagine the right to autonomy being undermined by withholding an offer of screening. Den Hartogh further stressed that the offer of screening should be made in as neutral a way as possible, but distinguished between neutrality of effect and neutrality of aim. If the screening is offered to the population by or in the name of the government, it is inevitable that screening and participating in it will be experienced as good choices for life. Otherwise, why would the government allow it? Neutrality of effect is impossible: nearly everything the government does has differential effects with regard to views of the good life. But further-more and above all: neutrality of aim is sufficient as far as respect for the different attitudes toward participation is concerned. Den Hartogh stated that regarding the concerns on the fact that a totally neutral wording of the offer is not possible, and the fact that people might process information in the wrong way, neutrality of aim is relevant. That principle demands that policy should be aimed at least at minimizing these effects, in-so-far they are unavoidable.

Comment about freedom of choice
The discussion about freedom of choice concerning preconceptional carrier screening concentrates on the question of whether a truly free choice is possible and, should that not be the case, whether the offer should therefore not be made. A crucially important point in Den Hartogh’s analysis of the issue is that we should avoid an unrealistic, abstract, concept of free choice. In real life we are constantly being influenced – which is not per se at odds with free and autonomous choice - without thinking that others undermine our free choice and our responsibility for, for example, market behaviour. Even if one assumes that the influences described under A through D do, indeed, inevitably occur, which Den Hartogh has doubts about, neither the principle of respect for autonomy nor the neutrality principle provide any reason for not making a screening offer. If the screening procedure is withheld, then people are also deprived of the freedom to make their own decisions about it.31
An important point is the aim of the screening. The primary aim is not the reduction of costs, i.e. to spare public resources, nor the prevention of suffering. Such an aim could only lead to turning what ought to be an autonomous parental decision into a means to achieve a collective goal or to pressurise prospective parents into making the ‘right’ preventive decisions - in Clarke’s terms: ‘genetic cleansing’. On the contrary, the primary aim of reproductive genetic screening is to provide the prospective parents with information and a reproductive choice, enabling them to determine the outcome of the possible pregnancy from their own perspective of the meaning of having a (severely) handicapped child, for the child, for themselves and for their family. This parallels debates on the aim of genetic counselling, in which the explicit prevention of birth defects is dismissed as a goal.

In our opinion, Den Hartogh rightly suggested that the possible undermining of autonomy might be minimised by the conditions under which the screening is offered. We argue that the major challenge with regard to reproductive genetic screening is to promote autonomous, informed decision making. Obviously, this view has major implications for the conditions and safeguards that must be imposed - and may probably relate to some of Tymstra’s concerns regarding the undermining of free choice in the context of genetic screening. To start with, the professionals who are involved should adhere to the ideal of non-directiveness. Tymstra argued that the offer of screening itself is directive, because it entails the (implicit) recommendation to participate in the screening programme - the so-called ‘structural’ directiveness. It is important to tell the members of the target group explicitly that they are not forced to participate in the screening, and that the balance of the pros and cons of participating is deeply personal. Furthermore, informed decision making is a fundamental prerequisite. An informed choice is based on relevant knowledge, and is consistent with the decision-maker’s attitude and behavior. The pre-test information should be well-balanced and neutral, and include all possible familial implications. To argue, like Tymstra did, that a free decision is impossible because people can not oversee these implications beforehand, is simply gratuitous. If we follow the argumentation of Tymstra and seriously doubt the concept of the “autonomous person”, this could have the undesired consequence that old-fashioned paternalism again is propagated in health care.

Furthermore, ensuring informed decision making is obviously not a sinecure. Unfortunately, in a systematic review of the literature on the psychosocial aspects of prenatal screening it is concluded that, on the whole, ‘levels of knowledge adequate for decision making are not being achieved’. Clearly, there is an urgent need for more attention to be paid to this problem in ongoing
and future reproductive screening programmes. In order to facilitate informed decision making, people should be given time to reflect on the pros and cons of screening. Time-constraint in any ‘active opportunistic’ screening is, therefore, problematic, but although prenatal carrier screening is far more practical to implement, preconceptional carrier screening reduces time-constraints as much as possible. Needless to say, in order to ensure a genuine choice between either avoiding or accepting (the risk of) the birth of a CF child, it is essential that the necessary facilities and conditions are guaranteed within society for the care, support and integration of people with chronic diseases and handicaps such as CF, and that research on therapeutic interventions continues. Therefore, when a preconceptional carrier screening programme is implemented, there should be simultaneous initiatives to raise public awareness, emphasising the importance of respect for freedom of choice and respect for the handicapped.

**Medicalisation of the preconception period (Verweij vs. Dondorp)**

Given that, until a few decades ago, a pregnancy occurred without medical interference, in the descriptive sense of the word it is undoubtedly true that the offer of preconceptional screening contributes to the medicalisation of the preconception period. Verweij stated his views on why medicalisation, in general, is undesirable and why medicalisation raises a moral problem for a preconceptional CF carrier screening programme, in particular. He argued that medicalisation gives rise to moral problems to the extent that it: 1) undermines people’s confidence in their (general) health status; 2) stimulates problematic moral views (e.g. moral responsibility for health and reduced solidarity for people who do not take up the offer of screening and then have a child with CF), and 3) makes it more difficult to develop views of life in which other values than health are more prominent. Verweij stated that it would be incorrect to suggest that a single programme of preconceptional CF carrier screening causes such effects. He argued, though, that a problem is caused by an accumulation of preventive practices and interventions. The moral problems of medicalisation arise, in particular, in the context of pro-active preconceptional screening programmes, given the importance of reproductive choices for the development of people’s moral outlook. Therefore, in Verweij’s opinion, these moral problems are a good reason to accept some reluctance with regard to the ever-increasing possibilities of preventive medicine. Verweij concluded that it might be better to limit the offer of CF carrier screening to couples who take the initiative to seek medical advice about their reproductive choices. In the latter case the problem of medicalisation will be of less concern.
Dondorp argued that the term ‘medicalisation’ does not really contribute to the ethical analysis of preventive medicine, and that it does not benefit the discussion about the pros and cons of preconceptional CF carrier screening. He stated that medicalisation is a hybrid concept with descriptive, normative and rhetorical uses. The difficulty that arises is how to keep description and evaluation separate. Claims about the “medicalisation of childbirth”, for instance, can be purely empirical claims, but messages of moral condemnation are also conveyed as by the term. According to Dondorp, it is more helpful to evaluate the consequences of medical practices by specifying the criterion that determines what is, indeed, unnecessary or unwanted. For prevention and screening, a central criterion is that the benefits must clearly outweigh the harms. The analysis of relevant issues (iatrogenic morbidity, improper informed consent) can do perfectly well without the term “medicalisation”.

Furthermore, Dondorp discussed Verweij’s point that CF carrier screening may lead to harmful psychological effects, and discussed some empirical studies of anxiety and screening. Some participants in CF carrier screening programmes did, indeed, report residual psychological effects. This finding was seen as something that deserves further investigation, in order to find out how such effects can be avoided. There is no empirical evidence for Verweij’s more general claim that the accumulation of prevention or screening programmes will cause people to lose confidence in their health.

Before the development of a genetic screening programme is justified, the screening should meet certain general criteria. The question of whether or not an offer of preconceptional CF carrier screening implies that the planning of a pregnancy becomes unnecessarily burdened with medical concerns, as Dondorp argued, has already been addressed in various pilot studies. Even though some aspects would require further attention, the CF carrier screening programme does, in principle, fulfil the requirements that justify genetic screening.

Comment on medicalisation of the preconception period
In the Netherlands, like in most countries, there is no consultancy setting for general preconceptional care. In the absence of an established preconceptional consultancy setting, all activities promoting health care in the preconceptional phase will no doubt lead to an increase in medical interference in the lives of people who are planning a pregnancy or, more generally, all people of reproductive age. What, then, about this ‘medicalisation’?
The term medicalisation is notoriously vague and ambiguous. There is no consensus on what medicalisation actually is. While the term may be used in a purely descriptive way, it often has an evaluative, rather negative, connotation. Instead of simply repeating the term, it would be more productive to ask what people actually fear or find problematic when they express concern about medicalisation – a strategy which has proven to be useful with regard to other often (mis-)used, but ambiguous terms, such as ‘eugenics’. The phenomenon of medicalisation, in itself, might also be experienced as positive. Some stakeholders who participated in the workshop mentioned that in the past when no genetic screening at all was available, there was simply no other option than to hope that children would be born healthy. In those days, the preconceptional period and pregnancy were, indeed, less subject to medicalisation, but surely not without concerns or feelings of anxiety. Medicalisation, therefore, might also help to reduce anxiety.

We welcome the efforts of Verweij and Dondorp to disentangle the moral concerns that are hidden behind the term ‘medicalisation’. However, they disagree about the question whether or not the concept of medicalisation adds something to the ethical analysis of preventive medicine. We support Dondorp’s view, i.e. that the concerns underlying medicalisation should be formulated more precisely in other, more traditional terms, like threats to autonomy and disproportionality of the risks and benefits of screening.

It is important to realise that what, at the outset, may have seemed to be two completely different possible objections to preventive medicine, appear on further consideration to be interwoven or partly overlapping objections. After all, the third moral problem of medicalisation, as defined by Verweij, is in fact clearly linked to the objection regarding the undermining of free choice or the imposition of a particular way of life.

Verweij’s first argument is that preventive screening programmes may undermine people’s confidence in their health. Increased anxiety or feelings of guilt triggered by screening are potential adverse effects that could provoke hesitance to provide this form of screening. Although various studies have reported increased levels of anxiety and feelings of being less healthy among people with positive results or risks identified through various carrier screening programmes, no significant difference was found between CF carriers and screen-negative individuals in the degree of general anxiety after three months, and no adverse long-term psychological consequences were found in carriers. Furthermore, only 5% of the non-participants in a CF carrier screening study reported as main reason for non-participation ‘testing would make us too anxious’. As Dondorp already mentioned, it may be concluded on the basis of these studies that a single prevention practice as CF carrier screening at least in itself does not undermine people’s confidence in their own health status. Studies of
the psychological effects of general preconception care, i.e. general information about the avoidance of alcohol abuse and the benefits of folic acid also reported no serious adverse effects. Preconception counselling, in general, was favoured by prospective parents, and did not lead to adverse psychological effects. In Hungary, the majority of couples reported that the programme had improved their self-esteem.

Verweij pointed out the possible adverse, medicalising consequences of the accumulation of preventive activities in general, and therefore argued in favour of reluctance. In his view preconceptional CF carrier screening could contribute to such an accumulation. But when exactly should we conclude: ‘enough is enough’? No doubt, the principle of proportionality obliges us to critically assess the pros and cons, not only of each individual activity, but also the combination of these various activities. The feeling of an (unwanted) increase in medicalisation of the preconception period might result from the offer of more information and more testing at one moment, or from the offer of testing for different disorders at more different moments. Would a combination of genetic screening in a general preconception consultancy setting, in which also other potential risk factors are assessed and discussed at one moment, amount to the kind of concerns behind the notion of ‘medicalisation’ in a normative sense?

Verweij’s second argument is that CF carrier screening stimulates problematic moral views, and especially that it might reduce solidarity. In debates on genetic screening, and in a few empirical studies cited by Dondorp, this potential harm is discussed in relation to the screened individual. However, in the case of carrier screening for CF the question is whether the undermining of solidarity will occur, because the results only provide information about the risk for a screened individual and couple of having affected offspring. We are not aware of any empirical data on lack of solidarity with people who choose not to have screening tests and then have a child with a disorder. We agree with the stance of Dondorp, that if financial implications in the context of health care insurance limit the possibility of genuine choice, then screening would become contradictory to its primary aim, namely to facilitate informed reproductive decision making.

Verweij’s third fear is that health will increasingly dominate central values in life, the view of how life is. We agree with Dondorp that health is a prerequisite for the realization of many goals one may set in one’s life. In a more historical approach, we can argue that health has made us what we are. Furthermore, in a pluralistic and democratic society, the freedom of choice as to what people consider to be the central values in their lives is undermined by Verweij: aren’t people free to value health as much as they want?
Scenarios for preconception care and CF carrier screening

What conclusions with regard to preconceptional carrier screening and preconception care should be drawn from the problem with informed decision making and the objection of medicalisation?

A first conclusion could be: ‘do not offer any ‘universal’ preconception care at all to prospective parents who are at low risk of having an affected child’. This policy would, we think, be both unrealistic and morally problematic in view of the clear preventive benefits of general information, for example about the avoidance of alcohol and the benefits of folic acid. In fact, this policy would be at odds with the legitimacy and desirability of public health in relation with the preconception period.53

A second conclusion could be: ‘do not include any carrier screening in universal preconception care offered to people who are at low risk of having an affected child’. One could, then, as suggested by Verweij, test only those prospective parents who take the initiative and ask for a CF carrier test. However, preconceptional CF carrier screening tests are not yet available in many health care systems for the low risk population. Therefore this solution is dependent on some form of implementation. Furthermore, the main drawback of this solution would be that people who lack awareness will de facto not have access to relevant tests. Another alternative for large-scale CF carrier screening might be cascade screening, i.e. the systematic offer of a test to the relatives of a proband or a carrier. However, critics like Verweij, who argue that people should take the initiative themselves, may also question the ethics of cascade screening. This approach to offering carrier screening is well accepted by relatives, and the uptake is high.54 In contrast to Super et al. who concluded that cascade screening is more effective than unfocused screening,54 Morris et al. concluded though, based on a computer simulation model, that cascade screening is too poor to justify its use as a screening tool for any autosomal recessive disorder, because of its low detection rates: most carriers would never be informed because they do not have a family history of the autosomal recessive disorder.55

A third conclusion could be: ‘do include CF carrier screening in the context of universally offered general preconception care’. Women or couples who are planning a pregnancy will generally be interested in any potential risk for their future child or pregnancy, and the risk of having a child with CF is just one of the many risks about which information could be given.43

If preconceptional carrier screening is included in a general preconception consultancy setting, this would not lead to an increase in ‘medicalisation’ in terms of the number of times preconceptional health information is given. We assume that such an integrated offer would not necessarily create
serious, long-lasting anxiety or undermine solidarity or people’s trust in their own (reproductive) health (cfr. Verweij’s first and second problem). We think that this combination of carrier screening and preconception care in general would primarily raise issues related to the principles of respect for autonomy, freedom of choice, and neutrality (cfr. Den Hartogh’s analysis). How to facilitate informed decision making and how to secure non-directiveness or neutrality regarding the handling of reproductive genetic risks in the context of an integrated offer?

What about informed decision making?

Informed decision making may be threatened if people are confronted with an overload of options or choices. Tymstra rightly refers to Schwartz’s concept of ‘the paradox of choice’. In the ethical literature, this issue has been addressed by Dworkin: Is more choice better than less? Tymstra suggests that offering a CF-carrier test may already be ‘too much’. Clearly, there is no evidence for this, but, at the same time, the issue of how much information and choice people can handle in the context of preconception care is very important. This should be a topic of further empirical research. If the results suggest that the range of choices or options regarding preconception care must be limited (‘enough is enough’), then, of course, the question that arises is which options or choices should be given priority?

What about the ideal of non-directiveness?

In clinical genetics, especially in ‘reprogenetics’, the general ideal is non-directiveness, i.e. to assist clients in making informed reproductive decisions that reflect their own values and ideals. However, in the context of preconception care in general, (unsolicited) professional recommendations aiming at primary prevention of problems in the health of future children will often be fully acceptable: ‘you’d better stop smoking if you want to become pregnant’, and: ‘don’t drink’. Assuming that such attitudes or types of counselling are generally justified in these different contexts, the question that arises is: what attitude should professionals take in the context of integrated preconception care, including both genetic and non-genetic preconception care activities? Is it feasible and desirable to combine the ‘prevention’ paradigm aimed at health promotion (accepting non-neutrality) and the ‘reproductive choice’ paradigm (requesting neutrality)?

We agree with the recommendation of the Health Council of the Netherlands in their report on preconception care that in the delivery of preconception care a clear distinction should be made between advice that is aimed at
modifying behaviour in cases where risks can be influenced and non-directive information aimed at an increasing reproductive autonomy where they cannot. In our opinion, traditional preconception care and repro-genetics information could be combined at one single moment, as long as the health care provider who is involved is aware of this combination of activities with different moral frameworks, and as long as informed decision making with regard to the genetic screening tests is facilitated. Clearly, the practical and normative pros and cons of the combined and the split approach deserve further analysis and debate.

Conclusion

Is the possible threat to freedom of choice a convincing moral objection to preconceptional (CF) carrier screening?

Absolute freedom of choice does not exist; choices are made in an environment that is co-determined by the choices of others. If a valuable test (such as a preconceptional CF carrier screening test) is not available, there is no freedom of choice; making the test available generates some freedom of choice. The discussion on freedom of choice in the context of preconceptional CF carrier screening should be redirected to the way in which the test is made available. The challenge is to offer the test in such a way that informed decision making is really facilitated. A neutral wording of the offer and the information that is provided (neutrality of aim) is crucially important.

Can medicalisation of the preconceptional period be considered as a convincing moral objection to preconceptional (CF) carrier screening?

In a descriptive sense, preconceptional care will undoubtedly lead to medicalisation, but this is not necessarily a moral problem. When unravelling the concerns behind the objection in terms of “medicalisation”, the main worries can be addressed, firstly by ensuring that the test is made available in such a way that facilitates informed decision making, and secondly by continuous efforts to improve adequate societal provisions and care for the handicapped and their families.
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seven implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies: a sociotechnical analysis

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Abstract

Objective: to obtain more insight into the process of potential implementation of a screening program, which aims to identify carriers of cystic fibrosis and haemoglobinopathies before pregnancy, in order to enable couples at high risk of having a child with these disorders, to make informed reproductive decisions.

Methods: Use of sociotechnical analysis, based on a model of co-evolution between technology and society, and, for comparison, the study of the implementation processes of two already existing health care programs with similar aspects to the screening program at issue.

Results: Factors important for success appeared to be the existence of socio-technical 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.

Conclusions: Successful implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies 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.
Introduction

Increasing knowledge about the human genome raises great expectations about new applications in several domains of health care, for example public health. Genetics and public health now seem to converge in community genetics, which aims to make optimal use of genetics in providing better health options for the entire population. In screening programs initiatives are taken to actively identify and inform high risk populations. However, in many European countries, genetic services currently mainly focus on care that is requested by an individual patient. Consequently, it will not be easy to implement new genetic screening programs in present health care systems.

This study is about the process of potential implementation of a new genetic screening program in the field of community genetics in the Netherlands: preconceptional carrier screening for cystic fibrosis (CF) and haemoglobinopathies (HbPs). CF and HbPs are serious, autosomal recessive disorders. In patients with CF, the production of abnormally thick mucus causes infections in the lungs and problems with digestion. HbPs are inherited blood disorders causing severe anaemia and variable, but often high morbidity.

When both partners in a couple are carriers of one of these disorders, in each pregnancy there is a 25% risk of having a child with that disorder. Carrier screening permits couples at risk to make informed reproductive decisions, including not getting pregnant, prenatal diagnosis and selective abortion, or accepting the risk. However, in most European countries CF and HbPs carrier testing is restricted to the families and partners of patients and carriers. Consequently, most healthy carrier couples are not aware of their risk of having a child with the disease and will not request medical care, because often there have been no previous cases of affected children in their families. As articulation of demand is not to be expected from couples planning a pregnancy, there is a need for an infrastructure, in which carrier screening is actively offered. While in previous decades and in clinical genetic settings the right not to know has always been stressed, the offer of genetic screening is based on the right to know. If we want to enable high risk couples to make informed reproductive decisions, new health care facilities must be created.

The aim of this study was to obtain more insight into the process of potential implementation of preconceptional CF and HbPs carrier screening. Therefore, the following questions will be addressed: 1) What are the constraining and enabling factors for this process in the present (Dutch) health care system? 2) What sociotechnical conditions on micro-, meso- and macro-level have to be created for a successful implementation?
Methods

Firstly, we performed a sociotechnical analysis, based on a model of co-evolution between technology and society, in which we tried to identify constraining and enabling factors for the implementation of preconceptional CF and HbPs carrier screening. Secondly, we studied the implementation processes of two cases of already existing health care programs with similar aspects to the screening program at issue. The first program about the protective effect of folic acid in the prevention of foetal neural tube defects, aims to inform women planning a pregnancy, who form a similar preconceptional target population that is difficult to reach and that currently lacks a health care infrastructure. The second program is cascade screening for familial hypercholesterolemia (FH) and, like preconceptional CF and HbP carrier screening, involves a large-scale application of DNA technology that did not fit into the existing clinical genetic setting, but rather followed a public health approach. Important lessons that can be learnt from these programs will be formulated and will lead to recommendations on the major issues and challenges relating to the implementation of preconceptional CF and HbPs carrier screening.

Sociotechnical analysis

Implementation of preconceptional CF and HbPs carrier screening: a process of co-evolution

The introduction of new technologies in society may be considered as a process of mutual shaping, in which new technological options are developing together with the emergence of new expectations, new practices, new skills and professions, changing supplier-user relationships, changes in the regulatory framework, etc. Such processes of mutual shaping have been described as co-evolution.12-14

A co-evolutionary approach will be used to make a detailed analysis of the potential implementation of preconceptional CF and HbPs carrier screening in the Netherlands, with a focus on different levels of sociotechnical development, including (1) a micro-level of laboratories and clinics, serving as sociotechnical ‘niches’ in which new technological options can be developed; (2) a meso-level of extended practices in society, serving as sociotechnological ‘regimes’ in which technologies can be embedded; (3) a macro-level of established institutions, infrastructure, and broadly shared values and beliefs, constituting a sociotechnical ‘landscape’ which creates opportunities or constraints for technological
developments. Consequently, it is possible to identify questions and challenges that have to be faced at each of these levels.

**Micro-level: sociotechnical niches**

Laboratories and clinics can be considered as niches which offer a relatively protected environment for research and experimentation, and which provide opportunities to investigate and to learn about the potentials of promising technologies. Preconceptional CF and HbPs carrier screening has only been studied at micro-level in most countries: a few pilot studies have been carried out in Europe. Except for Italy (Sardinia), Greece, Turkey, Cyprus, and also Taiwan, where premarital screening programs have been embedded in more extended health care practices.

**Meso-level: sociotechnical regimes**

Learning about a new technology also involves learning about its potential, effectiveness and acceptability in conditions outside the experimental setting. These conditions are formed by already established technologies, practices, suppliers, users, rules and values, constituting specific regimes at the meso-level of sociotechnical development. When an existing sociotechnical regime offers the conditions that are needed for successful implementation, the introduction and societal embedding of a new technology can be a quite straightforward process. However, since preconceptional health care settings are absent in most European countries, the implementation of a preconceptional carrier screening programme will require great changes in the practices, routines and attitudes in current reproductive health care.

**Macro-level: sociotechnical landscapes**

Sociotechnical regimes will be embedded in a relatively stable environment of institutions, material infrastructure, and economic, social, political, legal, cultural and demographic relationships. Thus, opportunities for technological change and the evolution of regimes will be determined by conditions at the macro-level of sociotechnical landscape. The high percentage (80-90%) of planned pregnancies in the Netherlands is a condition at landscape level which favours the implementation of preconceptional carrier screening. However, in the absence of a public health authority for reproductive health care in the Netherlands, it will be difficult to establish a new regime of preconceptional health care that could facilitate the implementation of a preconceptional carrier screening program.
Attunement between actors

Co-evolution could be regarded as a process of learning, which takes place at different levels of sociotechnical development, which involves both technology and society, and in which a variety of actors will be involved: scientists, physicians, patients, advisory councils, and regulatory authorities. A prerequisite for successful implementation of a new technological option will therefore be attunement between these actors with regard to various issues relating to the new technology (Figure 1).

![Figure 1](image)

Important issues to be addressed in these processes of learning and attunement are: (1) requirements to be met by the new technology, (2) facilities and services needed, (3) prospective users and demand, and (4) political and cultural acceptability. In these terms, the main issues to be resolved when considering the implementation of preconceptional CF and HbPs carrier screening are the following.

Attunement with regard to technological options

How should the available technological options for CF and HbPs carrier screening be further developed or adapted? There are some problems that need particular attention. Firstly, the sensitivity of CF carrier testing depends on the method of DNA analysis, the selected gene mutation panel, and the persons’ ethnicity. The sensitivity of the HbPs test also varies between different ethnic groups and different HbPs. Secondly, it is not easy to confirm a case of alpha-thalassemia, which shows the same blood test results as anaemia based on iron deficiency. Thirdly, genotype-phenotype correlations are impossible...
to predict, which complicates the process of informed decision-making for carrier couples.

**Attunement with regard to facilities and services**

How should preconceptional CF and HbPs carrier screening be offered and by whom? The involvement of general practitioners and community health services is one option, which only has been investigated for CF in a research setting in the Netherlands.\(^{33,34}\) Another option might be incorporation in a broader preconceptional health care setting, in which also other preconceptional advice can be given. Such a setting does not yet exist in the Netherlands, although initiatives have been taken at niche level.\(^{35}\)

Furthermore, what kind of infrastructure or complementary technologies, skills and facilities should be available? The involvement of general practitioners assumes a level of genetic knowledge that may not be provided for by their current professional education.\(^{36}\) Implementation will therefore require special training programs. In addition, laboratory capacity should be available for large-scale DNA analysis, a condition which, in the Netherlands, has only recently been established.

**Attunement with regard to users and demand**

Who belongs to the target population for preconceptional CF and HbPs carrier screening, and what are the prospective users’ needs and wishes? An important determinant of the risk of being a CF or a HbPs carrier is ethnicity. CF is common in people of European descent, and from the Middle Eastern and Mediterranean countries. HbPs are common in South East Asia, Africa, the Middle East and the Mediterranean countries. A choice must be made between targeted ancestry-based screening and universal carrier screening.

Furthermore, how can we inform the target population? An important issue in this respect is whether preconceptional CF and HbPs carrier screening will be a population-based, offered to everyone of reproductive age, or individual based, offered to couples attending a broader preconceptional health care service.

Finally, who will articulate a demand for preconceptional CF and HbPs carrier screening? The prospective users are not to be expected to articulate demand, because most healthy carriers are not aware of their risk of having a child with CF or HbPs. In the Netherlands, preconceptional care is advocated by the Dutch Genetic Alliance (VSOP), by clinical geneticists and other health care professionals. Moreover, studies investigating attitudes towards preconceptional
CF carrier screening show a clear interest among people in the target population.\textsuperscript{37,38}

\textit{Attunement with regard to political and cultural acceptability}

Does preconceptional CF and HbPs carrier screening meet internationally formulated criteria for genetic screening and is it consistent with important societal values? Henneman \textit{et al.} (2002) concluded that preconceptional CF carrier screening meets the general genetic screening criteria,\textsuperscript{39} but did not take the uncertainties of the test-sensitivity among various populations into account. When these criteria have been fulfilled, more specific criteria, especially concerning the conditions under which implementation can take place; will have to be investigated in pilot studies. Besides complying with criteria, there is also need for wider professional and public debate about the implications of CF and HbPs carrier screening for health care and society. On the one hand, worries exist about the medicalisation of the preconception period, discrimination of carriers, impairment of the freedom of choice, and the desirability of selective termination of a pregnancy after prenatal diagnosis.\textsuperscript{40,41} On the other hand, there are also positive aspects, such as the value of informed choice for all couples planning a pregnancy, and the availability of more reproductive options then prenatal diagnosis and selective abortion only.

In summary, from a multi-level co-evolutionary perspective, the major issues in the implementation process of preconceptional carrier screening have been identified. These issues include questions about the test characteristics, the organization of preconception health care, the accessibility of the target population, articulation of demand, and questions about political and cultural acceptability.

\textbf{Lessons from existing health care programs relevant for preconceptional carrier screening}

\textit{An example of preconceptional health care: folic acid advice}

Since the early 1990s, health authorities in several countries have advised women to increase their periconceptional folic acid intake, from four weeks before until eight weeks after conception, because of the beneficial effects of folic acid in the prevention of foetal neural tube defects.\textsuperscript{42-44} In the following, the implementation of this advice is discussed as an interesting attempt to realise a sociotechnical change focussing on the same target population as for
preconceptional carrier screening, namely women (or couples) planning a pregnancy.

To increase periconceptional folic acid intake, some countries have implemented the advice for folic acid supplementation with tablets, and others have opted for food fortification, or for a combination of both.\textsuperscript{45} However, in most countries both options were difficult to implement because of the lack of an existing regime in which they could easily be embedded. In the Netherlands, food fortification with folic acid was initially preferred,\textsuperscript{46} but prohibited under the Dutch legislation, resulting in folic acid supplementation with tablets as the only option available. Consequently, it was left to the individual choice of women planning a pregnancy to increase their folic acid intake. In the Dutch context, therefore, attunement with regard to periconceptional folic acid supplementation has been shaped by three important conditions at regime and landscape level: absence of a preconceptional health care setting, existence of legislation prohibiting food fortification, and a high percentage (80-90\%) of planned pregnancies.\textsuperscript{25,26}

However, as the Dutch experience shows, women planning a pregnancy constitute a population that is difficult to reach, rapidly changing, and generally unaware of preconceptional risks and options for prevention. Under these circumstances, the implementation of the folic acid advice required sustained and structural efforts to inform a constantly changing target group. The Dutch government policy-making has been ad hoc in this respect, perhaps also because certain groups (such as patient organizations and public health authorities) who might have expressed interest on behalf of the target population did not actively do so. Only one mass media campaign was organized in 1995 with limited effect. More recent initiatives to inform women who use contraceptives about the benefits of folic acid supplementation when they are planning a pregnancy, seem to be more effective.\textsuperscript{47}

More than 10 years after the first scientific publications, no significant improvement has been found in the trends of total prevalence of neural tube defects across Europe. Only in those countries or areas in which the government adopted the folic acid advice strategy at an early stage (England and Wales, Ireland, the Netherlands and Hungary), a slightly decreasing trend has been reported.\textsuperscript{48,49} Obviously the implementation of the folic acid advice has been less successful than was hoped for.
The most important lessons to be learnt from this preconceptional information strategy are the following:
- the target group of women planning a pregnancy is difficult to reach and rapidly changing;
- demand will not be articulated by the target group because women are generally unaware of preconceptional risks and options for prevention;
- a more structural implementation of the folic acid advice will require changes at regime and landscape level, including the establishment of a preconceptional health care setting and legislation permitting food fortification.

An example of large-scale application of DNA technology: screening for familial hypercholesterolemia

Familial hypercholesterolemia (FH) is an autosomal dominant disorder, in which a mutation in one of the Low Density Lipoprotein (LDL) receptor alleles causes a high cholesterol level, which may give rise to premature cardiovascular mortality. Maximum health benefit can be obtained if treatment is started as early as possible.

In the Netherlands a FH cascade screening program was established in 2003. After the identification of a FH mutation in an ‘index’ patient, family members who are at a high risk of carrying the mutation (often 50%, sometimes 25%), are invited for screening. The scope of the Dutch program is unique and offers a successful example of sociotechnical change at regime and landscape level.

In the 1990’s, a research group at the Academic Medical Center (AMC) in Amsterdam established a Foundation for the Detection of Inherited Hypercholesterolemia (StOEH) which developed a small experimental screening program and also laid the foundation for the nationwide program that started in 2003. Both the research setting and the experimental program provided a niche in which attunement could be achieved with regard to the technical options for FH carrier screening. For the nationwide screening program, it was decided that DNA analysis and cholesterol concentration measurements would be of complementary value.

Before the creation of a nation-wide program, various models for FH carrier screening have been discussed extensively. Should screening be offered to the whole population, to everyone visiting a physician, to families at risk, or only to people with a cardiovascular history? In this debate, the StOEH model – a screening program focussing on families at risk – was readily accepted as an approach which had proven its strengths. On the basis of this cascade approach, identification of the target group is straightforward, and it
can be easily reached. However, the direct approach of cascade screening has also been disputed in the Netherlands because of its limited scope, and initiatives have been taken to start a mass media campaign providing information about the health risks of high cholesterol levels.

In the 1990s, mutation analysis was dependent on a well-established regime of clinical genetic services in the Netherlands, according to which only clinical genetic laboratories were allowed to carry out DNA diagnostic tests. However, these laboratories were not adequately equipped to cope with the increasing number of people to be screened. Therefore, the Ministry decided that from 2001 onwards other clinical laboratories might also be licensed to carry out DNA diagnostic tests. This resulted in the initiation of FH screening in the vascular medicine laboratory at the AMC in Amsterdam, which had ample facilities for large-scale detection of mutations in the \( LDL \) gene. Thus, a new (screening) infrastructure was created, independent from the existing clinical genetics regime, which made large-scale DNA testing available for the thousands of participants in the FH screening program. The successful implementation of this program also highly depended on general practitioners and medical specialists who had to identify the FH (index) patients and on genetic fieldworkers, trained and educated by the StOEH, who were responsible for the contacts with family members and the collection of blood samples. At the political level, the National Health Care Insurance Board was given special responsibilities for national co-ordination, which was considered to be a vital requirement for the adequate organization and monitoring of the screening program.

In other words, whereas the implementation of the folic acid advice in the Netherlands was mainly restricted by existing sociotechnical conditions, the introduction of FH screening resulted in a change in conditions at both regime and landscape level. A number of factors may have been important in bringing about this change. Firstly, there was a strong articulation of demand for FH screening, thanks to the efforts of a Dutch patient organization (Stichting Bloedlink) which has been very active in putting FH on the scientific and political agenda. Secondly, wider interest in FH screening has been raised by the experimental program organized by the StOEH in close collaboration with various stakeholders and with financial support from a pharmaceutical firm and the government. In response to these activities, in 2001 the Dutch Minister of Health, Welfare and Sport explicitly supported the aim to identify all FH patients by 2010. And thirdly, the Dutch government also played an important role with regard to the problems that FH patients were experiencing in obtaining life insurance, by putting pressure on the relevant parties to come to an agreement.
In conclusion, the most important lessons to be learnt from the implementation of FH screening in the Netherlands are the following:

- articulation of demand has been clear-cut as a result of collaboration between an active patient organization and the various parties involved in clinical research;
- an experimental program, combining research with pilot screening, served as an important niche, in which various stakeholders were involved in the processes of learning and attunement with regard to the design, organization, demand for and acceptability of a nationwide screening program;
- large-scale implementation of DNA carrier screening required a change of regime, allowing DNA diagnostic tests to be provided independent of existing clinical genetic services;
- The Dutch government played an important role in orchestrating the processes of attunement between the various actors involved.

**Discussion**

The aim of this paper was to obtain more insight into the process of potential implementation of preconceptional CF and HbPs carrier screening in the Netherlands. Table 1 gives an overview of various processes of attunement, in which lessons learnt from two already existing health care programs, are related to preconceptional carrier screening.

Besides the advantages of the comparison with these existing programs, limitations should also be mentioned here. Firstly, in the folic acid advice, only women had to be reached, instead of couples planning a pregnancy. Furthermore, following the advice to take folic acid tablets for prevention of neural tube defects, gives the participating women more control than finding out to be a carrier couple with only difficult reproductive decisions available. Secondly, since FH cascade screening program also involves a large-scale application of DNA technology, the history of its implementation is clearly relevant for the program at issue. However, FH screening results in the identification of persons being at risk for a disorder themselves, as FH is an autosomal dominant disorder, whereas carrier screening identifies healthy couples with an increased risk of having a child with CF or HbPs. This fact might be one of the explanations for the successful implementation of the FH screening program.
Table 1
A sociotechnical analysis of the relation of two existing health care programs to preconceptional CF and HbPs carrier screening

<table>
<thead>
<tr>
<th>Existing health care programs:</th>
<th>Preconceptional CF and HbPs carrier screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>folic acid</td>
<td></td>
</tr>
<tr>
<td>FH cascade screening</td>
<td></td>
</tr>
</tbody>
</table>

Attunement with regard to:

Technological options
- Yes: food fortification - supplements by tablets
- Yes: technology allowed outside the regime of clinical genetics
- No: insufficient knowledge about:
  - test sensitivity for CF
  - detection methods for HbP variants

Facilities and services
- Insufficient: structural information is lacking
- Yes: StOEH - specifically trained genetic field workers outside the regime of clinical genetics
- No: unclear at this moment who should offer and perform the screening, because there is no preconceptional health care setting - deficient genetic knowledge among health care professionals

Demand
- No: target group is unaware
- Yes: Bloedlink
- No: target group is unaware - no articulation from government or public health organisation

Political and cultural acceptability
- Limited: food fortification was not allowed in the Netherlands - target group is reached insufficiently
- Yes: no discrimination in insurance: insurance companies were pressured by the government to achieve attunement
- Yes, probably: cultural acceptability among people in the target group in a pilot study for CF carrier screening

FH = familial hypercholesterolemia; CF = cystic fibrosis; HbPs = haemoglobinopathies, e.g. sickle cell disorders and thalassemia

a Foundation for The Detection of Inherited Hypercholesterolemia
b Dutch patient organisation for FH

Conclusion

What are the constraining and enabling factors for the implementation of preconceptional CF and HbPs carrier screening in the present (Dutch) health care system?

First of all, the lessons learnt from the implementation of the folic acid advice have made it clear that reaching couples planning a pregnancy is a major challenge. Demand will not be articulated by a target group unaware of options for prevention, and general information campaigns will only have a limited effect in raising awareness about options for carrier screening. Another
constraining factor is the current limitation to the sensitivity of CF carrier screening in various ethnic populations. On the other hand, the high percentage of planned pregnancies in the Netherlands favours the implementation of preconceptional carrier screening. Moreover, as a result of the implementation of nation-wide FH screening in the Netherlands, the national co-ordination of screening initiatives in the Netherlands has been strengthened and an infrastructure has been created which will also facilitate large-scale DNA testing for the purpose of preconceptional carrier screening.

What sociotechnical conditions on micro-, meso- and macro-level have to be created for a successful implementation of preconceptional carrier screening?

As became clear from the Dutch experience with FH screening, experimental programs, in which research is combined with pilot screening, may serve as an important niche in which professionals, patient organizations and other stakeholders can be involved in processes of learning and attunement with regard to the design, organization, demand for and acceptability of nation-wide preconceptional CF and HbP carrier screening. However, successful implementation will also depend on changes at both regime and landscape level, including the establishment of a new preconceptional health care setting. An important lesson that was learnt from the experiences with FH screening is that such regime changes will be difficult to achieve without an active orchestrating role of the government, especially when there is no articulation of demand from prospective users. In terms of the sociotechnical analysis, the government might act as the initiator of societal experiments, involving various relevant stakeholders in the processes of learning and attunement being necessary for a successful implementation. Evidently, as an important condition at landscape level, there is need for a clearly visible public health authority which can take the responsibility for the co-ordination, monitoring and evaluation of such initiatives in the domain of public health care.
Reference List


CFTR mutations in turkish and north african cystic fibrosis patients in europe: implications for screening

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Abstract

Aims: 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.

Methods: A survey among 373 European CF-centers asking which CFTR mutations had been found in Turkish and North African CF-patients.

Results: 31 and 26 different mutations were reported in Turkish and North African patients, identifying 64.2% (113/176) and 87.4% (118/135) alleles, respectively (p<0.001). The mean sensitivity (detection rate) of three most common CFTR mutation panels to detect these mutations differed between Turkish and North African people: 44.9% (79/176) versus 69.6% (94/135)(p<0.001), and can be increased to 57.4% (101/176) and 79.3% (107/135) (p<0.001), respectively, by expanding these panels with 13 mutations which have been found on two or more alleles.

Conclusion: 35.8% and 12.6%, respectively, of CF alleles in Turkish and North African patients living in Europe now, had not been identified. Among these populations, the test-sensitivity of common CFTR mutation panels is insufficient for use in screening programs in Europe, even after expansion with frequent Turkish and North African mutations. This raises questions about whether and how to implement CF carrier and neonatal screening in a multi-ethnic society.
Introduction

Cystic Fibrosis (CF) is one of the most common life-shortening autosomal recessive disorders in people of European descent. The disease is characterized by chronic bronchopulmonary infection, gastrointestinal problems (meconium ileus, pancreatic insufficiency, diabetes mellitus, liver cirrhosis), growth failure, and male infertility. The key diagnostic test for CF is a sweat-test, and further support for diagnosis is provided by the identification of two disease-causing mutations in the gene for CF transmembrane conductance regulator (CFTR). A concentration of chloride in sweat above 60 mmol/l is considered to be diagnostic of CF. The clinical severity and course of CF shows considerable variability. Although the medical care that is provided has greatly improved the life-expectancy and quality of life of patients with CF, the disease is still not yet curable. The current median life-expectancy of a newborn baby with CF is approximately 30-40 years. The overall CF carrier frequency among Caucasians is 1 in 20-30 individuals, resulting in 1 in 400-900 carrier couples, and a prevalence of CF at birth of 1 in 1600-3600. Although the relative frequency of CF carriers among people who are of non-European descent is not known very well, CF is found in these populations as well. For example, the estimated minimum CF carrier frequency among Turkish people is 1 in 50.

Since identification of the CFTR gene in 1989, more than 1400 mutations have been identified, most of which however are very rare (http://www.genet.sickkids.on.ca/cftr). Knowledge of these mutations is needed for diagnostic purposes, for counseling CF families, and for screening, both preconceptional and prenatal to facilitate informed reproductive decisions, or neonatal to improve prognosis. In 1997, the American National Institutes of Health (NIH) Conference recommended that genetic screening for CF mutations should be offered to adults with a positive family history of CF, partners of individuals with CF, couples currently planning a pregnancy, and couples seeking prenatal care. In most European countries, however, screening for CF and CF carrier status in individuals with no family history of CF is not current practice.

A challenge in the implementation of preconceptional CF carrier and neonatal CF screening is the fact that the commercially available CF carrier screening panels offer a limited panel of mutations, leading to insufficient sensitivity (detection rate) for certain groups within ethnically diverse populations. A standard panel of CFTR mutations should provide the greatest pan-ethnic detectability that can be practically performed. Therefore, in the U.S., standard recommendations have been made for the most appropriate CF mutation panel for screening purposes in different ethnic populations.
In Europe, the major immigrant groups with estimated carrier frequencies of at least 1 in 50 persons, are people of Turkish and North African origin. Common European mutations, like F508del, have a lower frequency in people of Turkish and North African origin, and high levels of mutation heterogeneity are found among CF-patients from these populations. Consequently, in Turkey and North Africa, there is a low detection rate using commercially available European CF carrier screening panels. This observed low detection rate might also be explained by the methods of DNA-analysis employed in these countries, which may not be sensitive enough, and additionally, it is possible that not all patients in the above-mentioned studies actually had CF.

In Europe, until now, there is insufficient attention for this lower CF (carrier) detection rate in the home-countries of major immigrant groups and the implications for (the implementation of) preconceptional CF carrier and neonatal CF screening. Probably, the quality of clinical diagnostics and the laboratory molecular diagnostic capacities are assumed to be better in Europe, than in Non-European countries. However, it is also possible that the non-random selection of immigrants happens to favor the CFTR mutations which can be detected yet. The goal of this study, therefore, was 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 CF-patients among these Turkish or North African immigrants. We hope that the results will enable us to formulate recommendations for the design of a CFTR mutation panel with a test-sensitivity that will also be suitable for CF (carrier) screening among Turkish and North African immigrants in Europe.

**Materials and methods**

**The procedure**

In November 2004, a survey was conducted among 373 CF centers in Northern and Western Europe. Addresses were obtained from the internet and from the personal database of a member (HGMH) of the board of the European Cystic Fibrosis Society (ECFS). All centers were sent an invitation and one specimen of a questionnaire, together with background information about CFTR mutations among CF-patients with ancestors from Turkey or North Africa. The letters were sent to pediatric as well as adult CF centers in Belgium (n=11), the Czech Republic (n=11), Denmark (n=2), Finland (n=2), France (n=67), Germany (n=113), Italy (n=26), the Netherlands (n=13), Norway (n=1), Romania (n=9), Slovakia (n=2),...
Spain (n=62), Sweden (n=4), Switzerland (n=9), and the United Kingdom (n=40). Two reminders were sent in January and April 2005, respectively. All centers received the questionnaire in English, except for the German and the French centers, who received the questionnaire in their native language. The study was approved by the Medical Ethics Committee of the VU University Medical Center.

**The questionnaire**

In the letter of invitation the centers were asked to complete a questionnaire for every CF patient, alive or deceased, with ancestors from Turkey and/or North Africa (Morocco, Algeria, Tunisia, Libya, and Egypt) who had been diagnosed in the past four years and earlier. The physicians were asked to make copies of the questionnaire if more than one CF patient met the criteria for inclusion in the survey. CF-patients who had only one parent originating from Turkey or North Africa should also be included. In addition to questions about gender, age, age at diagnosis, and paternal and maternal ancestral origin, the questionnaire also included questions about clinical aspects of the CF diagnosis (results of the sweat-test, presence and degree of lung disease, pancreatic insufficiency, etc.), whether molecular analysis had been performed, which molecular detection method had been used for DNA-analysis, whether CFTR mutations had been identified and, if so, which ones.

Between April 2005 and January 2006, some CF centers were asked by letter or e-mail to provide additional information about consanguinity of parents, whether or not the patients were related to each other, and information about specific unusual mutations that had been reported.

**Data-analysis**

To study the identity and frequency of the CFTR mutations reported in the questionnaires, we calculated the total number of independent alleles in our study. To do this, we included both alleles of patients with both parents originating from Turkey or North Africa and one allele of patients with one parent originating from these regions, if it was possible to find out by the physician who filled out the questionnaire, which allele was of Turkish or North African origin. Furthermore, only the questionnaires concerning unrelated CF-patients were included. For homozygous patients with consanguineous parents, one allele was excluded under the assumption of identity by descent of the two alleles in the patient.

To estimate the test-sensitivity of the most frequently used methods of DNA-analysis, we took the three methods of DNA-analysis that were reported most frequently in our survey, excluding the denaturing gradient gel electro-
phoresis (DGGE) technique and sequencing the entire coding region. Although these two latest methods are highly sensitive and can detect (almost) 100% of mutations, they are impractical for population screening on a great scale and also may produce indefinite results regarding pathogenicity of “mutations” found. We analyzed the ability of each of these three methods to detect a mutation on an allele as well as their ability to “detect” a CF patient who has on at least one allele a mutation that belongs to the CFTR mutation panel. As the sensitivities of these three methods of DNA-analysis did not differ significantly (see Results section), we summarized the sensitivity of all three methods as one mean test-sensitivity of frequently used methods of DNA-analysis. Finally, we studied whether CF-patients with no identified mutations, and patients with one or two reported mutations, differed in age, age at diagnosis and various clinical aspects: the results of the quantitative sweat-test (highest value when more than one sweat-test had been reported), the presence of pancreatic insufficiency, and the presence of lung disease (e.g. presence of chronic colonization, abnormal chest X-ray, and forced expiratory volume in one second, expressed as a percentage of the predicted values for gender and height [FEV1 %pred]). In the case of deceased CF-patients, their age at death was included in the analysis.

Among the related CF siblings, clinical heterogeneity was observed as could be expected. For the analysis of these clinical aspects, therefore, we performed a random selection among the related CF siblings. Restricting these analyses only to index patients may lead to a too pessimistic view on clinical presentation. The reason for this is that family members with of a patient with an autosomal recessive disorder, who already has been diagnosed with that specific disorder, are expected to be diagnosed earlier than patients without a previously diagnosed family member. For CF, the earlier diagnosis will lead to an earlier treatment and a better clinical presentation. In addition, only taking into account non-index CF-patients for this analysis, would give a too optimistic view. In general, the Chi-square test was used for the statistical comparison of proportions, and means were compared with the t-test. The 95% confidence intervals (CI) were also calculated, as an indication of the precision of our estimates. The data were analyzed in SPSS 11.0 for Windows.

Results

Response

Of the 373 invitations that were sent, 26 were undeliverable. In total, 60.2% (209/347) of the remaining centers responded: 34.0% (71/209) of them had one
or more CF patient(s) with parents originating from Turkey or North Africa, 56.0% (117/209) had no such CF-patients, and 10.0% (21/209) responded that they did not register ethnicity. Of the 258 questionnaires that were returned, 16 CF-patients were excluded because neither of their parents was of Turkish or North African origin. Of the remaining 242 questionnaires, 96 (39.7%) and 84 (34.7%) questionnaires were returned from Germany and France, respectively. No cases were reported from the Czech Republic, Finland, Slovakia or Sweden.

Table 1
Parental origin and number of mutations reported among CF-patients included in the survey

<table>
<thead>
<tr>
<th>Origin</th>
<th>Number of CF-patients</th>
<th>Number of CF-patients with an identified mutation on</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>With DNA analysis reported</td>
<td>Number of unrelated patients</td>
<td>both alleles, n (%)</td>
<td>one allele, n (%)</td>
</tr>
<tr>
<td>One parent from</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Turkey</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>- North Africa</td>
<td>27</td>
<td>27</td>
<td>24</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>36</td>
<td>32</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Both parents from</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Turkey</td>
<td>125</td>
<td>114</td>
<td>99</td>
<td>63</td>
<td>9</td>
</tr>
<tr>
<td>- North Africa</td>
<td>80</td>
<td>77</td>
<td>67</td>
<td>55</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>205</td>
<td>191</td>
<td>166</td>
<td>118</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>242</td>
<td>227</td>
<td>198</td>
<td>142 (72)</td>
<td>25 (12)</td>
</tr>
</tbody>
</table>

a Column B is a sub-set of column A; column C is a sub-set of column B.
b The percentages are based on the total of 198 unrelated cases in which DNA-analysis was reported.

Parental origin, number of mutations reported and consanguinity among homozygous patients

In Table 1, the 242 CF-patients reported are categorized according to their parental origin and number of mutations found. Information about DNA-analysis had been reported in the questionnaires concerning 227 of these 242 patients. There were 198 unrelated CF-patients among these 227 patients. In total, 166 out of these 198 had both parents originating from Turkey or North Africa. All 166 patients, including 7 deceased patients, had a clinical diagnosis of CF. They originated from Turkey (n=99), Morocco (n=34), Algeria (n=25), Tunisia (n=7) and Egypt (n=1), respectively. Of the patients originating from Turkey, 66.7% (66/99) and 12.1% (12/99) were living in Germany and France, respectively. Those with parents originating from Morocco or Algeria, 64.4% (34/59) and 13.6% (8/59) were living in France and Belgium, respectively and only one Algerian patient was living in Germany.
Among these 166 patients, there were 88 homozygous patients, 30 compound heterozygous patients, 18 compound heterozygous patients with one identified mutation; and 30 patients with no identified mutations. In 43 of the 88 homozygous patients consanguinity of the parents was reported, in 12 cases the parents did not have a consanguineous relationship. In addition, for 33 of the 88 homozygous patients we received no information about consanguinity of parents, and for the 30 patients with no identified mutations, we did not ask for further information about consanguinity of parents.

For 22 of the 32 CF-patients who had only one parent originating from Turkey or North Africa, it was known which allele was of Turkish (n=3) or North African origin (n=19), and which allele was from the non-Turkish or non-North African parent.

**Identity and frequency of CFTR mutations**

Table 2 shows the identity and frequency of the CFTR mutations described for a total of 311 independent alleles. This number is based on 332 alleles of 166 patients with both parents originating from Turkey or North Africa, including the 60 alleles of patients with no identified mutations, plus 22 alleles of 22 patients with one parent originating from these regions, minus 43 alleles of homozygous patients with consanguineous parents, of whom only one allele was taken into account. Of the 311 independent alleles, 176 and 135 were of Turkish and North Africa origin, respectively. Table 2 also presents the number of patients among the 166 CF-patients with both parents originating from Turkey and/or North Africa, with the individual CFTR mutations reported on both alleles (see column “Homozygote”), or reported on one allele (see columns “Compound heterozygote: two mutations found” and “Compound heterozygote: one mutation found”).

A total of 50 different CFTR mutations, were reported in the questionnaires, 27 of which on two or more independent alleles, and 7 of which on both Turkish and North African alleles (see Table 2). There was a significant difference in the frequency of CFTR mutations reported on Turkish and North African alleles: 31 and 26 different mutations were reported in Turkish and North African patients, identifying 64.2% (113/176; 95% CI: 57.1-71.3%) and 87.4% (118/135; 95% CI: 81.8-93.0%) alleles, respectively (p<0.001). One of them was F508del, which was identified on 18.8% (33/176; 95% CI: 13.0-24.5%) and 29.6% (40/135; 95% CI: 21.9-37.3%) of Turkish and North African alleles, respectively (p=0.03).
### Table 2
Identity and frequency of CFTR mutations on unrelated Turkish (Tr) and North African (NA) CF alleles

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Exon</th>
<th>Total number of alleles</th>
<th>Number of CF-patients with this mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All:</td>
<td>Tr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F508del c</td>
<td>10</td>
<td>73</td>
<td>33</td>
</tr>
<tr>
<td>N1303K</td>
<td>21</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>711+1G&gt;T</td>
<td>intron 5</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>G542X</td>
<td>11</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>R1162X</td>
<td>19</td>
<td>11</td>
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</tr>
<tr>
<td>2183AA-&gt;G</td>
<td>13</td>
<td>9</td>
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</tr>
<tr>
<td>W1282X</td>
<td>20</td>
<td>7</td>
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<tr>
<td>2789+5G&gt;A</td>
<td>intron 14b</td>
<td>6</td>
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<tr>
<td>L227R</td>
<td>6a</td>
<td>4</td>
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<tr>
<td>1677delTA</td>
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<td>2184insA</td>
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<td>R334W</td>
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<tr>
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<tr>
<td>L732X</td>
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<tr>
<td>2184delA</td>
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<td>3</td>
</tr>
<tr>
<td>del exon 1-4</td>
<td>14</td>
<td>3</td>
<td>3</td>
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<tr>
<td>del exon 19</td>
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<tr>
<td>3849+10kbC&gt;T</td>
<td>intron 19</td>
<td>2</td>
<td>-</td>
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<tr>
<td>S549N</td>
<td>11</td>
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</tr>
<tr>
<td>3120+G&gt;A</td>
<td>intron 16</td>
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<td>-</td>
</tr>
<tr>
<td>3601-2A&gt;G</td>
<td>intron 18</td>
<td>2</td>
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<tr>
<td>D1152H</td>
<td>18</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>E1104X</td>
<td>17b</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>S1159F</td>
<td>19</td>
<td>2</td>
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<tr>
<td>S977F</td>
<td>16</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>2347delG</td>
<td>13</td>
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<td>-</td>
</tr>
<tr>
<td>4096-3C&gt;G</td>
<td>intron 21</td>
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<td>1</td>
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<tr>
<td>E831X</td>
<td>14a</td>
<td>1</td>
<td>1</td>
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<tr>
<td>L619S</td>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1525-1G&gt;A</td>
<td>intron 9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F1052V</td>
<td>17b</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3130delA</td>
<td>17a</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>R352Q</td>
<td>17</td>
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<td>1</td>
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<tr>
<td>1812-1G&gt;A</td>
<td>intron 11</td>
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<td>-</td>
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<tr>
<td>R553X</td>
<td>11</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>IVS8-5T</td>
<td>intron 8</td>
<td>1</td>
<td>1</td>
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<tr>
<td>R1066C</td>
<td>17b</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>3129del4</td>
<td>17a</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>D110H</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>R117H</td>
<td>4</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>S945L</td>
<td>15</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>1716G/A</td>
<td>10</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>711+3A&gt;G</td>
<td>intron 5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>R75X</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>R764X</td>
<td>13</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>S1196C</td>
<td>19</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S492F</td>
<td>10</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>G551D</td>
<td>11</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>del exon 2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Subtotal: 231 113 118

No mutation: 80 63 17

Total: 311 176 135

---

a N=311 alleles, based on 166 CF-patients (332 alleles) with both parents and 22 CF-patients (22 alleles) with one parent from Turkey or North Africa, minus 43 alleles of homozygous CF-patients with consanguineous parents of whom only one allele was taken into account.

b N=166 CF-patients with both parents originating from Turkey or North Africa: n=88 homozygous, n=48 compound heterozygous, of which 18 CF-patients with only one identified mutation; and 30 CF-patients with no identified mutations (not in the table).

c In one situation two related CF-patients were cousins, instead of siblings, and compound heterozygous for F508del / 1525-1G>A. These F508del and the 1525-1G>A mutations were counted one time.

d 121_620-694del (53.498bp)ins53bp.
Most frequently used methods of DNA-analysis and sensitivity

Table 3 gives an overview of the methods of DNA-analysis that were reported in the questionnaires concerning 166 patients with both parents originating from Turkey or North Africa. The three most frequently reported methods of DNA-analysis (excluding denaturing gradient gel electrophoresis (DGGE) and sequencing of the entire coding region), were 1) oligonucleotide ligation assay (OLA, Celereja Diagnostics), 2) reverse dot blot analysis (INNOLiPA, Innogenetics), and 3) amplification refractory mutations system (ARMS) methods, such as Elucigene-29 and 30, Tepnel Diagnostics, in which 33, 36 and 35 CFTR mutations form a panel, respectively. A total of 26 CFTR mutations belong to the panels of all of three methods of DNA-analysis. As at this moment, the INNOLiPA-17 method is often used in combination with the INNOLiPA-19 (personal communication: JJP), we present the combined results of the INNOLiPA-17 and INNOLiPA-19 methods, and we also combined the results of the Elucigene-29 and Elucigene-30 methods.

Table 3
Methods of DNA analysis reported for 166 CF patients with both parents originating from Turkey or North Africa

<table>
<thead>
<tr>
<th>Method of DNA-analysis</th>
<th>All CF-patients, n (%)</th>
<th>CF-patients with a mutation identified on both alleles, n</th>
<th>one allele, n</th>
<th>no alleles, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLA a</td>
<td>26 (15.7)</td>
<td>21</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>DGGE b</td>
<td>22 (13.3)</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>INNOLiPA 12</td>
<td>6 (3.6)</td>
<td>4</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>INNOLiPA 17</td>
<td>9 (5.4)</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>INNOLiPA unspecified</td>
<td>3 (1.8)</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Elucigene CF29 / CF30</td>
<td>3 (1.8)</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Other ARMS method c</td>
<td>8 (4.8)</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SSCP-gel d</td>
<td>5 (3.0)</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fragment length analysis</td>
<td>3 (1.8)</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Sequencing</td>
<td>5 (3.0)</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miscellaneous e</td>
<td>15 (9.0)</td>
<td>11</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>No information</td>
<td>61 (36.7)</td>
<td>34</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>166 (100)</td>
<td>118</td>
<td>18</td>
<td>30</td>
</tr>
</tbody>
</table>

a Oligonucleotide Ligation Assay
b Denaturing Gradient Gel Electrophoresis
c Amplification Refractory Mutations System
d Single-Strand Conformational Polymorphism
e Various methods of DNA-analysis which have each been reported less than three times in the questionnaires.

The sensitivity to detect a mutation on one allele in the present sample (detection rate) did not differ significantly between these three methods of DNA-analysis, and was 56.6% (176/311; 95% CI: 51.1-62.1%) for the OLA method, 53.7% (167/311; 95% CI: 48.2-59.2%) for the combination of INNOLiPA-17 and 19, and 55.9% (174/311; 95% CI: 50.4-61.5%) for the ARMS methods Elucigene-29 and 30, combining the data from Turkish and North-African patients. The estimated mean sensitivity of these three frequent methods of DNA-analysis to detect a mutation on one allele in the present sample was significantly lower for the
Turkish than for the North African alleles: 44.9% versus 69.6% (p<0.001) (see Table 4). There was no significant difference in the mean sensitivity to detect a mutation on the alleles of different North African countries (e.g. Morocco, Algeria, Tunisia, and Egypt). Also, the estimated mean sensitivity to “detect” a CF patient with at least on one allele a mutation that belonged to the CFTR gene mutation panel of these methods was significantly lower for the Turkish than for the North African patients: 50.2% versus 82.1% (p<0.001) (see Table 4).

<table>
<thead>
<tr>
<th></th>
<th>Mean sensitivity (%) to detect:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a mutation on one allele (95% CI)</td>
<td>a CF-patient (95% CI)</td>
</tr>
<tr>
<td><strong>Current CFTR mutation panels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkish *</td>
<td>44.9 (37.5-52.2)</td>
<td>50.2 (40.3-60.0)</td>
</tr>
<tr>
<td>North African *</td>
<td>69.6 (61.8-77.4) *</td>
<td>82.1 (72.9-91.3) *</td>
</tr>
<tr>
<td><strong>After expansion †</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkish</td>
<td>57.4 (50.1-64.7)</td>
<td>63.3 (53.8-72.8)</td>
</tr>
<tr>
<td>North African</td>
<td>79.3 (72.4-86.1) *</td>
<td>92.5 (86.2-98.8) *</td>
</tr>
</tbody>
</table>

* The three most frequently used methods of DNA-analysis in our survey were OLA, INNOLiPA 17/19 and Elucigene 29/30.

† Mean sensitivity, based on the test-sensitivities of the three most frequently used methods of DNA-analysis, is defined as the ability of these methods to detect a mutation on one allele.

‡ Mean sensitivity to detect a CF-patient, defined as the ability to detect a patient who has on at least one allele a mutation that belongs to the CFTR mutation panel of one of the three most frequently used methods of DNA-analysis.

§ Turkish alleles (n=176); Turkish patients (n=99).

¶ North African alleles (n=135); North African patients (n=67).

* Sensitivity after expansion of the current mutation panels with 13 Turkish and North African mutations, which have been found on 2 or more alleles.

* Mean sensitivity to detect a mutation on one allele or to detect a CF-patient differed significantly for the Turkish and North African alleles and patients; χ² test; df=1; p<0.001.

Thirteen mutations that were reported for two or more Turkish and/or North African alleles do not belong to the mutation panels of these three frequently used methods of DNA-analysis: L227R, 1677delTA, 2184insA, R709X, L732X, del exon 1-4 (121_620-694del (53.498bp)ins53bp), del exon 19, 3601-2A>G, D1152H, E1104X, S1159F, S977F and 2347delG. These mutations were found with other methods of DNA-analysis, than the three most frequently used methods. For example with sequencing of the entire CFTR coding region (see Table 3). Expansion of these three methods of DNA-analysis by those 13 mutations would increase the sensitivity to detect a CF mutation on one allele to 57.4 % (95% CI 50.1-64.7%) and to 79.3% (95% CI 72.4-86.1%) for the Turkish and North African alleles, respectively. The sensitivity to “detect” a Turkish or North African CF patient, with at least one mutations that belongs to such an expanded panel, would increase to 63.3% (95% CI 53.8-72.8%) and 92.5% (95% CI 86.2-98.8%), respectively (see Table 4).

**Clinical aspects related to number of mutations found**

To investigate whether the patients with no identified CFTR mutations or with only one identified mutation are clinically different from the patients with a mutation found
on both alleles, we focused on the clinical aspects of the 166 patients with both parents originating from Turkey or North Africa. Table 5 presents age (or age at death), age at diagnosis and clinical aspects for all 166 CF-patients, as well as for three sub-groups of these patients: CF-patients with a mutation identified on both alleles, on one allele or on no alleles.

In 25.9% (43/166) of the cases, no sweat-test had been performed (n=7) or the results of the test had not been reported (n=36). There was no difference in the number of patients without any reported sweat-test results, among the three sub-groups defined according to the number of identified mutations. The mean of the reported sweat-test results was 100.2 mmol chloride/l (95% CI: 96.4-104.0 mmol/l), and no differences were found between patients with a mutation reported on both alleles, on one allele or with no identified mutations (see Table 5). There were also no differences in the presence of lung disease or pancreatic insufficiency between these three sub-groups of CF-patients, but the patients with no identified mutations were significantly older (p<0.05) and older at diagnosis (p<0.005) than the patients with a mutation reported on one or both alleles (see Table 5).

Table 5
Age, age at diagnosis and clinical aspects of 166 CF-patients with both parents originating from Turkey or North Africa

<table>
<thead>
<tr>
<th>CF-patients with a mutation identified on</th>
<th>both alleles</th>
<th>one allele</th>
<th>no alleles</th>
<th>All CF-patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CF-patients (n=164)</td>
<td>118</td>
<td>18</td>
<td>30</td>
<td>166</td>
</tr>
<tr>
<td>Mean (years) (n=164)</td>
<td>11.6</td>
<td>9.8</td>
<td>16.0</td>
<td>12.2</td>
</tr>
<tr>
<td>Range</td>
<td>0.3-39.0</td>
<td>0.5-19.0</td>
<td>0.7-39.0</td>
<td>0.3-39.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>10.1-13.2</td>
<td>6.7-12.9</td>
<td>12.7-19.4</td>
<td>10.9-13.6</td>
</tr>
<tr>
<td>Age at diagnosis (years) (n=158)</td>
<td>2.7</td>
<td>2.2</td>
<td>7.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Mean (years)</td>
<td>1.6-3.7</td>
<td>0.2-4.2</td>
<td>3.3-11.7</td>
<td>2.4-4.5</td>
</tr>
<tr>
<td>Range</td>
<td>0.0-34.0</td>
<td>0.0-16.0</td>
<td>0.0-32.0</td>
<td>0.0-34.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.6-106.6</td>
<td>85.0-102.0</td>
<td>91.6-106.2</td>
<td>96.4-104.0</td>
</tr>
<tr>
<td>Sweat test (mmol chloride/l) (n=123)</td>
<td>101.6</td>
<td>93.5</td>
<td>98.9</td>
<td>100.2</td>
</tr>
<tr>
<td>Mean</td>
<td>35.0-170.0</td>
<td>67.0-120.0</td>
<td>63.0-124.0</td>
<td>35.0-170.0</td>
</tr>
<tr>
<td>Range</td>
<td>96.6-106.6</td>
<td>85.0-102.0</td>
<td>91.6-106.2</td>
<td>96.4-104.0</td>
</tr>
</tbody>
</table>
| Lung disease
  Presence of lung disease (n=166)(%)    | 92 (78.0)   | 11 (61.1)  | 24 (80.0)  | 127 (76.5)     |
  Chronic colonisation (n=135)(%)          | 73 (74.5)   | 8 (72.7)   | 21 (80.8)  | 102 (75.6)     |
  Abnormal chest X-ray (n=119)(%)          | 63 (72.4)   | 5 (62.5)   | 17 (70.8)  | 85 (71.4)      |
  FEV1% pred (n=95)(%)                     | < 40        | -          | 3 (12.0)   | 11 (11.6)      |
  40-80                                    | 8 (12.5)    | -          | 3 (12.0)   | 11 (11.6)      |
  ≥ 80                                     | 37 (57.8)   | 3 (50.0)   | 10 (40.0)  | 50 (52.6)      |
| Presence of pancreatic insufficiency, n (%) (n=161) | 95 (83.3) | 14 (77.8) | 22 (75.9) | 131 (81.4) |

a CF-patients with no identified mutations were significantly older than CF-patients with one or two mutations (F(2,163)=4.1; p=0.018).

b CF-patients with no identified mutations were significantly older at diagnosis than CF-patients with one or two mutations (F(2,157)=6.1; p=0.003).

c When more than one result of a sweat-test was reported, the highest value was taken into account.

d FEV1% pred: Forced Expiratory Volume in one second, expressed as a percentage of predicted values for gender and height.
Table 6 shows that in seven patients with no identified mutations and with no reported results of the quantitative sweat-test, the diagnosis of CF was confirmed in another way.

Table 6
Age, age at diagnosis and clinical aspects of seven CF-patients with no reported results of the sweat-test and with no identified mutations

<table>
<thead>
<tr>
<th>Patient number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6</td>
<td>11</td>
<td>17</td>
<td>13</td>
<td>9</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
<td>2.0</td>
<td>&lt;0.5</td>
<td>-</td>
<td>12.0</td>
</tr>
<tr>
<td>Abnormal sweat-test without reported results a</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chronic colonisation:</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>- Pseudomonas aeruginosa</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Haemophilus parainfluenzae</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Serratia marcescens</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Candida albicans</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abnormal chest X-ray</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>FEV1% pred b</td>
<td>40-80</td>
<td>&gt;80</td>
<td>&lt;40</td>
<td>40-80</td>
<td>&gt;80</td>
<td>40-80</td>
<td>40-80</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Other method of diagnosis:</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Cirrhosis of the liver</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- DIOS c</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a In the questionnaires concerning patient 1-5, it was only reported that the sweat-test had an abnormal test result, but no exact values were reported.
b FEV1% pred: Forced Expiratory Volume in one second, expressed as a percentage of predicted values for gender and height.
c DIOS: Distal Intestinal Obstructive Syndrome

Discussion

Identity and frequency of CFTR mutations in Turkish and North African patients in Europe: consequences for test-sensitivity

With this concerted action of 209 CF centers all over Europe, a large heterogeneity of CFTR mutations was demonstrated among Mediterranean people, which confirms previous reports. A total of 50 different mutations were identified on 74.3% of CF alleles. However, only 12 mutations that were reported in our survey, were also found by Kilinç et al., who identified 36 CFTR mutations that accounted for 75% of all CF chromosomes in patients living in Turkey. In addition, only 16 of the total of 27 mutations found earlier among 168 unrelated CF chromosomes in Turkey were present in the later study of Kilinç, and 12 of these 27 were also reported in our survey. The available data on North African CF-patients is limited, but Loumi et al. reported five CFTR mutations on 60% of Algerian chromosomes, four of which have also been reported in our survey. None of the four mutations exclusively found in the Tunisian
CF-patients,\textsuperscript{21} have been reported in our survey.

Our results show that the identity and frequency of CFTR mutations found among our sample of Turkish and North African immigrant patients in Europe differ to some extent from the observations reported in the literature among CF-patients, who are living in Turkey and North Africa. This can be just a random effect, but it is also possible, that it reflects a 'real' difference in the identity or frequency of the CFTR mutations, as a result of the fact that the immigrants do not form a random selection of the population in their countries of origin.\textsuperscript{28}

A significantly lower frequency of identified mutations was found among Turkish compared to the North African CF-patients: 64.2\% versus 87.4\% (p<0.001), with a lower frequency of F508del among Turkish patients (18.8\%) than among North African patients (29.6\%; p<0.05). This is in line with earlier observations from these regions,\textsuperscript{10} probably reflecting their demographic histories in prehistoric times.\textsuperscript{29-31}

Consequently, a lower test-sensitivity of the three most frequently used methods of DNA-analysis, e.g. OLA, INNOLiPA 17 /19, and Elucigene 29 /30 was observed for the Turkish than for the North African immigrants in Europe. When applying widely accepted criteria for genetic screening,\textsuperscript{32} these three methods are definitely not considered to be suitable for CF (carrier) screening of Turkish immigrants and less suitable for North African immigrants in Europe. Even when the CFTR mutations panels of these assays would be expanded by the mutations that were reported on two or more alleles in the present study, the increased test-sensitivities would still not meet these criteria for CF (carrier) screening of Turkish and North African immigrants in Europe.

**Study limitations**

Our study has some limitations, and these should be mentioned here. Firstly, we were unable include all unrelated CF-patients of Turkish or North African origin living in Europe, since 39.8\% (138/347) of the CF centers did not respond at all, and 10.0\% (21/209) of those who did respond, reported that they did not register ethnicity and, of course, some patients may die before a diagnosis of CF is made. Our study population represents a collection of CF patients which have been diagnosed in different periods in time from clinical practices in various European countries with different molecular genetic capacities. However, due to the relatively large number of included patients, it can be assumed that we collected a database on Turkish and North African CF-patients in Europe that is both informative and unique. If more patients had been tested, this would not automatically have led to an increase in the detection rate, as this depends on
the identity of the mutations that are present on the alleles of these non-tested CF patients and whether these mutations do or do not belong to the panels of those three most frequently used methods for DNA-analysis.

Secondly, not all identifiable CFTR mutations had been identified in the patients included in our survey, which partly could be explained by the fact that the mutation spectrum was biased by the mutation detection technology used. In 33.3% (16/48) of CF-patients with a mutation reported on only one allele or on no allele at all, standard mutation panels, such as OLA, INNOLiPA 12, INNOLiPA 17/19, and Elucigene 29/30, were used for DNA-analysis. However, these methods have a low test-sensitivity for Turkish and North African CF-patients. Furthermore, in 56.3% (27/48) of the CF-patients with a reported mutation on only one allele or on no allele, no information was available with regard to the method of DNA-analysis which had been used. If additional techniques for DNA-analysis, such as DGGE or sequencing of the entire CFTR coding region had been used in these cases, more CFTR mutations would have been identified among Turkish and North African CF-patients.

Thirdly, for homozygous patients with consanguineous parents, one allele was excluded under the assumption of identity by descent of the two alleles in the patient. However, homozygosity in patients with known consanguinity of the parents is not necessarily always caused by identity by descent, but may reflect identity by state in some cases. Furthermore, for 33 of the 88 homozygous patients and for the 30 patients with no identified mutations we did not receive information about consanguinity of parents.

Finally, we constructed a mean test-sensitivity for the three most frequently used methods of DNA-analysis reported in the questionnaires. We did not perform or ask for additional methods of DNA-analysis of all CF-patients with no identified mutations or with only one identified mutation (for example, DGGE or sequencing of the entire CFTR coding region), because this was not the goal of our study.

As a consequence, the mean test-sensitivity could be over-estimated or under-estimated. However, the implications of our results for preconceptional CF carrier and neonatal CF screening of Turkish and North African immigrants in Europe remain the same (see below).

**Implications for CF carrier and neonatal CF screening**

Based on the presented data, it can be concluded that one of the general screening criteria that should be met before implementation of CF (patient and carrier) screening, namely the availability of a suitable test, cannot be met for immigrants of Turkish and North African origin in Europe, when applying (one of) the three most frequently used methods of DNA-analysis. The test-sensitiv-
ity of such frequently used methods is unacceptably low for these immigrants, and therefore forms one of the challenges in the implementation process of CF (patient and carrier) screening in most European countries.

Not offering CF carrier screening at all (the current situation in many countries) results in the situation in which the majority of carrier couples are unable to make informed reproductive decisions if there is no family history of CF, neither carrier couples of European descent nor Turkish and North African carrier couples with unidentified mutations. Moreover, not offering neonatal CF screening withholds from CF-patients who are of European, Turkish, North African and other origins, the benefits of early diagnosis. 34–36

In the U.S.A., it was therefore recommended that CF carrier screening should also be made available for ethnic groups in which there is low test-sensitivity to detect a CFTR mutation, on condition that these people would be informed about their lower rate of detection through educational brochures, the informed consent process, and/or other efficient methods. 17

**Lessons for implementation**

*CF carrier screening*

What should we do with the fact that the sensitivity of common CFTR mutation panels is insufficient for use in screening programs in Turkish and North African immigrants in Europe, even after expansion with frequent Turkish and North African mutations? Various options are mentioned here. Firstly, CF carrier screening can be made available to all couples, on the condition that people of various ethnic origins with low test-sensitivity will be informed about their lower rate of detection. Secondly, another option is to offer CF carrier screening only to ethnic (sub) populations for which the current test-sensitivity of the commercially available CFTR mutation panels is acceptable, according to the genetic screening criteria. Thirdly, another strategy is not to implement CF carrier screening at all until a better test has been developed with higher test-sensitivity for the Turkish and North African people, as long as the methods of DGGE analysis or sequencing of the entire coding region are still too expensive and impractical for screening purposes. And fourthly, meanwhile the test characteristics should be improved by expansion of the mutation panels with identifiable Turkish and North African CFTR mutations. Furthermore, efforts should be made to identify the yet unidentifiable mutations. Moreover, additional screening for large deletions or gross genomic rearrangements, using quantitative multiplex polymerase chain reaction (PCR) of short fluorescent fragments (QMPSF), should be considered. 37
Neonatal CF screening

What are the options for neonatal CF screening? At this moment, a strategy that is frequently used in a number of European countries in neonatal CF screening is the determination of Immunoreactive Trypsinogen (IRT) in blood spots, followed by CFTR gene analysis using a selected mutation panel. Sarles et al. have recently suggested another method for neonatal CF screening, i.e. combining IRT with pancreatitis associated protein (PAP) assays, instead of CFTR gene analysis. This avoids the drawbacks of genetic analysis, and is cheaper and easier to implement than the current IRT/CFTR mutation strategy. When both IRT and PAP are above certain concentrations, babies have to be recalled for a sweat-test, but this strategy unfortunately has a high false-positive rate: it is estimated that only 1 in 12 babies who are recalled for a sweat-test will turn out to have CF. Another possible strategy for neonatal CF screening might therefore be IRT/PAP followed by sequencing of the entire CFTR coding region and flanking intronic sequence, before recalling for a sweat-test. However, such a scenario will result in the identification of mutations, not yet known to be disease-causing or not.

From our results, we conclude that the CFTR mutation panels should be expanded further to achieve higher pan-ethnic detectability. However, an acceptable sensitivity to identify CF carriers and patients among people in Europe who are of Turkish or North African descent will not be reached, as most mutations are rare. In the implementation process of preconceptional CF carrier and neonatal CF screening programs, we call for sufficient attention to the consequences of this problem. The existing neonatal screening programs, based on an IRT/DNA approach, for example, seem to fail to identify an acceptable proportion of CF-patients who are of Turkish (or North African) descent. Sequencing the entire CFTR coding region could be helpful in this problem, but also will bring up other difficulties as producing indefinite results regarding “pathogenicity” of unknown or rare CFTR “mutations” found.

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Turkish and North African CFTR mutations in Europe

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Reference List


general discussion and summary
nine

general discussion
Objective of the thesis

The main objective of this thesis was to evaluate the feasibility and desirability of an offer of combined targeted ancestry-based preconceptional cystic fibrosis (CF) and hemoglobinopathies (HbPs) carrier couple screening. CF and HbPs are relatively common, severe, incurable and life-shortening autosomal recessive disorders. Preconceptional carrier couple screening for these disorders enables prospective parents to make reproductive decisions before pregnancy. However, in the Netherlands, as in many other European countries, preconceptional CF and HbPs carrier screening is not current practice. There has been debate about whether or not this kind of screening should be introduced, and if so, how, because at the time of the study there was no established general preconceptional consultancy setting in which this kind of preconception care could easily be implemented.

CF and HbPs have different prevalences among various groups, according to ancestry. Therefore, in previous studies targeted carrier screening based on ancestral origin has been advised, but negative experiences, like discrimination and stigmatisation of carriers, after implementation of sickle cell screening in the USA in the early 1970s resulted in hesitations toward targeted ancestry-based screening. An offer of preconceptional combined targeted ancestry-based CF and HbPs carrier couple screening could, however, reduce the 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.

In this Chapter various aspects of the feasibility and desirability of combined targeted ancestry-based preconceptional CF and HbPs carrier couple screening are discussed, based on the results of the studies outlined in Part I and II of this thesis. These studies aimed: 1) to evaluate 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); and 2) to evaluate other relevant aspects concerning the decision as to whether or not to implement this kind of screening (ethical, sociotechnical and test-sensitivity aspects) (Part II).

First, the main findings of these studies will be presented, as well as the study limitations. The results will be then discussed and evaluated against genetic screening criteria. This Chapter ends with recommendations for implementation and further research, and several concluding remarks.
The screening study (Part I)

During the screening study which was carried out in 2005 preconceptional ancestry-based CF and HbPs carrier couple screening was offered to nearly 10,000 individuals, including 50-60% non-Western immigrants, in Amsterdam, the capital of the Netherlands. 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. Participation in the carrier testing was conditional on survey-participation (questionnaires). 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.

The following research questions were addressed to evaluate this screening study:

1. Is it possible to develop and validate a decisional instrument for preconceptional ancestry-based carrier couple screening for CF and/or HbPs in the Netherlands, 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 both partners’ ancestry? *(Chapter 2)*

2. What is the response of couples planning a pregnancy to such an offer of ancestry-based preconceptional carrier couple screening, making use of the above-mentioned decisional instrument? And does an approach in which the GP sends the invitations lead to a different response than an approach in which the invitations are sent by the MHS? *(Chapter 3)*

3. What determines the intention to participate or not to participate in preconceptional ancestry-based CF and/or HbPs carrier couple screening among those who accepted and those who declined the screening offer? And is there a difference in these determinants between people of Western and non-Western origin? *(Chapter 4)*

4. What are the psychological consequences of test-participation, how is the understanding and satisfaction of the screening, what are the reproductive intentions, and do people share the test-results with their relatives? Are there differences between participants of Western and non-Western origin? *(Chapter 5)*
Other relevant aspects for the implementation of the screening (Part II)
In part II of this thesis, the following research questions were addressed in order to investigate several other aspects that are also relevant in considering whether or not preconceptional ancestry-based CF and HbPs carrier couple screening should be implemented in the Netherlands:

5. Can the possible threat to freedom of choice, and can medicalisation of the preconception period be considered as convincing moral objections to preconceptional carrier screening? (Chapter 6)

6. What are the constraining and enabling factors for the process of potential implementation of preconceptional CF and HbPs carrier screening in the current (Dutch) health care system? And what sociotechnical conditions at micro-, meso- and macro-level have to be created for a successful implementation? (Chapter 7)

7. Which CFTR mutations have been found in CF patients of Turkish or North African origin who are now living in Europe? Is it possible to formulate recommendations for the design of a CFTR mutation panel with a test-sensitivity that will also be suitable for CF (carrier) screening among Turkish and North African immigrants in Europe? (Chapter 8)

Main findings

Part I: The screening study
Prior to actually carrying out the screening study, a decisional instrument was developed successfully for the assessment of a couple’s eligibility for CF and/or HbPs carrier testing, based on the ancestry of both partners. The instrument was found to have a good validity (Chapter 2). Subsequently, this validated instrument served in the screening study as a pre-screening tool to assess a couple’s eligibility for the CF and/or HbPs test(s). The uptake in the screening study was lower than expected: only 3% of those who belonged to the target population of invitees with a partner with whom they were planning a pregnancy (33% of the invitees) participated in the carrier testing, and non-Western invitees were under-represented (Chapter 3). Invitations sent by the GPs compared to the MHS led to a higher uptake (Chapter 3). Furthermore, not only those who accepted, but also those who declined the current offer of preconceptional carrier screening had a generally positive attitude towards participation in the screening. Their intention to participate or not to participate was mainly influenced by whether or not they perceived practical barriers in terms of the
time and effort needed for participation. This applied to Western and non-Western study participants alike. Moreover, no major feelings of stigmatisation or discrimination were reported (Chapter 4), and among those who participated there were no major adverse psychological outcomes. The participants were satisfied, and none of them regretted participation. They further reported that they would draw reproductive consequences from the test-results if they had been identified as a carrier couple (Chapter 5). Knowledge 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).

Part II: Other relevant aspects concerning the decision to implement the screening

Ethical aspects: 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).

Sociotechnical aspects: 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.

Test-sensitivity aspects: 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 (Chapter 8).

Limitations of the studies

In the interpretation of the main findings of the screening study (Part I), several limitations of the studies outlined in this thesis should be taken into account: (1) couples were offered screening within a specific multi-ethnic and limited geographical area in Amsterdam, so uptake, acceptance and attitude may differ in other parts of the Netherlands and elsewhere; (2) the size of the target population (invitees with a partner with whom they were planning a pregnancy) had to be estimated, thereby resulting in an estimated uptake
which, therefore, might be an under-representation or an over-representation; (3) there is no available information about the large majority of the invitees, because only a small number of the nearly 10,000 invitees actually participated in the testing and questionnaire-survey; (4) only two invitational approaches and one educational approach were studied, so the results might be different with other approaches; (5) only three CF carriers and seven HbPs carriers and no carrier couples were identified; (6) the long-term consequences of being identified as a carrier were not investigated; (7) the written material was available in the Dutch language only; (8) because participation in the testing was conditional on participation in a questionnaire-survey some people may not have been interested in study-participation for that reason; (9) there was a short time-limit for making an appointment for a GP pre-test consultation (one month); and (10) participants were invited as couple; individual visits to the GP were not allowed.

**Evaluation of the feasibility and desirability of the screening**

Genetic screening programmes should meet certain criteria before they can be introduced into the community. In the following, several aspects of the feasibility and desirability of an offer of combined preconceptional ancestry-based CF and HbPs carrier couple screening will be discussed by evaluating them, where possible, against genetic screening criteria that were derived from a general evaluation framework formulated by the Health Council of the Netherlands (Gezondheidsraad) with reference to internationally applied criteria (Table 1). In this evaluation, all criteria of this framework will be addressed, but the exact order of these criteria as presented in Table 1 will not be followed, because the criteria will be mentioned and discussed in relation to the several aspects of the feasibility and desirability of the screening as discussed below.

**Feasibility of preconceptional ancestry-based CF and HbPs carrier couple screening**

*Defining the target population*

In the screening study presented in this thesis, couples who were planning a pregnancy were considered to be the target population, because the aim of the programme was to identify carrier couples before pregnancy. As such, it was feasible to clearly define the target population. (Table 1, criteria 2 and 12c). Approaching future parents before pregnancy, instead of during pregnancy, provides a maximum number of reproductive options and a minimum of time constraint. Screening all individuals of reproductive age, irrespective of their
Table 1
Criteria to be met by a genetic screening programme

1. A genetic screening programme must relate to an important health problem or to a condition which can lead to such a problem in those being tested or in their descendants.

2. The target group of the screening programme must be clearly defined.

3. The purpose of the programme must be to enable the participants to determine the presence or the risk of a disorder or carrier status, and to take a decision on the basis of that information.

4. Practical courses of action must be open to the participants.

5. Participation in a genetic screening programme should be completely voluntary and should be conditional on consent based on good information.

6. The target group should be supplied with good quality, comprehensible information.

7. A test method should be available which is suited to the objective of the screening.

8. There should be sufficient facilities for follow-up testing, to carry out the selected courses of action and to inform and support the participants.

9. The procedures used for the storage of medical information and cellular material must incorporate adequate measures to protect both the personal privacy of the participants and their rights regarding their personal data and cellular material.

10. If scientific research is carried out within the framework of screening, the participants should be properly informed about this in advance.

11. Provision should be made for continual quality assurance of the effectiveness, efficiency and safety of the test procedure, any follow-up work, as well as information and support given by the participants.

12. When weighing up the benefits and drawbacks for the participants in the programme, the final balance should be clearly biased to benefits. To assist with this evaluation, those proposing a screening programme must provide information about:
   a: the prevalence of the disease or disorder in the target group;
   b: the natural course of the disorder, and the variation in degrees of severity;
   c: Those target groups which are eligible for testing and the considerations which led to selection of the proposed target group and the proposed time of life for testing;
   d: The specificity, sensitivity and predictive value of the test method to be used and the burden which such testing imposes on participants;
   e: The available courses of action if a health problem or carrier status are revealed;
   f: The time allowed by the procedure for consideration and possible implementation of the choice made;
   g: The potential psychological, social and other repercussions (both positive and negative) of an offer and of participation or non-participation in the screening, for the persons to be tested and for members of their family or for groups within the community;
   h: The likelihood of erroneous results, the possible consequences of this for participants and the measures taken to limit any harm which such an error might cause;
   i: What guarantees there are to prevent participants experiencing unjustified impediments (as a result of their participation or non-participation in the screening programme or follow-up testing) to obtaining employment or private insurance cover;
   j: The costs which are linked to the screening and to the attainment of the requisite infrastructure.

reproductive plans, has the disadvantage that many people might not consider the testing to be relevant, although some high school carrier screening programmes appeared to be successful in raising awareness about carrier status over a longer period of time.

Despite of the fact that it is feasible to clearly define that couples who are planning a pregnancy are considered to be the target population, some points with the definition of this target population need further consideration. First, it should be defined whether or not invitations for participation in the carrier screening should be restricted to prospective parents of a certain age-range, and if so, whether or not there should be a difference between the age-range of women and of men. In the present study, similar to the procedure followed in the previous CF carrier screening study carried out by Henneman et al., invitees were selected on the basis of reproductive age (range 20 to 35 years). This age-range inevitably resulted in the exclusion of some prospective parents who might have been interested in the screening, because they were too young or too old. If preconceptional carrier screening is implemented within the health care system, it would be better to send an open invitation to prospective parents in general with a wide range of age, based on information about parental age at the time of planning a pregnancy. Irrespective of the setting in which the screening would be implemented it should be studied, though, whether or not such a wide range of age will be cost-effective. Second, because of the fact that not all pregnancies are planned, prenatal carrier screening could be used as a “safety net” for pregnant couples who do not attend preconceptionally and who are interested in the carrier screening. Third, both men and women should be invited to participate in preconceptional carrier screening, and not only women, because of the fact that preconceptional carrier screening for autosomal recessive disorders and informed reproductive decision-making concerns both partners in a couple. Furthermore, it was found that a higher uptake was achieved when both partners had received an invitation (Chapter 3).

Eligibility for CF and/or HbPs carrier testing was further based on the ancestry of both partners. It was feasible to develop, validate and implement a decisional instrument as a pre-screening tool for targeted ancestry-based preconceptional carrier screening (Chapter 2). Assessment with the decisional instrument, which also takes the possibility of mixed ancestry into account, appears to be better than risk-assessment based on data obtained from the population register that only provides data on individual and parental native countries (Chapter 3).
Target population accessibility

Reaching the target population for the purpose of preconceptional carrier screening is difficult in the absence of a general preconception consultancy setting (Table 1, criterion 2, 3 and 6). Therefore, in the present study, as in the Henneman et al. CF carrier screening study, invitees (20 to 35 years) were selected by the MHS from the population register and by the GPs from their practice records. No problems were reported in the selection of names and addresses of invitees or in sending the invitations. One advantage of invitations sent by the GP is the possibility to exclude individuals for whom the screening is considered to be inappropriate, or who are not, or no longer (expected to be) contemplating a pregnancy. However, in a study carried out by Elsinga et al., in which preconceptional counselling was offered by the GP, and in which women with adverse social circumstances were excluded by the GP beforehand, 33% of the pregnancies occurred in the group of women who had been excluded. Otherwise, when the invitations will be send by the MHS, the possibility to exclude invitees beforehand for whom the screening might be inappropriate is absent, but this might be felt to a lesser extent as a problem than when their own GP (who knows their medical history) is sending the invitations. However, in the present screening study, it was difficult to find GPs who were willing to provide the pre-test consultation (Chapter 3): only 20% of the GPs who had been invited, were willing to participate in the screening study.

The majority of the invitees (67%) were not eligible for the screening because they did not belong to the target population. Although the invitational approaches were feasible in the present study, an approach in which it is possible to offer the screening directly to actual prospective parents, for example within a future general preconception consultancy setting, might be more desirable, but only if the number of prospective parents who are aware of and interested in the existence of such a setting will be high enough.

Enabling test-participation among those who are interested

There were major differences between attitudes and uptake in our study: the general attitude towards participation in the screening was positive, but the uptake was low. Based on the results of Chapters 3 and 4 it could be suggested that the uptake of 3% reflected an under-representation of the number of people who would like to participate in this kind of screening if it is implemented in health care, since the current uptake was not just a reflection of attitude towards participation in the screening. The majority of Western and non-Western participants in the study had a positive attitude towards participation in the screening programme. Practical barriers related to the study-design (e.g. the invitees were offered only one month in which to make an appointment for
pre-test consultation, and both partners in a couple had to be present during this consultation) and the fact that test-participation was conditional on completing the questionnaires, had contributed to this relatively low uptake (Chapter 4). The relatively lower uptake among non-Western immigrants could not solely be attributed to negative attitudes towards testing, but might have been the result of limited command of the Dutch language, and invitees with a lower level of education might have experienced problems due to the fact that the offer was made in writing. Moreover, not all people who had been invited by the MHS were able to make an appointment for pre-test consultation with their own GP, which might have resulted in under-representation. Therefore, with this study-design test-participation was not possible for a (large) number of invitees who were interested in participating in the carrier screening. If preconceptional ancestry-based CF and HbPs carrier couple screening is implemented, test-participation should not be conditional on survey-participation, and practical barriers need to be resolved to facilitate access to the screening among those who are interested.

Achieving informed decision-making
Accepting or declining an offer of preconceptional ancestry-based CF and/or HbPs carrier couple screening should be based on an informed choice, which was defined by Marteau et al. as ‘one that is based on relevant knowledge, consistent with the decision-maker’s values and behaviorally implemented’. In other words, all people in the target population should be informed to ensure that they have the possibility to gain the relevant knowledge with regard to the testing. Subsequently, those with positive attitudes towards the testing ideally participate in the screening and those with negative attitudes ideally refrain from participation, according to Marteau’s definition. The decision to participate or not, therefore, should be completely voluntary and conditional on consent based on good information (Table 1, criterion 5).

In the present study, voluntary informed decision-making based on consent was facilitated in various ways. In contrast to a more opportunistic approach, there was a period of one month in which invitees could consider making an appointment with the GP. Moreover, after the pre-test consultation and the sampling, the participants were offered one week in which to decide whether or not they wished the samples to be tested, instead of having to sign a consent form immediately. Finally, if they did wish the samples to be tested, they had to act accordingly by returning a signed informed consent form. Both acceptors and decliners of the current screening offer reported a low level of social influence (Chapter 5), suggesting that it had indeed, been a voluntary decision to participate in the screening.

The next question is whether or not informed decision-making was indeed achieved among: a) those who accepted the screening offer by stating on a reply form that they intended to participate in the testing; b) those who declined test-participa-
Among those who intended to participate in the screening, the large majority actually participated. These test-participants had made a decision that corresponded with their positive attitude towards the screening (Chapter 4), and at least half of them also had a high level of knowledge which enabled them to make an informed decision, according to Marteau’s definition. However, the question that arises is: what specific knowledge is necessary in order to make an informed decision? Does the person who makes the decision to participate or not to participate, need to know everything about autosomal inheritance, risks for carrier couples and test-sensitivity? Knowledge that is relevant for that individual's decision-making process, of course, should be gained, but what is relevant may differ between the invitees, and should not solely be measured as the number of correct answers on the knowledge questions in the questionnaire.

For the majority of those who declined the current screening offer and for those who intended to participate but who eventually had not participated, practical barriers had hindered informed decision-making, because their positive attitude did not result in participation (Chapter 3 and 4). However, some decliners of the screening offer stated that the test-results would not influence their reproductive behaviour, suggesting that their decision not to participate was an informed choice.

Among the large majority of the invitees (>85%) who did not respond at all (the non-respondents), there is no available information on the attitude and knowledge about preconceptional ancestry-based CF and HbPs carrier couple screening. The results of the telephone survey (Chapter 3) among a sample of 201 non-respondents suggested that they also evaluated the screening as positive.

In conclusion, on the one hand, it is likely that informed decision making would have been achieved among more invitees when they had faced fewer practical barriers. However, on the other hand, absence of any practical barriers at all may threat the voluntariness of participation in the screening. Therefore, the practical barriers in terms of effort and time needed for participation should be diminished, but according to criterion 5 of Table 1, participation should always be based on informed consent and good information.

Supplying the target group with good and comprehensible information

The target group should be provided with good quality, comprehensible and balanced information (Table 1, criterion 6). In the present study, the invitees received information about the clinical and genetic aspects of the disorders
(Table 1, criterion 12b), prevalence according to ancestry (Table 1, criterion 12a), the screening procedure (Table 1, criterion 12f), the test-sensitivity (Table 1, criterion 12d), the meaning of the test-results and the reproductive options that are available for carrier couples (Table 1, criteria 4 and 12e), and the fact that they participated in scientific research (Table 1, criterion 10). This information was provided at three different moments during the study: 1) in an information leaflet, that was validated among 112 mostly non-Western and low-educated people (Chapter 2), enclosed to the letter of invitation, 2) during the pre-test GP consultation; and 3) in a validated detailed brochure that they took home after the pre-test consultation.

Knowledge did improve significantly from before to after the pre-test consultation, contributing to informed decision-making with regard to whether or not to return the informed consent form for the actual testing. This finding suggests that it was feasible to have the pre-test counselling in itself carried out by the GPs (Chapter 5). However, as mentioned already, it was difficult to find GPs who were willing to participate in the screening study: only 20% of all the GPs who were invited were willing to participate. Poppelaars et al. found that 40% of the GPs did not think that the GP was the most appropriate person to provide such counselling. It seemed, therefore, not feasible to have the pre-test counselling performed by GPs on a large scale in health care. However, GPs may think differently about this subject when preconceptional carrier screening is part of general health care instead of a scientific pilot study only.

The increase in knowledge that occurred after the pre-test consultation was not sustained. However, this might only become a problem for carriers if they are planning a pregnancy in the future with another partner, and if they do not realize that their new partner should also be tested. In the screening study, almost half of the participants, but more importantly four carriers with partners who tested negative, thought that there was no residual risk of having an affected child (Chapter 5). To provide the participants with correct information about the meaning of test-results it is necessary to find out whether a proactive offer of post-test counselling to carriers would, indeed, improve their knowledge when preconceptional carrier screening for CF and HbPs is implemented. If post-test counselling is offered, it should also be available in the participants’ own language.

On the other hand, a screening procedure usually aims to identify high versus low risk groups. High risk groups should consider interventions and low risk groups generally should not. In that context, it might not be considered as a big problem that the carriers with negative tested partners forgot about their results.
**The carrier tests**

CF-carriers are detected by the identification of one disease-causing mutation in the *CFTR* gene, and HbP-carriers are detected by the evaluation of red cell indices and morphology, followed by more sophisticated haematological testing and molecular analyses. Participants must be provided with information about the specificity, sensitivity and predictive value of the test method to be used and the burden which such testing imposes on them (Table 1, criteria 7 and 12d).

The test-specificity of both the CF and the HbPs carrier test is approximately 100%, if stringent quality assurance guidelines are adhered to. Both tests also have a high, positive predictive value, so that there will be hardly any burden due to false positive test results (Table 1, criterion 12h). With regard to the test-sensitivity, there is an important difference between the CF and the HbP carrier test. The sensitivity of the HbPs carrier test varies between different ethnic groups and different HbPs, but is estimated to be 95-99%, and therefore seems acceptable for carrier screening purposes. With regard to CF carrier screening, the 1992 recommendation of the American Society of Human Genetics was that general population screening to identify CF carriers should not be carried out until the carrier detection rate is at least 90%. According to this recommendation, the test-sensitivity of commonly available commercial *CFTR* mutation panels seems to be sufficient for Caucasian people. However, 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 (Chapter 8). The relatively low test-sensitivity of the CF carrier test among these people results in a higher proportion of false-negative test-results: with a negative test-result there is still a considerable residual risk of being a carrier (Table 1, criterion 12h). This raises questions about whether, and if so, how to implement preconceptional CF carrier screening in a multi-ethnic society. It can be decided not to implement CF carrier screening at all, or to exclude Turkish and Moroccan people from the screening until a better test has been developed with higher test-sensitivity for Turkish and North African people. However, it would be better to make CF carrier screening available to all couples, because not offering the CF carrier test for screening purposes will definitely lead to absence of any carrier detection among those with no family history of CF. Such an offer of CF screening should be made on the condition that people of various ethnic origins with low test-sensitivity will be informed about their lower rate of detection, as was recommended in the USA in 2001. Meanwhile, the test characteristics should be improved by expanding the mutation panels of the commonly available commercial *CFTR* mutation panels with
known pathogenic Turkish and North African CFTR mutations. Furthermore, efforts should be made to identify the as yet unknown mutations.

Nevertheless, if mutations have been identified, other problems may arise which make the counselling of a carrier couple more complex: 1) for both CF and HbPs the genotype-phenotype correlations cannot be predicted with certainty; 2) mutations with no known clinical consequence or unproven or uncertain clinical relevance may be identified; and 3) with regard to CFTR mutation analysis, mutations that result in a CFTR-related disorder like congenital bilateral absence of the vas deferens (CBAVD) can be identified. These issues complicate the process of informed decision-making for couples.

Registration and test-results
In the present project the registration of participants, the recording of the test-results, and the data-management took place at the Research Centre. The procedures used for the storage of medical information and cellular material incorporated adequate measures to protect both the personal privacy of the participants and their rights regarding their personal data and cellular material (Table 1, criterion 9).

Both partners in a couple were informed about the test-results by means of one single letter that was sent to their home address, and copies of all test-results were also sent to the GPs of all participants. A minority of 6% of the test-participants could not remember their test-results, including two HbP carriers (Chapter 5). If preconceptional carrier screening for CF and HbPs is implemented, discussion is needed about the best place to keep the test-results, for example not only in the general practice records, but also in patient files in a future general preconception consultancy setting. On the one hand the protection of privacy is important, but on the other hand it is desirable that the test-results are available whenever they are relevant for reproductive decision-making.

Desirability of preconceptional ancestry-based CF and HbPs carrier couple screening
Both CF and HbPs are serious autosomal recessive disorders that are relatively common among various population groups according to ancestry. As such, both disorders meet the first screening criterion, i.e. that an important disease or health problem should be involved (Table 1, criterion 1). However, for both disorders genotype-phenotype correlations are rather poor: it is difficult to make a precisely and accurate prediction of phenotype on the basis of genotype, which complicates the process of informed decision-making for carrier couples.

A carrier screening programme for CF and HbPs should only be considered if its benefits outweigh its potential harmful effects (Table 1,
criterion 12). It is not only important that the offer of preconceptional carrier screening should be desirable among prospective users, there is also need for political and cultural acceptability (Chapter 7). The benefits and potential harmful effects for participants, for members of their family and for groups within society will be discussed below (Table 1, criterion 12g).

**Benefits for participants**

The aim of preconceptional carrier screening for autosomal recessive disorders is to enable prospective parents to make informed reproductive decisions (see Table 1, criterion 3). As such, the screening offer increases the individual autonomy of a carrier couple with regard to their reproductive decisions. Information about the various different reproductive options that are available was provided in the information leaflet, during the pre-test consultation, and in the information brochure. Invitees were thus informed before testing about the practical courses of action for carrier couples (Table 1, criterion 4).

As might be expected, in our small screening study no CF or HbPs carrier couples were identified. However, the participants stated that they would have considered making use of the available reproductive options if they had been identified as a carrier couple. Like in other studies, they stated that they would have tried to prevent the birth of an affected child by not having children, or would have considered prenatal diagnosis followed by pregnancy termination in case of an affected child (Chapter 5). These results resemble the reproductive choices that have actually been made in β-thalassemia population screening programmes for adults at child-bearing age in the Mediterranean area, in which the large majority of couples at risk opted in favour of prenatal diagnosis, resulting in a substantial decline in the birth rate of thalassemia major. Furthermore, in a previous study on premarital screening of β-thalassemia trait in Turkey, it turned out that 6 out of 15 at risk couples opted for prenatal diagnosis, while 2 couples cancelled their marriage. In general, termination of pregnancy for CF and HbPs is considered acceptable by many, also among immigrant people and couples from Muslim countries. Nevertheless, knowledge about CF or HbPs carrier status in general also seemed to limit plans to have more children, and have resulted in requests for pre-implantation diagnosis.

In the present screening study, if any carrier couples were identified they would have been invited for counselling at a Clinical Genetic Center where the reproductive options would have been explained to them again and they would have received support in making a choice (Table 1, criterion 8). In general, if the
screening is implemented in health care in the Netherlands, it is expected that the current Clinical Genetic Centres have sufficient capacity to counsel the carrier couples who will be identified by the screening programme.

It should be noted, however, that the most important reasons for participation were the wish for a healthy child and the need for reassurance. Therefore, the great majority of individuals and couples, namely those who tested negative will thus benefit from participation, because their absolute risk of having an affected child decreases compared to the risk in the general population.

In addition, the effectiveness of genetic testing can be judged in terms of its ability to convey information that participants find useful. As in other studies, the participants in our preconceptional carrier screening programme (both Western and non-Western) were generally satisfied, none of them regretted their participation. Furthermore, the large majority of study-participants had a positive attitude towards participation in the screening, and were in favour of a standard screening offer for all couples planning a pregnancy (Chapters 3 and 4). These results suggest that at least those people from the target population who completed the questionnaires valued the offer of preconceptional ancestry-based CF and HbPs carrier screening as positive and desirable.

**Benefits for relatives**

Another potential benefit of identifying CF or HbPs carrier status is to offer carrier testing to the relatives of an index carrier (or proband). As also reported by Henneman et al., we are not aware of any request for testing from any relatives (so far). In contrast to other studies, we found that only five out of nine carriers shared their results with parents and siblings, even though this was advised to do in the letter informing them about their test-results. This poor sharing with relatives might be due to difficulties in understanding the test-results (Chapter 5), or difficulties in disclosing the results to relatives, due to geographical separation and/or irregular contact, or the wish that relatives should not be tested. An alternate hypothesis is that individuals who have never experienced the birth of an affected child in the family may perceive it to be unlikely that such a thing could ever happen. However, we did not ask the carriers whether or not they were planning to tell their siblings in the future, for example when those relatives are planning a pregnancy, and whether or not they had any siblings at all. Neither did we offer the carriers any support in sharing the results with relatives, for example by means of a family letter.

The relatives of participants with negative test-results experience no
additional benefits from this negative test-result, because their risk of being a CF or HbP carrier is hardly reduced by the fact that a family member was tested negative.

_Potential harmful effects for test-participants_

Potential harmful effects of (preconceptional) carrier screening, such as negative psychological outcomes (e.g. stress, anxiety, excessively worrying) should be avoided, as well as adverse social consequences, such as stigmatisation and discrimination of carriers (see Table 1, criteria 12g and 12i). Multiple studies have demonstrated that both carriers and ‘non-carriers’ may experience some negative feelings, such as anxiety and worry, when participating in genetic screening, but others reported no major adverse psychological outcomes.

The results of the studies outlined in this thesis provide no evidence that participation in preconceptional ancestry-based carrier couple screening for CF and/or HbPs will cause major adverse psychological effects (Chapter 5). A minority of the non-Western (38%) and Western participants (22%) reported that they were worried while waiting for the test-results, but only two participants, including a CF carrier, reported that they were still worried three months after receiving the results. The period of waiting for the test-results should be as short as possible and the maximum time should be available beforehand.

In general, no predominant feelings of stigmatisation and/or discrimination were reported, but the minority who thought that carriers might be discriminated (14%) were mainly non-Western participants. None of the carriers identified in the present screening study perceived themselves as being less healthy, and this was also found in other carrier screening studies. Only a few studies reported that carriers perceived their health as less positive.

In the present study four non-Western HbP carriers with partners who tested negative were unaware of the small residual risk of having an affected child (Chapter 5). In the longer term such couples might suffer from false reassurance if this small chance of having an affected child becomes a reality.

In previous studies it was found that people refrained from test-participation because of fear of potential discrimination by insurance companies and/or in obtaining employment. There is no rationale at all for discrimination of this kind, because carriers of autosomal recessive disorders are unaffected. So far, discrimination based on the risk of having an affected child does not seem to be warranted. Therefore, this aspect of being a carrier should be clearly emphasized in the information that is provided.
In addition, with regard to the method of testing, harmful effects for the test-participants may be related to the test-procedure, including inconvenience resulting from the test itself, which is more likely for the HbPs carrier test (vena punction) than for the CF carrier test (mouthwash sample). However, it is unlikely that either of the tests could cause any medical complications.

**Potential harmful effects for non-participants**

People may decide to refrain from test-participation because of a negative attitude towards preconceptional carrier screening, based on cultural and/or religious beliefs, or just because they do not want to know whether or not they are a carrier couple. A couple who refrained from participation might regret doing so or feel guilty, and/or might suffer from social stigmatisation if they subsequently have an affected child. Otherwise, when the two partners in a couple have a different attitude towards participation in the screening, the offer in itself may stress their relationship. Nevertheless, the choice that some people make, i.e. not to participate in the carrier screening because they do not want to be informed, must not hinder the freedom of choice of others who do want to be informed about their carrier status and their risk of having an affected child. Not offering this kind of screening will result in no freedom of choice at all (Chapter 6).

Additionally, as stated before, because of the fact that not all pregnancies are planned, prenatal carrier screening it should be considered to make prenatal carrier screening available as a “safety net” for those pregnant couples who are interested in carrier screening, but did not attend before pregnancy. If carrier screening will be withhold from these couples, they will be disabled to make informed reproductive decisions with regard to that pregnancy.

**Potential harmful effects for relatives**

Family relationships may be influenced negatively if family members are confronted with an increased risk of being a CF and/or HbPs carrier, because they might not want to know this in the first place. Moreover, relatives may feel pressurized to participate in the carrier testing, and carriers may feel guilty towards their children because of the possibility that they did pass the carrier status to them, which may stress the mutual relationship in a family. However, Henneman et al. reported no short-term changes in inter-family relationships due to the results of CF carrier screening. Nevertheless, informing couples about the consequences for family members of a positive test-result, will give them the opportunity to first ask family members whether or not they wish to be informed about the test-results. Informing family members may become less significant if there is a routine offer of CF and HbPs carrier screening in the
future. Informing relatives about a negative test-result might also lead to false reassurance among these relatives.

Potential harmful effects for patients with CF and HbPs
Patients with CF or HbPs might feel disrespected by an offer of preconceptional carrier screening for these disorders, although Henneman et al. reported that the majority of adult CF patients supported carrier couple identification within CF families, and the results of their study suggested that CF patients will also accept the reproductive choices of carrier couples identified in population screening programmes.79

In order to ensure a genuine choice between either avoiding or accepting (the risk of) the birth of a child with CF or HbPs, it is essential that the necessary facilities and conditions are guaranteed within society for the care, support and integration of people with chronic diseases and handicaps such as CF and HbPs, and that research on therapeutic interventions continues. Therefore, when a preconceptional carrier screening programme would be implemented, there should be simultaneous initiatives to raise public awareness about reproductive decision-making in preconceptional genetic carrier screening, emphasising the importance of respect for freedom of choice and respect for the handicapped.

Potential harmful effects for society
Medicalisation of the preconceptional period and pressure from the social environment threatening freedom of choice have been mentioned as negative aspects of offering preconceptional carrier screening.80-82 After investigating the ethical tension between maximizing reproductive options for carrier couples and the protection of individuals and society from unwanted side-effects, it was concluded that the possible threat to freedom of choice and medicalisation of the preconceptional period could not be considered as convincing moral arguments against the implementation of preconceptional carrier screening. Offering preconceptional carrier screening is desirable if the offer is made in such a non-directive way that informed decision-making is, indeed, facilitated (Chapter 6).

Another potential harmful effect for society is the additional cost of offering of preconceptional carrier screening for CF and HbPs. Preconceptional CF carrier screening has been reported to be cost-effective, or to result in acceptable costs, under certain assumptions.83 However, the cost-effectiveness of this combined ancestry-based offer has not been assessed (see Table 1, criterion 12j), but a screening offer in which the two disorders are combined will undoubtedly be less expensive than separate offers of screening for each of the disorders. Fur-
thermore, it is expected that the integration of preconceptional carrier screening for CF and HbPs within a future consultancy setting for general preconception care will be even more cost-effective.

**Do the potential benefits outweigh the potential harmful effects?**

Currently, due to the autosomal recessive inheritance pattern of CF and HbPs, affected children are mostly born in families with no family history of these disorders. In this situation, prospective parents, who are a carrier couple, may be confronted totally unexpectedly with the birth of an affected child suffering from a serious life-threatening disorder. Therefore, the most important beneficial aspect of offering preconceptional CF and HbPs carrier couple screening is the fact that it respects the reproductive autonomy of the individual couple planning a pregnancy, enabling them to make informed reproductive decisions before pregnancy (Table 1, criterion 3). The participants in the present study stated that they would have made use of the available reproductive options if they were identified as a carrier couple.

If the screening is withheld from prospective parents, then there will be no informed choice at all. Conversely, with the offer of preconceptional carrier screening, the so-called ‘right not to know’ about this screening will be withdrawn and, as stated above, there is some risk of various harmful effects for the participants and their relatives. Nevertheless, the results of the present study showed that the participants were generally satisfied, and no major harmful psychological or social consequences resulted from the current preconceptional carrier screening offer among Western and non-Western participants. Furthermore, providing not only the target population and the participants, but also society in general with correct and comprehensible information regarding all aspects of this kind of screening, in a non-directive way in which informed decision-making is facilitated, will counteract the majority of these potential harmful effects. Furthermore, no moral objections were identified. Therefore, based on the results of the studies outlined in this thesis, the beneficial aspects of preconceptional ancestry-based CF and HbPs carrier couple screening do outweigh the possible harmful effects.

**Should preconceptional ancestry-based combined CF and HbPs carrier screening be implemented?**

Is a combined ancestry-based preconceptional CF and HbPs carrier couple screening programme, as was presented in this thesis, both feasible and desirable? The results of the studies outlined in this thesis have demonstrated the feasibility of the decisional instrument developed for ancestry-based CF and
HbPs carrier screening, as well as the feasibility of the invitation procedure for the carrier screening, the actual pre-test consultation and the carrier testing. It was difficult, though, to find GPs who were willing to provide the pre-test consultation. The results of the studies outlined in the present thesis showed that, although preconceptional ancestry-based CF and HbP carrier screening is desirable for many couples, practical barriers were an important reason for declining to participate in the carrier testing. Therefore, the way in which the screening was offered and carried out in the present screening study, in which test-participation was conditional on survey-participation, did not make test-participation possible for a (large) number of invitees who would have been interested in participation. However, the results of this screening study did not differ from the results of previous studies on preconceptional carrier screening, and an offer of combined ancestry-based CF and HbP carrier screening seems to be advisable. Conclusively, the answer to the question as to whether or not preconceptional ancestry-based CF and HbPs carrier couple screening should be implemented on in the Netherlands, is a positive one.

**Strategies for implementation**

At this moment, the possibilities of different implementation strategies should be investigated and evaluated simultaneously to find out whether or not implementation on a larger scale is, indeed, possible and also desirable. For example, by carrying out a more extensive pilot study it will be possible to find the answers on those questions which could not have been answered by this relatively small screening study.

To find out whether or not carrier testing for CF and HbPs, would fit within a general preconception consultancy setting, as suggested by the Health Council of the Netherlands, the ideal situation would be to perform such a recommended experimental programme within a general preconception care setting. This would be the best setting in which to investigate the feasibility and desirability of a simultaneous offer of, on the one hand, general information primarily aimed at health promotion, and on the other hand, information on genetic testing aimed at enabling informed reproductive decision-making. However, such a general preconception consultancy setting must first be organized, because in the Netherlands, there is currently no consultancy setting for general preconception care. Nevertheless, there are already several initiatives on a smaller scale in which general preconception care is offered to individual prospective parents, for example preconception counselling in general practice, or provided by midwives. In these smaller settings, an implementation study of ancestry-based preconceptional CF and
HbPs carrier couple screening could more easily be embedded and evaluated.

Another strategy which could be used simultaneously for providing personal genetic risk information to prospective parents is the Internet. For example, it should be considered to include an offer of preconceptional ancestry-based CF and HbPs carrier screening on the website (www.zwangerwijzer.nl), which is developed to inform people who are planning a pregnancy. Information about a couple’s personal risk of having a CF or HbPs affected child should be made available by filling out the ancestry-based decisional instrument. Furthermore, possibilities for genetic counselling and carrier testing should be provided.

In addition, it should be considered also to inform couples who already have a child about the existence of preconceptional carrier screening for HbPs and CF, because they might want to participate in the preconceptional carrier screening if they want to have more children in the future. Information about the screening could be provided, for example, at home during the visit of a health care professional who takes the blood from the baby for the neonatal screening, or at the mother and child health centres.

In addition, it should be considered to simultaneously offer active (preconceptional) cascade-testing to the family members of patients and carriers who are identified, for example by means of the neonatal screening programme (see below). Other approaches of offering the carrier testing include carrier detection in high schools, prenatal carrier screening, using the moment of contraceptive consultation, and offering consultancy hours in a general preconception care consultancy setting. Furthermore, people might increasingly make use of commercially available genetic testing, which might result in an increase in the uptake of preconceptional CF and HbPs counselling.

Neonatal CF and HbPs carrier screening
Since 2007 the Dutch neonatal screening programme includes HbPs, and at January 1st 2008 a large scale pilot for neonatal CF screening started. It is important to recognize the fact that preconceptional carrier screening and neonatal screening for these disorders both have totally different purposes. As preconceptional screening offers carrier couples most reproductive options before pregnancy, neonatal screening will improve the quality of life of already born CF or sickle cell disease patients. Therefore, preconceptional CF and HbPs carrier screening and neonatal CF and HbPs screening should not be seen as two alternatives, but as two complementary strategies. It has been discussed, though, whether or not community-wide screening for cystic fibrosis carriers could replace newborn screening for the diagnosis of cystic fibrosis. These
strategies will probably remain complementary, since the uptake in preconceptional and/or prenatal screening, followed by selective abortion, will never be 100%. Patient and carrier detection in the neonatal CF screening programme in Brittany, in France, has for instance resulted in an increase in prenatal diagnosis and a global decrease in CF prevalence at birth of 30.5%.90

The greatest psychological risk related to neonatal screening has been reported when a healthy infant is identified as a carrier, and psychosocial difficulties can occur when a clear diagnosis is not possible (i.e. one CF-related gene mutation and a borderline, non-diagnostic sweat test result) or when a patient with milder forms of the disease is identified where no long-term prognosis or care issues have been clarified.91-93

Genetic education
A key element in improving the quality of genetic testing services is the provision of appropriate genetic education for health professionals. In the Netherlands, and also among health care professionals in other countries, genetic education is known to be currently inadequate.94-98 Therefore, parallel to the performance of an implementation study and/or an extensive pilot study, a professional educational programme must be provided for participating GPs, midwives, gynaecologists and other professionals in preconception care.

In addition, because of insufficient knowledge about genetics in the general population,57;99;100 genetic screening programmes must also include educational and counselling components, not only for the target population, but also for the population in general (school education programmes, leaflets, mass media campaigns, the Internet). This education will be important for increasing public knowledge, for shaping attitudes towards genetic testing, and for the avoidance of stigmatisation.12;25;99 Furthermore, community-based initiatives that aim to inform and educate people about a certain genetic disorder should also be stimulated, like for example the development of the Dutch website www.ikhebsikkelcel.nl, which aims to inform people about sickle cell disorders and carrier testing.

Recommendations for future research
In general, as stated above, based on the results of the present thesis, a more extensive pilot study and/or implementation study are now warranted to address those questions which could not be answered by this relatively small screening study and to find out whether or not implementation on a larger scale is possible and desirable. Irrespective of the setting in which such an extensive pilot study or implementation study will be embedded:
1) In targeted ancestry-based CF and/or HbPs carrier screening, assessment of a couple’s eligibility for the CF and/or HbPs testing should be based on the developed decisional instrument instead of data obtained from the population register, because the latest does not take the possibility of mixed ancestry into account.

2) Test-participation should not be conditional on participation in a questionnaire survey.

3) Practical barriers resulting in non-participation in the screening offer should be resolved:
   - there should be no limited time-span in which an appointment has to be made
   - translated copies of all written material should be available
   - the offer should not be made in writing only
   - participation should not depend on a limited number of health care professionals who are willing to participate in this kind of screening.

4) Attention should be paid to the (small) differences that were found in the present screening study between Western and non-Western participants, for example in uptake and understanding of the test-results.

5) Both partners in a couple should be invited for participation in the screening (Chapter 3).

6) Future research should investigate the reproductive decisions that are actually made by carrier couples who have been identified by means of a screening programme, but have no experience with the disorders in their families.

7) It is important to determine (as Mitchell et al. did), whether or not an active offer of post-test counselling for carriers, in a couple in which the partner tested negative, is feasible and desirable, in addition to offering counselling by letter only.

8) It is important to investigate whether or not the provision of family letters for those with a positive test-result stimulates:
   a) understanding of the consequences of the test-results, and b) sharing of the test-results with relatives. In general, barriers in sharing the results with relatives should be investigated more extensively.

9) Follow-up studies should be performed to assess the actual impact of carrier status on a larger scale.

10) It should be investigated whether there are any major adverse psychological or social outcomes in such an extensive pilot study and/or implementation study, and whether or not the participants are satisfied, in a similar way as in the screening study presented in this thesis.
11) An infrastructure for carrier screening, information and counselling is needed, as well as service monitoring. Laboratory services must be established, as well as a system for reporting the results and information storage (Table 1; criterion 11).

12) Efforts should be made to provide the test-results within the shortest time period as possible, and it should be studied whether or not (CF) double testing of both partners should be offered, as double testing (and full disclosure of test-results) were preferred by couples in the Henneman et al. preconceptional CF carrier screening study.

13) With regard to the limited test-sensitivity of the CF carrier test for Turkish and North African people, one should follow the example of the USA, in which people of various ethnic origins with low test-sensitivity will be informed about their lower rate of detection, and thus one should inform the Turkish and North African participants about the limitations of the DNA analysis. It is recommended that the commonly available commercial CFTR mutation panels should be expanded with 13 pathogenic mutations which have been found on two or more alleles among Turkish and North African CF patients. Meanwhile, further efforts should be made to identify the yet unknown pathogenic mutations among these populations. Furthermore, it should be studied whether different carrier screening methods of the entire CFTR coding region, such as ARMS (amplification refractory mutation system)-PCR, SSCP (single stranded conformation polymorphism) analysis, restriction enzyme digestion analysis, direct sequencing, and MLPA (Multiplex Ligation-mediated Probe Amplification) are sufficient or (still) too expensive and/or impractical for screening practices. Moreover, additional screening for large deletions or gross genomic rearrangements, using quantitative multiplex polymerase chain reaction (PCR) of short fluorescent fragments (QMPSF) should be considered.

14) The actual costs of an offer of preconceptional ancestry-based CF and HbPs carrier couple screening should be studied. It has already been reported that an offer of preconceptional carrier screening for CF only would not lead to unacceptable costs (Table 1, criterion 12).

Concluding remarks
The screening study presented in this thesis has provided better insight into the feasibility and desirability of preconceptional ancestry-based CF and HbPs carrier screening. The decisional instrument that is now available 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. Although, uptake in the CF and HbPs carrier testing was low in the present study, the
general attitude among Western and non-Western people towards participation in the screening was positive. Practical barriers, such as the time and effort needed for participation, were important reasons for declining, suggesting that this low uptake not just reflects peoples’ preferences but more their limited opportunities. 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.

Reference List


14. Williamson R. Universal community carrier screening for cystic fibrosis?


General discussion
ten
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.
samenvatting
Preconceptionele screening op dragerschap voor cystic fibrosis en hemoglobinopathieën
Een aanbod, afhankelijk van etnische origine, in een multi-etnische samenleving

Cystic fibrosis (CF) en hemoglobinopathieën (Hb-pathieën), zoals sikkelscelziekte en α- en β-thalasemie, zijn relatief veel voorkomende autosomaal recessieve aandoeningen waarvoor dragerschaptesten zijn ontwikkeld. Voor autosomaal recessieve aandoeningen geldt dat er in iedere zwangerschap een kans bestaat van 1 op 4 (25%) op het krijgen van een kind met die aandoening als beide partners drager zijn van deze aandoening. Meestal weten mensen pas dat ze drager zijn, nadat de aandoening bij hun kind gediagnosticeerd is.

Preconceptionele screening op dragerschap stelt toekomstige ouders in staat om een geïnformeerde reproductieve keuze te maken voordat er sprake is van zwangerschap. Het voordeel van preconceptionele screening ten opzichte van prenatale screening is dat er voor de zwangerschap meer keuzemogelijkheden zijn dan tijdens de zwangerschap: dragerparen kunnen dan niet alleen kiezen voor prenatale diagnostiek gevolgd (of niet) door zwangerschapsafbreking bij een aangedaan kind, maar ook voor het accepteren van het risico, het afzien van het krijgen van (meer) kinderen, adoptie, het gebruik maken van donorzaad of donor eicellen, of van pre-implantatie genetische diagnostiek. Daarnaast is er de mogelijkheid van het aanpassen van de partnerkeuze, zoals in sommige culturen niet ongebruikelijk is. In Nederland en in de meeste andere Europese landen is dragerschaps screening voor CF en Hb-pathieën geen onderdeel van de standaard zorg.

De prevalentie van autosomaal recessieve aandoeningen zoals CF en Hb-pathieën verschilt naar etnische subgroep en is afhankelijk van de oorspronkelijke afkomst van de (verre) voorouders. Zo is CF een relatief veel voorkomende aandoening onder Europeanen en hun afstammelingen, maar komt ook voor bij Noord-Afrikanen (o.a. Marokkanen), Turken en mensen afkomstig uit het Midden-Oosten. Hb-pathieën komen juist veel voor bij mensen die oorspronkelijk afkomstig zijn uit gebieden waar malaria heerst(e), bijvoorbeeld Afrika, het Middellandse Zeegebied, gedeeltes van India en Zuidoost Azië.

In de meeste (Europese) landen, waaronder Nederland, is er sprake van een multi-etnische samenstelling van de bevolking. Dit leidt ertoe dat er etnische subpopulaties bestaan met verschillende dragerschap frequenties van CF en Hb-pathieën. Het aanbieden van dragerschaps screening voor zowel CF als Hb-pathieën aan alle toekomstige ouders in een samenleving is daarom niet
alleen kostbaar, maar ook onnodig. Een oplossing zou kunnen zijn om gericht 
landerschapscreening aan te bieden, waarbij paren die op basis van hun 
afkomst een verhoogd risico lopen op het krijgen van een kind met CF in 
aanmerking komen voor een CF landerschapstest en paren die een verhoogd 
risico hebben op het krijgen van een kind met sikkelscelziekte en thalassemie 
toegang hebben tot een landerschaptest voor Hb-pathieën. Echter, het aan- 
bieden van landerschapscreening door vooraf te selecteren op oorspronkelijke 
afkomst zou kunnen leiden tot stigmatisatie en discriminatie. Het in eerste 
instantie *gecombineerd* aanbieden van beide landerschapstesten voor zowel CF 
as Hb-pathieën aan alle paren met kinderwens zou daarentegen dit potentiële 
risico op stigmatisatie en discriminatie van subgroepen kunnen verminderen, 
omdat ieder paar dan het aanbod krijgt. Pas in tweede instantie zou dan moeten 
worden bepaald voor welke test het paar in aanmerking komt, afhankelijk van 
de oorspronkelijk afkomst, waarbij bijna ieder paar, onafhankelijk van de 
overspronkelijke afkomst, in aanmerking zou komen voor een bepaalde 
vorm vanlanderschapscreening: voor CF, voor Hb-pathieën of voor beide 
aandoeningen.

De belangrijkste doelstelling van het onderzoek zoals beschreven in dit 
proefschrift was om de haalbaarheid en de wenselijkheid te evalueren van 
landerschappenele, op oorspronkelijke afkomst gebaseerde landerschap- 
screening op CF en Hb-pathieën. Naast de evaluatie van een screeningstudie, 
waarin daadwerkelijk preconceptionele, op oorspronkelijke afkomst gebaseerde 
landerschapscreening op CF en Hb-pathieën werd aangeboden in een multi- 
etnische populatie (Deel I, Hoofdstuk 2, 3, 4 en 5), is gekeken naar andere 
relevante aspecten van die van belang zijn voor de beslissing om een dergelijke 
screening wel of niet te implementeren (Deel II). Er is gekeken naar ethische 
aspecten van preconceptionele landerschapscreening in het algemeen (Hoofd- 
stuk 6) en naar sociotechnische aspecten van de mogelijke implementatie van 
landerschappenele, op oorspronkelijke afkomst gebaseerde landerschapscreening 
op CF en Hb-pathieën (Hoofdstuk 7). Tot slot is de testsensitiviteit van de CFTR 
mutatiepanels van de huidige veel gebruikte methoden van DNA onderzoek 
voor Turkse en Noord-Afrikaanse migranten in Europa onderzocht. Ten tijde 
van het onderzoek bestond er geen algemene setting voor preconceptiezorg 
waarin preconceptionele landerschapscreening eenvoudig geïmplementeerd 
kon worden.
De screening studie

De haalbaarheid en wenselijkheid van preconceptionele, op oorspronkelijke afkomst gebaseerde dragerschapscreening op CF en Hb-pathieën werd geëvalueerd aan de hand van een screeningstudie die werd uitgevoerd in 2005. In deze studie werd de screening aangeboden aan 9453 inwoners van Amsterdam in de leeftijd van 20 tot en met 35 jaar, waaronder 50-60% allochtonen. Tot de doelgroep behoorden personen met een partner én kinderwens. Voor aanvang van de screeningstudie werd eerst een beslisinstrument ontwikkeld dat tot doel had om vooraf te bepalen voor welke dragerschapstesten het paar in aanmerking zou komen gebaseerd op de oorspronkelijke afkomst van beide partners: voor CF, voor Hb-pathieën, voor beide aandoeningen of voor geen van beide aandoeningen.

Het ontwikkelde beslisinstrument bleek een goede validiteit te hebben (Hoofdstuk 2) en werd vervolgens gebruikt tijdens de screeningstudie om te bepalen of een paar in aanmerking kwam voor de dragerschapstesten op CF en/of Hb-pathieën.

Tijdens de screeningstudie werden twee manieren van het uitnodigen van personen voor de dragerschapscreening met elkaar vergeleken: de uitnodigingen werden verstuurd door ofwel de eigen huisarts of door de Gemeentelijke Gezondheidsdienst (GGD) van Amsterdam. Degenen die geïnteresseerd waren in deelname aan de dragerschapstest(en) moesten binnen één maand samen met hun partner een afspraak maken bij hun huisarts voor voorlichting en afname van testmateriaal (een venapunctie voor de test op Hb-pathieën en een mondspoelsel voor de CF test). Deelname was gratis. Voorwaarde voor deelname aan de dragerschapstesten was tevens deelname aan een vragenlijstonderzoek. De gegevensverzameling vond plaats met behulp van vier gestructureerde vragenlijsten, waarvan er één gebaseerd was op de Theory of Planned Behaviour. De eerste en tweede vragenlijst werden ingevuld voor en na de voorlichting bij de huisarts. De deelnemers aan de dragerschapstesten werden gevraagd om de derde en vierde vragenlijst respectievelijk een week en drie maanden na het ontvangen van de uitslag van de dragerschapstest(en) in te vullen. Als mensen wel tot de doelgroep behoorden maar geen interesse hadden in deelname aan de dragerschapstesten werd hen gevraagd of zij de eerste vragenlijst wilden invullen. De grootte van de doelgroep en de respons werden geschat aan de hand van: 1) een antwoordformulier, en 2) een telefonische enquête die verricht werd onder een steekproef van mensen uit de groep non-respondenten.

Van de 9453 personen die een uitnodiging ontvingen, stuurden 1365 respondenten het antwoordformulier terug. Naar schatting behoorde 33% van
alle genodigden tot de doelgroep (personen met partner én kinderwens). an hen nam 3% samen met hun partner deel aan de dragerschaptesten (n=143). Er was sprake van een onderrepresentatie van genodigden van niet-westerse afkomst (n=46). Er was een hogere respons in de groep waarin de huisarts de uitnodigingen had verstuurd vergeleken met de groep waarin de GGD de uitnodigingen verstuurde (Hoofdstuk 3).

In totaal hebben 418 personen, die allen tot de doelgroep behoorden, deelgenomen aan het vragenlijstonderzoek. Van deze 418 personen zagen 247 personen direct af van deelname aan de dragerschaptesten en hebben enkel de eerste vragenlijst ingevuld. De overige 171 personen hadden wel de intentie om deel te nemen aan de dragerschaptest(en). Echter, van deze laatste groep hebben uiteindelijk 143 personen daadwerkelijk mee gedaan en zagen 28 personen in tweede instantie af van deelname, maar waren wel bereid om de eerste vragenlijst in te vullen. Een grote meerderheid van zowel de genodigden die het aanbod van screenen aannamen, als van de genodigden die het aanbod direct afwezen, hadden in het algemeen een positieve attitude ten opzichte van deelname aan de dragerschaptest(en): 98% en 83%. Van degene die het huidige aanbod om zich te laten testen op dragerschap voor CF en/of Hb-pathieën afslagen, had 68% de intentie om in de toekomst wel deel te nemen aan dergelijke testen als deze screening routinematig aangeboden zou worden. Hun intentie om nu niet deel te nemen, werd voornamelijk beïnvloed door praktisch bezwaren: er was beperkte tijd voor deelname (43%) of deelname kostte hen teveel moeite (38%). Dit gold voor zowel de westerse als de niet-westerse deelnemers aan het vragenlijstonderzoek. Andere personen die afzagen van deelname aan de dragerschaptest(en) gaven aan dat de uitslag van de test geen invloed zou hebben op hun keuzes met betrekking tot het krijgen van kinderen. De deelnemers aan de testen rapporteerden in het algemeen geen belangrijke negatieve psychologische gevolgen, noch gevoelens van discriminatie of stigmatisatie. Echter, een minderheid (14%) van de deelnemers aan het vragenlijstonderzoek verwachtte dat dragers mogelijk gerijmde dragerspeurderwijs gediscrimineerd zouden kunnen worden. Onder hen waren significant meer deelnemers van niet-westerse dan westerse afkomst (Hoofdstuk 4).

De deelnemers aan de dragerschaptest(en) waren in het algemeen tevreden en niemand had spijt van zijn/haar deelname. Er werden in totaal drie CF dragers en 7 Hb-pathie dragers geïdentificeerd. Er werden geen dragerparen gevonden. Drie maanden na ontvangst van de testuitslag voelde geen van de dragers zichzelf minder gezond, zes dragers waren opgelucht, en één drager was teleurgesteld en bezorgd. Vier niet-westers dragers waren zich niet bewust van het restrisico op het krijgen van een aangedaan kind. Vijf dragers bespraken de
resultaten met familieleden (Hoofdstuk 5). In het algemeen gaven de deelnemers aan de dragerschapstest(en) aan dat de testresultaten van invloed zouden zijn geweest op hun keuzes ten aanzien van zwangerschap en het krijgen van kinderen als uit de testen was gebleken dat zij tot een dragerpaar behoorden: 27% zou overwegen om af te zien van een zwangerschap en in geval van zwangerschap zou 89% prenatale diagnostiek overwegen. Het kennisniveau over autosomaal recessieve overerving verbeterde significant na de voorlichting bij de huisarts, maar was drie maanden na ontvangst van de testuitslag weer gedaald tot het niveau van voor de afspraak bij de huisarts. De westerse deelnemers aan de dragerschapstest(en) waren ongeveer gelijk aan de niet-westerse testdeelnemers: zij hadden een hoger kennisniveau en waren zich vaker bewust van het feit dat er na de testuitslag sprake was van een restrisico op het krijgen van een aangedaan kind. In het algemeen leidde het hoge kennisniveau niet tot gevoelens van angst, maar de westerse deelnemers scoorden wel lager op de gebruikte angstschala dan de niet-westerse deelnemers (Hoofdstuk 5).

**Ethische aspecten van preconceptionele dragerschapscreening op CF en Hb-pathieën**

In veel Europese landen wordt discussie gevoerd over de vraag of en zo ja, hoe preconceptionele dragerschapscreening voor ernstige autosomaal recessieve aandoeningen moeten worden ingevoerd. In die discussie wordt onder andere gesproken over mogelijke nadelige en onwenselijke consequenties van een dergelijk aanbod van screening. Zo wordt genoemd dat sociale druk van de omgeving de keuzevrijheid van het individu zou beperken en ziet men deze vorm van preconceptionele zorg als een ongewenste vorm van medicalisering van de periode voor de zwangerschap. In 2003 werd een landelijke workshop georganiseerd waarin het ethische spanningsveld werd geëxploreerd tussen enerzijds het aanbieden van een vrije geïnformeerde keuze en het vergroten van de reproductieve keuzemogelijkheden, en anderzijds het beschermen van het individu tegen mogelijke ongewenste effecten van een dergelijk aanbod. Vier experts hielden een betoog over de voor- en nadelen van twee ethische hoofdthema’s, te weten ‘keuzevrijheid’ en ‘medicalisering’. Er werd geconcludeerd dat de mogelijke bedreiging van de keuzevrijheid en de medicalisering van de preconceptionele periode niet beschouwd mogen worden als overtuigende morele argumenten tegen een aanbod van preconceptionele dragerschapscreening (Hoofdstuk 6). Eén van de conclusies was dat absolute keuzevrijheid niet bestaat, omdat keuzes altijd worden gemaakt in een omgeving die ook wordt bepaald door de keuzes van anderen. Als pre-
conceptionele dragerschaps screening niet beschikbaar is, dan is er helemaal geen keuzevrijheid. Het is hierbij cruciaal dat de dragerschap testen en de benodigde informatie voor het nemen van een geïnformeerde keuze op neutrale wijze worden aangeboden. De zorgen die men heeft ten aanzien van de medicalisering van de preconceptionele periode kunnen worden beperkt. Ten eerste door de test beschikbaar te maken op een wijze waarbij men het proces van het nemen van een geïnformeerde beslissing serieus neemt, en ten tweede door te blijven investeren in adequate sociale voorzieningen en zorg voor gehandicapten en hun families. De discussie over autonomie en medicalisering zou zich daarom vooral moeten richten op de manier waarop preconceptionele dragerschaps screening zou moeten worden aangeboden (Hoofdstuk 6).

**Sociotechnische aspecten van preconceptionele dragerschaps screening op CF en Hb-pathieên**

Om meer inzicht te verwerven in het proces van de mogelijke implementatie van een programma voor preconceptionele screening op dragerschap voor CF en Hb-pathieên werd een sociotechnische analyse uitgevoerd, gebaseerd op het zogenaamde dynamische co-evolutie model van vraag en aanbod. Het concept co-evolutie wil zeggen dat technologie en maatschappij ontwikkelen over de tijd en onder invloed van elkaar (Hoofdstuk 7). Daarnaast werden de implementatieprocessen bestudeerd van twee reeds bestaande gezondheidsprogramma’s met vergelijkbare aspecten zoals die zich bij een programma voor preconceptionele dragerschaps screening voordoen: 1) de implementatie van het preconceptio nele informatie aanbod rond het foliumzuuradvies ter preventie van neurale buisdefecten, en 2) de implementatie van de cascade screening bij familiale hypercholesterolemie, waarbij DNA onderzoek in een screenings programma wordt uitgevoerd.

Het feit dat in Nederland de grote meerderheid van de zwangerschappen gepland zijn, biedt een goede gelegenheid voor de implementatie van preconceptionele dragerschaps screening op CF en Hb-pathieên, maar het bereiken van paren met kinderwens is een enorme uitdaging in afwezigheid van een algemene setting voor preconceptiezorg. Verscheidene factoren dragen bij aan een mogelijk succesvolle implementatie: 1) het bestaan van sociotechnische niches, waarin vernieuwingen ontwikkeld en uitgeprobeerd kunnen worden in een experimentele setting; 2) een structurele aanpak van informatie voorziening aan toekomstige ouders; 3) een partij van waaruit er een vraag naar deze vorm van screening geformuleerd wordt; 4) regelgeving van overheidswege in samenspraak met verschillende belanghebbenden; en 5) een
infrastructuur geschikt voor de screening waarin DNA-diagnostiek op grote schaal beschikbaar is. Succesvolle implementatie van preconceptionele screening op dragerschap voor CF en Hb-pathieën is afhankelijk van veranderingen op regime en landschap niveau, inclusief de realisatie van een setting voor preconceptiezorg en een duidelijk zichtbare gezondheidsautoriteit die zorg draagt voor de coördinatie, monitoring en evaluatie van een dergelijk initiatief in de gezondheidszorg (Hoofdstuk 7).

Sensitiviteit van de CF dragerschapstest voor Turken en Noord-Afrikanen

De behoefte bestond om meer inzicht te verwerven in: a) de variabiliteit van mutaties in het CFTR gen bij niet-westerse CF patiënten die woonachtig zijn in Europa, en b) de testsensitiviteit van de huidige veel gebruikte methoden van DNA onderzoek om CF dragers en patiënten op te sporen, onder immigranten van Turkse en Noord-Afrikaanse afkomst. Derhalve werden de artsen van 373 CF centra in heel Europa gevraagd deel te nemen aan een vragenlijstonderzoek waarin gevraagd werd of zij CF patiënten behandelden van Turkse of Noord-Afrikaanse afkomst, of er CFTR mutaties waren aangetoond, en zo ja welke en met welke test.

Bij de gerapporteerde CF patiënten van Turkse en Noord-Afrikaanse origine, die in Europa wonen, waren respectievelijk 31 en 26 verschillende mutaties in het CFTR gen aangetoond, resulterende in de identificatie van respectievelijk 64% (113/176) en 87% (118/135) van de allelen (p<0.001). De testsensitiviteit van de huidige veel gebruikte methoden van DNA onderzoek om CF dragers en patiënten op te sporen, onder immigranten van Turkse en Noord-Afrikaanse afkomst, bedroeg respectievelijk 45% en 70%. Indien deze panels zouden worden uitgebreid met 13 pathogene mutaties die werden beschreven op minstens twee of meer allelen bij de CF patiënten van Turkse en Noord-Afrikaanse afkomst uit het studiecohort, zou dit leiden tot een toename van de testsensitiviteit tot respectievelijk 57% en 79%. De testsensitiviteit is daarom verre van ideaal voor screening van subpopulaties in Europa van Turkse en Noord-Afrikaanse afkomst, omdat na een negatieve testuitslag er nog steeds een behoorlijk restrisico overblijft op dragerschap. Het advies is om screening op dragerschap voor CF voor alle (sub-)populaties beschikbaar te maken voor alle paren met een verhoogd risico en daarbij de Turkse en Noord-Afrikaanse paren te informeren over de beperkte waarde van een negatieve testuitslag. In de tussentijd is het uiteraard wenselijk om te proberen de onbekende pathogene CFTR mutaties in deze populaties te achterhalen en om de mogelijkheden te onderzoeken om het gehele CFTR gen te analyseren (Hoofdstuk 8).
Conclusies
De studies die gepresenteerd worden in dit proefschrift hebben bijgedragen tot verbeterde inzichten in de haalbaarheid en wenselijkheid van preconceptionele, op oorspronkelijke afkomst gebaseerde dragerschapscreening op CF en Hb-pathieën. Het bleek haalbaar om een aanbod te doen gebaseerd op de oorspronkelijke (etnische) afkomst van beide partners. Er is een beslisinstrument ontwikkeld dat kan dienen als screeningshulpmiddel om vooraf te bepalen voor welke dragerschapstesten het paar in aanmerking zou komen gebaseerd op de oorspronkelijk afkomst van beide partners: voor CF, voor Hb-pathieën, voor beiden aandoeningen of voor geen van beide aandoeningen. Verder werd de haalbaarheid aangetoond van het versturen van uitnodigingen voor deelname aan de dragerschapscreening, van het uitvoeren van erfelijkheidsvoorlichting door de huisarts en van het laten verrichten van de dragerschapstesten.

Preconceptionele screening op dragerschap voor CF en Hb-pathieën, gebaseerd op oorspronkelijke (etnische) afkomst, bleek daarnaast ook wenselijk voor mensen die tot de doelgroep van paren met kinderwens behoorden. Hoewel het percentage daadwerkelijk deelnemers aan de dragerschapstest(en) laag was in de screeningstudie, hadden zowel de testdeelnemers, als zij die afzagen van deelname, in het algemeen een positieve attitude ten opzichte van deelname aan de dragerschapstesten voor CF en Hb-pathieën. Tijdgebrek en de mening dat deelname aan de testen teveel moeite zou kosten, waren de belangrijkste redenen om af te zien van deelname. De deelnemers aan de dragerschapstest(en) waren tevreden en geen van hen had achteraf spijt. De positieve aspecten van deelname aan preconceptionele dragerschapscreening op CF en Hb-pathieën overtreffen de mogelijke negatieve aspecten. Na uitvoerige ethische exploratie werden er geen overtuigende morele argumenten tegen het aanbod gevonden, en overheersende gevoelens van stigmatisatie en/of discriminatie waren evenmin aanwezig. Op basis van de resultaten van de studies in dit proefschrift wordt aanbevolen om een meer uitgebreide screening of implementatie studie uit te voeren onder paren met kinderwens om te onderzoeken of een dergelijk aanbod van preconceptionele dragerschapscreening op CF en Hb-pathieën ook op grotere schaal haalbaar en wenselijk is in een multi-etnische samenleving. Aanbevolen wordt een dergelijke implementatie studie uit te voeren in een setting voor algemene preconceptiezorg.
Dankwoord

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Curriculum vitae

Phillis Lakeman was born on December 12th, 1974 in Bovenkarspel, the Netherlands. After secondary school (Gymnasium) at the Scholengemeenschap Werenfridus in Hoorn, she successfully passed the Propadeutics in the Educational Sciences at the University of Amsterdam (cum laude). In 1994 she started studying Medicine at the Academic Medical Centre, University of Amsterdam. In 1998 she participated in a research project at the Department of Medical Physics, the Department of Obstetrics and Gynaecology, and the Laser Centre of the Academic Medical Centre. This project focussed on beneficial effects of polyhydramnios in monochorionic twins that are haemodynamically connected by arterio-venous plus arterio-arterial placental anastomoses.

After graduation from Medical School in 2000 (cum laude), she started working as a physician at the Department of Obstetrics and Gynaecology in De Heel Zaans Medisch Centrum, in Zaandam.

In June 2002 she started her PhD project in the Division of Community Genetics, which is part of the Department of Clinical Genetics and the EMGO-Institute of the VU University Medical Center in Amsterdam. She worked under supervision of Professor Leo P. ten Kate and Professor Martina C. Cornel, on the feasibility of an offer of combined ancestry-based preconceptional carrier couple screening for cystic fibrosis and hemoglobinopathies in a multi-ethnic population in the Netherlands (this thesis, 2008).

During this project she attended the postgraduate master programme in epidemiology at the EMGO-Institute and the Department of Clinical Epidemiology and Biostatistics of the VU University Medical Center and the title Master of Epidemiology was conferred upon her (2006).

Since September 2006, she has been working as a physician at the Department of Clinical Genetics of the VU University Medical Center. In January 2008 she started her training as a clinical geneticist at this department under the supervision of Professor Hanne Meijers-Heijboer.
List of publications

In vitro placental pressure-flow behaviour is non-linear and depends on the external pressure.

Polyhydramnios and arterio-arterial placental anastomoses may beneficially affect monochorionic twin pregnancies.

Developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society.
Lakeman P, Henneman L, Bezemer PD, Cornel MC, Ten Kate LP.

Implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies: a sociotechnical analysis.
Achterbergh R, Lakeman P, Stemerding D, Moors EHM, Cornel MC.

CFTR mutations in Turkish and North African cystic fibrosis patients in Europe: implications for screening.

Three-month follow-up of Western and non-Western participants in preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies
Lakeman P, Plass AMC, Henneman L, Bezemer PD, Cornel MC, Ten Kate LP.
Accepted for publication in Genetics in Medicine.

An offer of combined ancestry-based preconceptional carrier couple screening for cystic fibrosis and hemoglobinopathies: response in a multi-ethnic population.
Lakeman P, Henneman L, Bezemer PD, Gille JJP, Giordano PC, van Zwieten R, Cornel MC, Ten Kate LP.
Submitted for publication.
Preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies: determinants of the intention to participate or not.
Lakeman P, Plass AMC, Henneman L, Bezemer PD, Cornel MC, Ten Kate LP.
Submitted for publication.

Preconceptional carrier screening: will the offer impair freedom of choice and lead to medicalisation?
Lakeman P, de Wert GMWR, Henneman L, Cornel MC, Ten Kate LP.
Submitted for publication.
Appendices

The letter of invitation to participate in the screening study, the information leaflet, the reply form, and the brochure for test-participants, as well as the questionnaires 1 to 4, and the questionnaire for those who refrained from test-participation can be found at: www.emgo.nl/dissertations/Care/plakeman_dissertation.asp or can be applied for at the author at: p.lakeman@vumc.nl.

In a workshop on ethical issues regarding preconceptional CF carrier screening which was held in October 2003 in Utrecht, the Netherlands, the ethical tension between maximising reproductive options for carrier couples and protecting individuals from the unwanted side-effects was investigated. Four experts presented their opposite points of view on two main ethical issues: ‘freedom of choice’ and ‘medicalisation’ with regard to preconceptional CF carrier screening (Chapter 6). Tymstra and Den Hartogh presented opposite views about the question of whether or not the threat to freedom of choice represents a convincing moral objection to preconceptional CF screening, and Verweij and Dondorp discussed the question of whether or not medicalisation of the preconceptional period should be considered as a convincing moral objection to preconceptional CF screening.

In Chapter 6 of the present thesis the first paper of a series of five papers is presented on the ethical investigation of ‘freedom of choice’ and ‘medicalisation’ regarding preconceptional (CF) carrier screening. In the following appendices the other four papers of this series are presented, i.e.:


Appendix 1

“But that’s your decision!” About the limits of self-determination

Tjeerd Tymstra

Abstract
Modern biotechnology has made it technically possible for prospective parents to determine their risk of having a child with cystic fibrosis (CF). Preconceptional carrier screening enables carrier couples to make an informed reproductive decision. In deciding whether or not to implement preconceptional CF carrier screening, it should be questioned whether the offer of the screening procedure will make people feel less at liberty to ignore it. Can one really speak of ‘voluntary participation’? There is no absolute freedom of choice, and belief in the capacity of people to make rational and autonomous decisions is questionable. Offering CF carrier screening does not necessarily contribute to freedom of choice. Psychological factors, such as anticipated decision regret and difficulty in dealing with risk information (the tendency to think binary), as well as environmental factors, such as the normative expectations of one’s culture, hinder a truly free decision. The very fact that the subject is raised by a health worker conveys the message that it is a good idea to participate, otherwise the screening would not have been offered. Even when a person makes a truly free decision to participate, the test results are also of importance for the members of participant’s family, which implies an additional responsibility. It is concluded that CF carrier screening has consequences which people have difficulty in overseeing beforehand - so a truly free decision does not exist. However, if a screening procedure is withheld from people, they are also deprived of the freedom to make their own decisions about participation.

Introduction
In the Netherlands, 1 in 30 people is carrier of a CF-gene mutation (i.e. more than half a million people), and in 1 out of 900 couples both partners are carriers. Their children have a 1 in 4 risk of having CF. Modern biotechnology has made it possible for all prospective parents to determine their risk of having a child with CF. If it is established that both partners are carriers, then there are a number of possibilities that are open to them, e.g. choose not to have (their own) children, choose to have prenatal diagnosis, choose to take the risk. There are a number of arguments for and against the large-scale introduction
of preconceptional CF carrier screening. Some of these can be quantified with empirical research, e.g. epidemiological parameters (number of participants, attainable health gain, etc.) and the financial profits and losses. Other aspects of screening, such as the social and psychosocial consequences are far more difficult, if not impossible, to measure.

The offer of screening raises the question of whether people feel at liberty to ignore it. Can one really speak of ‘voluntary participation’? This is the question that is discussed in the following article.

**Political regulation**

In the United States, where the health care system is strongly based on the free market principle, preconceptional CF carrier screening is already on offer. It is also an option in other countries, but in the Netherlands, health care is traditionally centrally regulated, and therefore genetic screening will involve political decision-making. Not until it has been ascertained that there is a favourable balance between profit and loss, and that screening can provide a significant contribution to healthcare, will action be taken to introduce it. Within the Dutch health service, values such as solidarity, equal access for all, and just distribution play an important role. The standpoint is that if a medical provision can be considered significant, then it should be made available to each and every inhabitant. However, this central governmental regulation is under increasing pressure. Modern information and communication technology (the Internet), the process of internationalisation and globalisation, and the accentuation of the importance of ‘a free market’, all leads to the increasing difficulty experienced by government bodies in regulating access to health care facilities. This has been apparent, for example, in the case of antenatal screening: in spite of the fact that the Dutch government prohibited the offer of systematic serum screening, a diffusion of the maternal serum screening (the triple test) still took place. When such a situation occurs, the question arises as to whether it might be better to opt for organised screening implementation, so that the uncontrolled developments can be counteracted.

**Organised offer**

If the conclusion is drawn that preconceptional CF carrier screening is important and should be on offer, then there are several options for implementation. The following discussion is based on the assumption that the aim is to provide prospective parents with explicit information which will make them aware of the availability of CF screening. Evidently, in such a situation, a good screening infrastructure setup is needed (laboratory
facilities, registration, information for people with questions/unfavourable results, etc.). Unlike antenatal screening, there is no health worker/client relationship, and therefore information campaigns in the form of leaflets/posters in waiting rooms, articles in daily and weekly publications and informative radio and television programmes will have to be organised to alert potential parents to the possibility of screening. It is particularly important to approach those people (women?), of whom it is known that they are ‘looking for information about getting or being pregnant’. The screening option could be incorporated in websites visited by people who are ‘busy with wanting to get pregnant’ (recently such a site was introduced in the Netherlands).

As far as this approach is concerned, a comparison can be made with information campaigns that have been held in the past to promote the use of folic acid. The use of folic acid by (potentially) pregnant women can reduce the risk of having a child with a neural tube defect. The information that was disseminated has led to vast increases in the use of folic acid. In the Netherlands an increasing number of women take it in the weeks leading up to and after conception, although not always as directed. Some pharmacists are putting stickers on the packaging of contraceptive pills emphasizing the importance of folic acid (a procedure which could also be employed for CF screening).

Although folic acid and CF carrier testing both offer the possibility of preventing congenital defects, technically there are considerable differences between the two forms of prevention. Folic acid involves, once a day, taking a small pill which is readily available from a chemist or pharmacy; something which the (potentially) pregnant woman can easily arrange for herself. It is a ‘preconceptional decision’ which does not require a lot of serious consideration and which will probably be supported by her partner. However, testing for heterozygote CF carrier status is a different story altogether: it is a test which relates to a person’s genetic make up and it cannot be carried out independently by the person concerned (at least, not at the moment; self-testing may be a possibility in the future). The consequences of both types of prevention are also very different.

A free choice?

Advocates of screening claim that its purpose is to offer people the possibility to make informed choices about an option which can be to their advantage (health promotion). Their premise is that people are able to oversee the pros and cons of their actions, and can therefore come to an unforced and rational conclusion, but this is an approach which does raise some questions. Research into the psychology of decision-making has made it clear that man is not a
homo economicus who makes a decision after logical consideration of all the pros and cons. A number of factors play a role in the choices people make, and no one is fully aware of all the influences which determine the final decision. The American psychologist Wilson states in his book ‘Strangers to Ourselves’,\(^2\) that people are not even aware of the reasons for the major decisions which they make in their lives. It is above all the emotional aspects which appear to play a role in decision-making behaviour. People tend to anticipate how the situation will be once they have made the decision. An important motive in this is the wish to avoid negative feelings about a possible wrong choice. People express this in such terms as “I want to avoid the risk of having to think: if only I’d........”. This ‘anticipated decision regret’ sometimes makes it difficult for people to turn down the chance that is offered.

From research on the psychology of decision-making, it appears that people have difficulty knowing how to deal with chances and risks, especially when the issues concerned are those of sickness and health. It would appear that a real, objective risk - the statistical probability - only plays a minor role in the decisions people make. It is, above all, factors such as ignorance of the consequences of a risk, the degree of control and the catastrophic potential of the threat which determine the reaction to risk-information. Even a risk which, viewed objectively, is only slight can in this way be seen as threatening and damaging. What is more, people tend towards ‘binary thinking’. A risk is then interpreted in terms of “For me it’s a case of yes or no” or “What if you are that one?”. The (objectively viewed) not very high risk of 1 in 3,600 of having a child with CF can still be experienced as high. ‘Binary thinking’ and ‘anticipated decision regret’ form the basis of what is called the ‘technological imperative’.\(^3,4\)

**Knowledge brings responsibility**

Participation in screening trials is strongly dependent on the way in which the screening test is offered. Often, people do not feel the need to subject themselves to all sorts of diagnostic testing of their own accord, but given an explicit invitation, then the uptake is high. This is, for example, true in the case of early detection of breast cancer. A general offer of screening would result in only a small number of women wishing to have a mammogram, whereas a personal approach –as used in the Netherlands- leads to a high uptake. The method of approach is also important in the field of reproductive technology. In the beginning of the 1980s, women registering for antenatal care in the University Hospital in Groningen were informed about the possibility of being tested to determine their chances of giving birth to a child with a neural tube defect. This involved a simple blood test (the serum-AFP-screening). The women were sent a
leaflet explaining the test and informing them that, should they be interested in having the test, then they should raise the matter themselves during a consultation. In the course of time, however, it became apparent that only a few expectant mothers had taken up the offer. Research was carried out to investigate which factors had played a role in the decision as to whether or not to undergo the test. It appeared that the open-ended offer had led to quite a few (communication) problems. Some of the pregnant women had, in fact, wanted to have the test, but had not got around to arranging it (“I hadn’t done enough to ensure that I had the test, although I would really have liked to have had it”). Others had put the leaflet aside because they did not want to be confronted with it (“I’m a bit wary of this sort of thing, I’d rather not think about it”). At a later date the clinic changed its policy, and it was decided that the gynaecologists would explicitly ask each and every pregnant woman whether she was aware of the possibility of serum-AFP-screening. This resulted in a marked increase in the uptake of the serum test.

The above examples sketch the dilemma which the offer of screening brings with it: an open-ended offer means for some people that there has been ‘an opportunity missed’, but a personal approach forces them to make a decision which they sometimes would rather have avoided. Some people are inclined to take a ‘risk-information avoidance attitude’, but the more personal the screening offer is, the more difficult it is to make the case for an ‘intra-psychic defence’. Moreover, if a health worker brings up the subject of a diagnostic option, this can never be completely neutral or without obligation. After all, the very fact that the subject was raised suggests that ‘it would be a good idea to think about it’ and, in fact, brings with it an implicit approval of the test (“If it wasn’t important, then they wouldn’t offer it”).

What is the significance of the above with regard to preconceptional CF carrier screening? As previously stated, this article assumes a situation in which CF screening would be offered by way of general information and would, therefore, basically be without obligation. Prospective parents would have to take the initiative themselves to have the test. This means that, at the moment, there would be plenty of opportunity to ignore the screening option. A situation which -according to expectation- could change if an increasing number of prospective parents seek preconceptional advice and if CF screening becomes an explicit topic of discussion.

**Normative expectations**

In addition to personality factors, (sociological) environmental factors also play an important role in the decisions people make. Every civilisation develops
values, standards and ideas which form a guideline for the behaviour of those who are a part of it. Because people are social beings who wish to be accepted and valued by others, everyone’s freedom of action is curtailed by the prescribed behavioural patterns of their culture. People are far more of a slave to their environment than we like to believe.

Also in the area of sickness and health, there are all sorts of ideas and guidelines with which people are confronted. “Social norm” plays a role in decisions about almost any health promotion activity. It is generally expected that the women who receive an invitation for breast cancer screening will accept it. Participation has become the norm and departure from this must, to a degree, be explained and defended. The principle behind this norm obligation is the assumption that early detection can provide important health gains.

In the field of reproductive technology there are also standards and values which determine people’s behaviour, and which can limit their freedom of action. Studies of decision-making concerning prenatal genetic screening show that perceptions of social norms, i.e. what health professionals and friends/family think the woman should do, play a role in a woman’s prenatal testing decisions. Especially older pregnant women can be confronted with the expectation that they ‘should make use’ of prenatal testing. However, this pattern of expectation is not so strong that it can not be ignored, because less than half of the older pregnant women in the Netherlands make use of this diagnostic option. This has, above all, to do with the fact that, in this case, there are no real treatment options on offer; termination of the pregnancy being the only one. As this is not an acceptable alternative for everyone, fewer compulsive standards have evolved in this area. Simple test procedures have recently been developed, from which it is possible to work out the degree of risk for younger pregnant women of giving birth to a child suffering from Down’s syndrome. The question that arises is whether or not these new test procedures will lead to a normative pattern of expectation (“Surely you’re going to have the test?”).

Up until now, a 28 year old pregnant woman who indicates that she does not want this kind of test and that “every child is welcome” will meet with little social disapproval in our society (and maybe, to an even greater degree, admiration). Such a ‘natural approach’ is, at the moment, most certainly acceptable. As for the possibility of allowing preconceptional CF carrier testing, there is no expectation that a compulsive norm will come into being which prescribes that this is “something for which you should be tested”. It is less certain whether this will remain so in the future, taking into consideration the ever-increasing techno-diagnostic developments.
Individual autonomy?

If the above refers to ‘widely felt’ social standards and values, each and every one of us is also affected by the ideas of those in his or her direct surroundings. It is for the opinions of these people that we are most sensitive. Moreover, decisions concerning procreation must, by definition, involve two people. Besides, it also concerns the responsibility for a future life: that of the child which they wish to bring into the world. These are decisions which men and women want to share and about which they hope that they are of a like mind. In practice, however, the latter is by no means always the case. Prospective parents can have vastly differing opinions and feelings about the subject of pregnancy and child-bearing. A diagnostic offer can, therefore, easily lead to tension and cause disharmony within a relationship. Women often experience matters concerning pregnancy and childbirth differently to men. Research into the uptake of prenatal screening has shown that women sometimes participate in screening because their partner wanted it. When it comes to preconceptional CF carrier testing, men and women are also likely to differ in their opinions. The question then will be what, in this case, is ‘a free choice’: individual autonomy or couple autonomy?

Assignment of responsibility

Hereditary illness means family illness. This implies that, if a hereditary illness or the predisposition for it is ascertained, a change in the distribution of responsibility between people takes place. This is also true in the case of preconceptional CF screening and it is, in fact, the cause of one of the problems. If a woman wishing to have a child allows herself to be tested and she is found to be a CF carrier, she is then aware of the genetic profile of her child: there is a 50% chance that her son or daughter will also be a carrier. What does she do with this information, and (at what point) does she tell the child? It will also bring about a change in her relationship with other members of the family. If it becomes known that a woman is a carrier, then it means that her brothers and sisters also have a 50% chance of being a carrier (and there is a 25% chance for the children of her aunts and uncles, etc.). This means that, from the moment she knows that she is a carrier, she becomes, to some degree, responsible for the potential CF of her future nephews and nieces (their risk of CF is 1 in 240). Therefore, knowledge of the fact that she is a carrier leads to a certain moral duty to inform the other members of the family, but to what extent are people aware of this, and do the other family members want to know? On the other hand, should a preconceptional CF screening programme become operational, then family communication is not crucial any more because all members of the
population (including members of the family) will be offered screening. One of the solutions for this ‘problem of responsibility’ would appear to lie in allowing family members to be allowed to choose to remain ignorant (“Leave me out of this”). This is, in fact, difficult to put into practice. If a woman carries the CF gene and her partner does not, then, as far as CF is concerned, there is no reason to refrain from getting pregnant. The birth of a child, however, would be misleading for her ‘risk-information-avoiding’ brothers and sisters: they could, after all, think that ‘there’s nothing wrong’. If the woman is not a carrier, but fails to get pregnant, this could also give rise to the wrong interpretation (“The result of the test must have been unfavourable”). It illustrates the complex character of this sort of screening and brings into doubt the concept of the ‘person acting autonomously’.

**Observation and conclusion**

In a modern society, people are forced to make ever more choices. So much so that the psychologist Schwartz, in his book ‘The Paradox of Choice’, states that it could become a problem which would not be to the good of our own welfare. Medical science also requires that we take more and more decisions, amongst other thing because of the development of diagnostic procedures with which the risk of illness or defects can be charted. Some of these test procedures are suitable for large-scale application, but there are a number of advantages and disadvantages involved in the implementation of such screening programmes, some of which are difficult to quantify. This is also true of preconceptional CF carrier screening. Anyone raising the matter within a group, will discover that ideas vary drastically about whether or not ‘it’s good to do this’, but even those who have their doubts will often point out that ‘everyone must be allowed to decide for themselves what to do about the offer of screening’.

Arising from the eighteenth century School of Enlightenment, there is a universal belief in the origin of the rational and autonomous man. This assumes that a person must be considered capable of taking responsibility for his or her own decisions, and of doing so intelligently. It has led to the principle of autonomy, which is characteristic of and dominant within our society; man is regarded as a free individual, who makes autonomous decisions and whose only limitation lies where it curtails the freedom of choice of others. To decide that others should not be allowed to make a certain decision is contrary to this liberal concept of autonomy.

Social scientists query more and more the existence of these ‘rationally calculating citizens’. Research has shown that decision behaviour is a very complex matter and that individuals are not inclined to be influenced by,
in the economical sense, rational arguments. All sorts of interwoven psychological and sociological factors appear to influence the decisions that people make. On a personal level, there is above all the need to ‘be left with a good feeling’ when the decision has been made. A particularly motivating factor is the need to avoid feelings of regret afterwards. This latter is at the core of people’s inclination to avoid oncoming disaster at all cost, however small this chance may be when viewed objectively. It must also be taken into consideration that people live in social relationships and are sensitive to the judgement of others around them. Therefore, individual decisions always involve responsibilities towards others and can be held responsible for changes in them.

The above describes what this means in relation to CF screening: consequences which people often have difficulty in overseeing beforehand.

In the liberal ethic, a lot of emphasis is laid on personal autonomy; people have the right to make free choices, without these choices being forced upon them or dictated to them by others. In this article, the notion of autonomy is analysed from a social-scientific viewpoint, and questions are raised concerning this concept of autonomy. If a screening procedure is withheld from people, then they are also deprived of the freedom to make their own decision about it. However, the decision to offer the screening does not necessarily mean that there is freedom of choice.

Reference List


Appendix 2

Offer and autonomy

Govert A. den Hartogh

Abstract
This paper examines the validity of the following argument: “The aim of preconceptional screening for cystic fibrosis (CF) is to increase the freedom of choice of individuals. For that it is crucial that the decision whether or not to accept the screening offer is made in complete freedom. However, it is impossible to make the offer in such a way that the decision is made in complete freedom. That is why the offer should not be made.” Factors that could possibly undermine complete freedom are discussed. It is concluded that absolute freedom of choice does not exist, because choices are always made in an environment that is co-determined by the choices of others. If a preconceptional carrier screening test is not available, there is, however, no freedom of choice at all. A screening offer should therefore not be withheld, but the offer should be made as neutral as possible.

Introduction
“The aim of preconceptional screening for cystic fibrosis (CF) is to increase the freedom of choice of individuals. For that it is crucial that the decision whether or not to accept the screening offer is made in complete freedom. However, it is impossible to make the offer in such a way that the decision is made in complete freedom. That is why the offer should not be made.”
I aim to examine the validity of this argument.

Explanation of the argument
The argument, of course, does not only apply to screening for CF. The first time I heard it was when it was presented by obstetricians who were not prepared to tell their clients about the possibilities of prenatal screening for spina bifida and Down’s syndrome. I still remember very well how amazed I was at this line of reasoning. Since then I have repeatedly come across it in all sorts of connections.
“Offer” in this context has a specific, almost technical meaning, which may lead to misunderstandings. Screening is not “offered” in the way a bakery offers cakes close to their sell-by date at a vastly reduced price, that is, in order to get something in return. That’s why the argument differs from the contention that there can be “coercive offers”, dubious proposals that, owing to the extent of the
reward and/or one’s precarious situation, can hardly be refused. Nor is screen-
ing offered in the way that a colleague offers to swap a working day with you so that you can celebrate your grandson’s birthday, that is, in the supposition that it is something you would very much like to do. Someone who is offered screen-
ing merely receives adequate information about the possibility of having a test, about the significance of positive and negative results, and about possible subsequent steps. That information can be given personally by the general practitioner or in a brochure that comes through the letterbox. If the offer is not made, the possibility of screening remains open only to those who ask for it on their own initiative.

If that is all an “offer” means, how could it render impossible the complete freedom that is involved in the decision whether or not to accept it? Which fac-
tors could exercise a problematical influence? The following possibilities suggest themselves:

A. A totally neutral wording of the offer is not possible; it is always coloured by the attitude of the one who makes the offer. That of course applies particularly, though not exclusively, to personal information. Doctors, for example, generally favour taking action: they would rather see their patients using the existing medical potential than not using it.

B. Even if the offer is made in a totally neutral form, the sheer fact that it is made is important. People will think that the offer is not made without reason.

C. As soon as a substantial number of those people, let us say more than half of them, take up the offer, a spiralling effect occurs. The next person to whom the offer is made gets the feeling that it would be odd not to accept it, which increases the chance that she or he will, in fact, accept it, which in turn increases the “pressure” on the next person.

D. People can process information in the wrong way, especially over a longer period of time. In the case of a negative result, for instance, after three months they will think that they know for certain that they do not carry the disease, whereas this is still a real possibility. They insufficiently realize that the prognosis for CF is highly variable, etcetera.

It is sometimes said (E) that if the offer is made, some people will take it up because they wish to prevent any regret about not having accepted the offer, should the unhoped-for event occur that they do have a child with CF. They follow a decision principle known as “minimax regret”: minimize the maximum regret that a choice may cause. But people do this in many different situations and it is not an evidently irrational decision principle. Therefore I propose to discard this factor.

As regards the remaining factors, it is a matter of speculation to estimate their
significance and even to suppose that they play any part at all. To my knowledge nothing empirical is known about that. It is difficult to research the influence of such factors: it cannot be deduced from the decisions that people actually make, not even if 99% make the same decision. Self-reporting is unreliable, since people have a tendency to adapt their assessment of a procedure to their satisfaction with the outcome.

But I will not dispute that the supposed effects (A) through (D) do, in fact, occur. My question is merely: supposing they do occur, is the argument valid?

**Does the conclusion follow from the premises?**

The starting point of the argument is: people should be offered both alternatives (screening or not) as fully equal options, as in the case of a coin without weights that falsify the result. In fact they get a coin that, when tossed, yields heads more times than tails. How many times? 51, 55, or 60 times out of a hundred? A higher number is not likely. The effect of factors such as those mentioned (A through D) can only be smaller than the effect of such actions as the following: openly recommending, advertising, rewarding those who will (not) let themselves be screened. Not to mention the use of force.

On the other hand, if you do not make the offer, because of the falsifying weights, and screening is therefore only available for those who ask for it, some people will have no choice at all, not even a choice between unequal alternatives. They simply do not know that the possibility of screening exists. They will get tails 100 out of 100 times.

One could raise as objection to this that in our society medical information is so widely available —through television, the Internet, etcetera—that most people will be aware of screening possibilities. I very much doubt that. People constantly have to select from the enormous supply of information those things that they give their attention to, and there must be a special reason for a person to direct concentrated attention to screening possibilities. (This also applies to the proposal to spread information about CF independent of the screening offer. Why would people be seriously interested in that?)

But even if most people already possess the relevant information, this cannot be a reason not to inform the rest. Respect for autonomy applies to individuals; it is not a matter of maximizing freedom of choice at population level. One cannot take away completely the freedom of choice from one person in order to increase it by 10% for 11 others.

That the recommended medicine is worse than the diagnosed illness seems to me to be so evident that it makes me suspect that the people who put forward the argument are not as interested in maintaining full freedom of choice as
they pretend to be. They are against screening for other reasons, and use the argument because they believe it must appeal to their more liberal fellow citizens; so it’s really more a matter of driving out the Devil with Beelzebub. In the case of the obstetricians it soon appeared that they objected to people choosing abortion if its purpose was to prevent children being born with Down’s or spina bifida.

Is autonomy at issue?
As I said earlier, I accept that the choice of those involved is indeed influenced by the factors listed under A through D in the explanation of the argument. The argument assumes without question that this circumstance destroys the autonomous nature of the choice. But is that true? On the free market of social interaction we are constantly exposed to the influence of others on our choices. That often takes the more persuasive forms I mentioned earlier: openly recommending, advertising, making attractive offers at a low price, giving small rewards. Yet these are all types of behaviour that we naturally tolerate without thinking that they undermine our free choice and our own responsibility for market behaviour. But maybe we are wrong about that. Let us examine more closely what it means to make a free or autonomous choice.
I have the impression that the argument is put forward on the assumption that only that choice is free that has undergone no outside influence whatsoever. Freedom is uncaused causation. If that were so, no choice would or even could be free. As soon as we live with others we are being influenced; without such influence we could learn nothing, not even how to think or speak, and therefore certainly not how to make choices. A choice that was totally uninfluenced would, by the way, not be a free choice but merely a random one. A somewhat less improper view of freedom of choice allows for influences, but only those that appeal to purely rational considerations, for example information provided in an absolutely neutral fashion. Yet such a view is subject to the same objection: there is no such freedom of choice, nor could it even exist. As soon as we live with others there are emotions, prejudices, the need for recognition and status, an imperfect processing of information, jumping to conclusions and other things that affect both others and ourselves. The factors A through D mentioned above are merely a small selection from the interaction patterns created by such influences. But what is more, beings that processed information exclusively in a rational way would not even get round to acting and making choices. Emotions, evaluations and desires are part of the necessary input of the decision-making process. Emotions, evaluations and desires are,
after all, not irrational, although specific emotions, evaluations and desires can be just as irrational as specific views about the facts. So the fact that they play a part in making choices does not detract from the rationality of those choices. We could now develop a concept of autonomy in which we allow emotions etc. as input in decision-making, but nevertheless demand that all available information is processed correctly, and for the rest there are no inadequacies in rationality. Even if this were a defensible concept of autonomy (in fact it is extremely one-sided), it is in any case only an ideal. It is ludicrous to demand that this ideal must always be realized to the fullest extent in practice. In fact, we use notions of voluntariness and autonomy in a normative context in two different ways:

- First as an ideal: worthy of pursuit, but possibly in conflict with other worthwhile matters against which they must be balanced.
- Then as a threshold notion. A decision is seen as “autonomous” in this sense if no force or deliberate manipulation is involved, and if the actor is capable of making a reasoned choice.

We can now construct a dilemma for the argument. Only one of the following two statements can be true:

- Either: the suggested undermining of autonomy can, in principle, be avoided. In that case the correct conclusion would not be ‘don’t make the offer’, but instead ‘make sure to indeed avoid any future undermining of autonomy’.

  Suppose, for instance, that the information material is composed by the same doctors who will subsequently carry out the screening, and that this material may consequently be criticized with a view to neutrality. That would be a good reason to have the brochure written by someone else.

- Or: the undermining is (as the argument really suggests) unavoidable. In that case, the conclusion must be ‘that’s a pity, but nobody can be obliged to do the impossible’. There is no reason to grumble about that, as long as we stay above the threshold value of “enough” voluntariness. If this value is not reached, not only does one not come up to the ideal of autonomy but one undermines the right to autonomy.¹ A major weakness of the argument is that it does not make this distinction. But influences such as those described under A through D certainly do not undermine the possibility of exercising the right to autonomy of those involved. Even the much stronger influences that we accept on the free market of social interaction do not do so. Otherwise you could ask your money back every time you have bought an advertised product. On the other hand, I can well imagine the right to autonomy being undermined by failing to present a screening offer. That point seems to have been reached with regard to prenatal screening for Down’s syndrome and spina bifida.
Is neutrality at issue?

It is generally accepted that the screening offer should be made in as neutral a way as possible, without “pushing” the person involved in one direction or another. I believe that the argument wrongly presupposes that this requirement is based exclusively on considerations of autonomy and freedom of choice. To me, considerations regarding the equality of citizens appear to be of primary importance. The screening offer is made in the name of all of us, so it may not be aimed at promoting or serving one particular view of the good life held by only part of the population. That would show a lack of respect for the others.²

Do the influences mentioned under A through D impair this neutrality principle?

To answer that question we must distinguish two types of neutrality: neutrality of effect and neutrality of aim.

Neutrality of effect is impaired when a particular policy, carried out by or in the name of the government, in fact benefits a particular view of the good life. Neutrality of aim is impaired when that policy aims to benefit a particular view and can only be justified by that aim.

If we look at our list once more, it becomes evident that the factors B and C exclusively relate to neutrality of effect, not to neutrality of aim. As regards A and D, neutrality of aim is relevant: that principle demands that policy be aimed at least at minimizing these effects insofar as they are unavoidable.

In the literature on the neutrality principle it is almost universally recognized that this principle requires neutrality of aim, not of effect. To start with, neutrality of effect is absolutely impossible: nearly everything the government does has differential effects with regard to views of the good life. But furthermore and above all: neutrality of aim is sufficient as far as respect is concerned.

Freedom of religion, to give a prominent example, will favour some views of life above others, for instance those views that are not overly strict in their demands regarding the beliefs and way of life of the faithful. (Or possibly those views, on the contrary, that are very strict.) Inevitably, effects will occur, such as the spiralling effect mentioned under C: choices people make are co-determined by the choices they see other people make. (Many people don’t wish to deviate from the general pattern, but some do). It is always difficult to swim against the current. That is no reason for the government to give subsidy to the Old-Reformed Church or the Rosicrucians. Every free choice has to be made in an environment that is co-determined by the free choices of others. That is not an impairment of freedom; that is freedom. It is also the market principle.

One objection to the argument of the spiralling effect which is sometimes
made, is that in the Netherlands it won’t come to that: not all women who are offered prenatal screening for Down’s syndrome accept the offer. That argument wrongly tries to defend screening in terms of neutrality of effect. Suppose that the uptake of prenatal screening for CF was 90%, would it then be right to discontinue the offer of screening because of the 10% who did not accept the offer?

**Conclusion**

I conclude that the argument is invalid. Even if one assumes that influences like those described under A through D do, indeed, inevitably occur - which as I said is rather a matter of speculation - neither the principle of respect for autonomy nor the neutrality principle provides any reason not to offer screening.

**Reference List**

Appendix 3

Preconceptional CF screening and the problem of medicalisation

Marcel F. Verweij

Abstract
Preconceptional carrier screening for cystic fibrosis (CF) might be an important way to reduce the morbidity and mortality of cystic fibrosis (CF) and to inform couples who are planning a pregnancy, about the risk that their child will have a serious disease. However, these advantages of preconceptional carrier screening might contribute to medicalisation, and this raises moral problems. Medicalisation is a general problem caused by an accumulation of preventive practices and interventions. The moral problems of medicalisation arise, in particular, in the context of pro-active preconceptional screening programmes. Carrier screening undermines peoples confidence in their (general) health, stimulates problematic moral views (e.g. moral responsibility for health and reduced solidarity for people who do not take up the offer for screening and do have a child with CF), and makes it more difficult to develop views of life in which other values than health are more prominent. These moral problems are, therefore, a good reason to accept some reluctance with regard to the ever-increasing possibilities of preventive medicine. It might be better to limit the offer of CF carrier screening to couples who take the initiative to seek medical advice about their reproductive choices, in which case, the issue of medicalisation will be of less concern.

Introduction
Preconceptional screening might be an important way to reduce the morbidity and mortality of cystic fibrosis (CF). Screening requires that couples who are considering a pregnancy will be informed about the possibility that they are CF carriers and the risk that their child will have a serious disease, that they are invited to give a blood sample for DNA analysis, that their samples are analysed, and that they are informed about the results. If both of them are carriers, their children will have a 25% chance of developing CF, and in such a case, the couple can decide to refrain from procreating, to opt for prenatal diagnosis, or to accept the risk and hope for the best.

In this paper, I will not question the efficacy of such screening, but I will discuss a possible moral problem that it might cause. Notwithstanding the important contribution of preventive medicine to public health, preventive interventions
are sometimes considered to be morally problematic because they contribute to medicalisation. The term ‘medicalisation’ was coined by Emile Zola, denoting the trend to see social problems as medical problems, requiring medical intervention and control. In the context of prevention, considerations of medicalisation are often put forward to criticise the fact that preventive practices invite healthy persons to undergo medical examination, screening, preventive treatment, or to change their way life according to medical recommendations. Authors such as Ivan Illich, Petr Skrabanek and James MacCormick have pointed out numerous harmful effects and other drawbacks of preventive medicine – notably screening. Illich emphasised the iatrogenic effects of medical practice, and rhetorically claimed “The medical establishment has become a major threat to health.” Skrabanek raised doubts about the effectiveness of mass screening for breast cancer, and pointed out that inevitably a number of participants would suffer serious harm as a result of screening. It is doubtful whether such sweeping statements are applicable to preconceptional carrier testing for CF. The procedure seems to be free of risks to the health of the participants. Furthermore, I presume that with a valid test and high quality organisation, screening will be an effective way to inform couples about their risks, thus giving them options to avoid having a child that will suffer from CF.

**What is medicalisation?**

There are good reasons to avoid using a relatively vague concept of medicalisation for such important dimensions: obviously screening practices must be safe and effective, but such requirements are obscured rather than clarified if they are framed in terms of medicalisation. Elsewhere I have defined medicalisation in the context of preventive medicine as referring to two related processes. One is on the level of language and concepts: terms such as ‘health’, ‘(un)healthy’, and ‘illness’ are used in other areas, such as personal behaviour, and events and problems that are usually part of everyday life. On a practical level ‘medicalisation’ refers to the phenomenon that healthy persons tend to adjust their life and life-style according to medical information, advice and procedures. This definition is relatively free of moral assumptions. Yet some reasons can be given for the not uncommon opinion that medicalisation can be morally undesirable. These reasons, however, are not as clear-cut as the requirements for safety, nonmaleficence, effectiveness, or respect for autonomy. Moreover, the phenomena of medicalisation, and the moral reluctance they cause, do not normally arise in one preventive intervention carried out by one health
professional; they arise as a result of preventive medicine in general. Nowadays, people are informed about numerous health risks, they are invited to participate in screening programmes, they are told to avoid eating unhealthy food and to refrain from other risky behaviour, they are urged to have vaccinations, etc. Moreover, these preventive measures are recommended in almost all areas in their lives: not only when they talk to their family physician, but also at school, at work, in sports clubs, and through the mass media. Obviously, some level of health is extremely important for a reasonably good life, but it is not self-evident that being reminded all the time of risks and measures to avoid illness would contribute to well-being. I argue that medicalisation processes can lead to three different moral problems. These problems cannot simply be avoided by imposing specific requirements on preventive practices – they are mainly reason to accept some reluctance to applying the ever-increasing possibilities of preventive medicine. After briefly discussing the three problems, I will come back to the specific case of preconceptional carrier screening for CF.

**Why would medicalisation be undesirable?**

First of all, it is probably inevitable that many forms of prevention, and notably screening programmes, cause people to worry and feel uncertain about the possibility that they will develop a specific disease. However, this inconvenience will often be surmountable, and can be minimised through a careful information process. The worries and uncertainties caused by screening programmes will normally be resolved if a test result is negative - if the result is positive, the worries will probably increase, but in that case the worries are obviously justified.

The first moral problem of medicalisation is not that such feelings are inconvenient, but that if they occur (and are taken away) very often, this might affect a person’s basic confidence in the stability of his or her health. Nowadays, people are given information about the dangers of many activities that used to be common and normal. Numerous activities, substances and habits need to be avoided in order to reduce the risk of a serious disease, and many other activities need to be performed in order to protect or promote health. The effects of preventive care programmes on people’s confidence in their health should not be assessed for each particular programme as such. They accumulate, so they should be evaluated as a whole. For those people who take all offers of preventive care seriously, it may seem as if health is a fragile equilibrium, and as if human beings must constantly anticipate threats against their health. Such a view of health is detrimental to feelings of confidence and security with regard to health and well-being.
A second moral problem of medicalisation as a result of preventive medicine concerns moral responsibility for illness. Preventive medicine gives people the opportunity to reduce risk and to avoid disease. If someone decides not to take the opportunity that is offered, and later on contracts the disease in question, it will be no surprise that people will say: “it’s his own fault”. In the case of preconceptional CF carrier screening: a decision to forgo the screening offer seems to imply that, in the unhappy case that the child is subsequently diagnosed with CF, the parents are at least partly responsible. To some extent, such a judgement is correct. Screening aims to promote autonomy by providing couples with knowledge and reproductive options; responsibility is simply the flipside of their increased autonomy. Though it often makes sense to give people a sense of responsibility so that they can make their own choices and face the consequences, in health care such promotion of responsibility is not always appropriate. Many European health care systems uphold the values of solidarity in which the financial burdens of health care are shared by all, assuming that all citizens are to some extent willing to contribute to health care for the unfortunate who become ill. Solidarity is most strong if it is not only based on compassion for the worse off, but also on a common interest: the knowledge that sooner or later everyone might need health care. If we come to believe that many individuals are partly responsible for the health care they (or their children) need, this could undermine the second pillar of solidarity - a prospect that many would consider undesirable.

A third moral problem of medicalisation concerns the tendency for people to see health as a central value in their lives. Arguably, a certain level of health is important in any account of human well-being, and prudent individuals who aim to live well should not constantly neglect risks to their health. For that matter, it would be equally imprudent for individuals to endorse health as the ultimate value in their lives, if only because one can be certain that sooner or later one’s health will decline. Now, I do not think that medicalisation processes force people to adopt such a ‘healthism’ view of life, but I do argue that the numerous interventions and offers of preventive care and health information make it more and more difficult for individuals to develop a way of life in which the value of health is not over-prominent. Such a problem might not trouble health professions and physicians, but in a pluralistic and democratic society it is undesirable if certain reasonable life-styles are suppressed. For example, I think it is quite reasonable if a person aims to achieve specific goals in his life and only bothers about his health if he becomes ill or if there is an apparent and clear risk. Yet the more one is confronted with offers of screening and preventive care, the more difficult it is to develop and sustain such an attitude.
Often the conception of how to live is not an explicit life-plan that has already been made or deliberately chosen; it is formed, developed and adjusted in situations in which people need to think about their way of life, and consider which things they want to avoid, and which things they want to pursue. People’s view of life will be influenced by the kind of questions they are confronted with. Should I go to church or is my belief in God failing? Do I want to have children or not? Should I care for my immobile parent? Should I be faithful to my spouse? Nowadays such questions are considered to belong to the private realm, and few of these questions are raised and discussed in public institutions. Choices concerning health and risk are notable exceptions. By providing information about opportunities to reduce or avoid the risks of disease, preventive health care institutions encourage people to consider how they should live. But the more a person is urged to consider life in a context of opportunities for health and risks of disease (instead of contexts of religion, politics, parenthood, etc.), the more the view of life that is developing will be ‘biased’ by this theme. This bias may be positive or negative. In both cases, health-choices are a relatively important determinant for the view of life. People either consider health as important, or they attach less importance to health, but even in the latter case, health is an issue that cannot simply be ignored.

**CF carrier screening and medicalisation**

I have argued that medicalisation raises moral problems to the extent that it (1) undermines people’s confidence in their health; (2) stimulates problematic moral views, such as lack of solidarity, and (3) makes it more difficult to develop views of life in which other values than health are most prominent. It would be incorrect to suggest that a single programme of CF carrier screening causes such effects. I have already stated that medicalisation is a problem caused by an accumulation of preventive practices and interventions. This makes it difficult to verify the empirical claims in my argument, which can be considered as a major weakness in the argument. Yet my ultimate claim is relatively vague, and therefore modest: it is not desirable that people consider all choices and events in their life in terms of the potential negative effects on their health. This claim does not yield clear moral requirements for preconceptional CF carrier screening, yet there are some features in such a screening programme that make the concerns of medicalisation especially relevant.

One of the central moral problems of medicalisation is that offers of preventive care affect people’s abilities to develop conceptions of the good life. Such conceptions develop, in particular, through the way people deal with important life events, the choices they make in such situations, and the way in
which they conceive and interpret such choices. It is plausible to assume that choices about reproduction are extremely important in this respect. Thinking about pregnancy and future children implies thinking about how one wants to live, about what a good life means for oneself and one’s children, about one’s capacities to care for a vulnerable human being, and hence about accepting responsibilities in the strongest sense of the word – responsibility as a parent for a child’s well-being. Now, if a couple is offered preconceptional genetic screening, they are urged to consider questions and events like these from the point of view of avoiding disease and promoting health. There is a small chance that their child will develop a very serious disease, and as potential parents they are expected to take that into account. In this way, prospective parents are invited to consider essential questions of life from the point of view of health and disease, and that will affect their moral outlook. Moreover, it is not just that a couple is invited to think about the possibility that their future child might have a disease like CF, preconceptional screening enables prospective parents who appear to be CF carrier to make choices concerning prenatal diagnosis, adoption, or not having any children at all. Hence, they are given the opportunity to reconsider for medical reasons what might have been their most important life decisions and desires. In this way, they will have little opportunity to develop a view of life in which health is not an extremely important value. Obviously these problems will mainly arise if screening is offered pro-actively, and not at the request of the couples themselves. If, on the other hand, a couple takes the initiative to seek medical advice in the context of their reproductive desires, there is little reason to worry about the implications or the fact that this medical advice will affect their reproductive choices. Finally, a routine, pro-active offer of preconceptional screening does not just ‘promote autonomy’ in the sense that parents are given specific options that might help them to avoid specific diseases for their future child. With those options they also acquire some responsibility for the health of their future child, and, while they are free to forgo the preventive options, they cannot avoid this responsibility. Hence, it is not just that offers of screening might affect prospective parents’ conceptions of the good life, it also affects their moral responsibilities in a way that they cannot avoid. The latter phenomenon also raises doubts about the often-held assumption that genetic screening, by enabling prospective parents to make choices, enhances their autonomy.
Conclusion
The offer of preventive medicine, and notably screening programmes, inevitably contributes to medicalisation. Moral concerns about medicalisation cannot easily be solved by imposing specific requirements and conditions for preventive practices; yet they do support an attitude of restraint regarding new preventive measures in ‘new’ areas of life.\(^5\)

CF is a very serious disease, and technological developments that lead to a reduction of suffering due to this condition are therefore to be welcomed. On the other hand, preconceptional carrier screening affects the lives of all couples who are invited, and this is something that cannot be neglected. Given the importance of choices concerning reproduction in the development of moral outlooks, the moral problems of medicalisation arise especially in the context of a pro-active preconceptional screening programme. However, the offer of screening might also be limited to couples who take the initiative to seek medical advice about their choice to have children. In the latter case, the problem of medicalisation will be of less concern.

Reference List

Appendix 4

The problem with medicalisation. Why preconceptional CF carrier screening is better evaluated in different terms.

Wybo Dondorp

Abstract
In the debate about the desirability of universal preconceptional CF carrier screening, it has been argued that introduction of this practice would lead to an unwanted ‘medicalisation’ of decision-making about childbearing. This paper states that the concept of medicalisation is no useful tool for ethical analysis. Medicalisation is a hybrid concept with descriptive, normative and rhetorical uses. Descriptively, it is certainly true that the proposed screening would lead to a further medicalisation of childbearing and pregnancy. But whether that renders it morally problematic is a different question. By not keeping these questions separate, the concept qualifies as an ideal instrument for rhetorical purposes. If taken as a purely evaluative term, medicalisation refers to a range of negative consequences of medical expansion, both for those involved and for society as a whole. This includes unnecessary physical and mental burdens, iatrogenic harm caused by unnecessary interventions, and unnecessary costs. However, classical medical ethical principles are more appropriate tools for addressing these issues, as has already quite extensively been done with regard to the possible introduction of preconceptional CF carrier screening. Even if some aspects, including residual psychosocial effects, deserve further attention, this has led to a cautious green light. Medicalisation does not refer to any real disadvantages not already accounted for in this analysis and will only serve to rhetorically confuse the debate about the pros and cons of this type of screening.

Introduction
In the Dutch debate about the desirability of preconceptional carrier screening for cystic fibrosis (CF) as an offer to all persons of reproductive age, it has been argued that the introduction of this practice would lead to an unwanted ‘medicalisation’ of a couples’ decision-making about childbearing. In a workshop convened by the Department of Community Genetics of the VU University Medical Center in Amsterdam, the Netherlands, some participants said that this ‘medicalisation’ effect was overlooked in the arguments supporting the view that the proposed screening would, under
certain conditions, be morally acceptable. A typical statement was that “after pregnancy has become increasingly medicalised, we should think twice before doing the same to the preconceptional period”. Together with the paper submitted by Verweij, my paper is also a contribution to this debate, and I have written this paper as a response to his.

My argument is that ‘medicalisation’ is a hybrid concept, somewhere between description and evaluation, and that this makes it unfit to serve in an ethical argument. As this does not mean that there cannot be any valid moral concerns behind its use, the question arises as to what these would be and what they might add to the debate about introducing preconceptional screening for CF carrier status. I argue that none of the concerns mentioned by Verweij require a reconsideration of the earlier conclusion that the screening deserves a cautious green light.

‘Medicalisation’: a hybrid concept
The concept of medicalisation has its roots in sociology. The term is used to express the tendency that more and more aspects of human life are understood in terms of health and illness, and in so far, thus belong to the competence of the medical profession. Phenomena that have previously not been seen as related to health are being construed as medical problems that require a medical solution. Examples of this are the medicalisation of deviant behaviour, of educational problems, of sexuality, of pregnancy, of the menopause, of old age, etc.

In a review of the history of the concept since its introduction around the beginning of the seventies, Nye shows that medicalisation was initially conceived of and criticized as the outcome of an unholy alliance of interests between the medical profession and the state. This conflict-model approach has given way to multi-dimensional analyses, in which medicalisation is considered to be fuelled by social notions about health and responsibility, of which the citizens of modern liberal societies are both the addressees and the carriers. Notwithstanding this development, which Nye describes in terms of less ideology and more respect for the facts, the concept has remained a tool of social criticism. Or, as Nye says: “a generally critical outlook on medicalisation still prevails”. The term has a strong connotation of moral disapproval: medicalisation is unwanted, and should be avoided. Even in Nye’s own reassuring conclusion, that we have “consistently overestimated the dangers of medicalisation”, this normative meaning makes itself heard. Whoever uses the term without wanting to convey a message of moral disapproval, should either
explain himself very cautiously, or reckon with his being understood as doing just that.

The claim that a specific area or domain of human life is in the process of being medicalised, can therefore be understood as having both a descriptive and a normative meaning. Descriptively, it says that whereas until recently area X has not been the subject of medical discourse, nor have labels of health and illness been attached to it, this is now increasingly the case. Normatively, it says that this expansion of medical discourse into area X is wrong. But what is the basis of that condemnation? The mere fact that the expansion has been observed cannot be the reason that makes it wrong. There must be other reasons, referring to what we might agree would be wrong-making consequences, or other characteristics of that expansion. Or disagree, of course, which could then lead to debate about whether there are, indeed, grounds for moral condemnation of what happens to area X. But since ‘medicalisation’ describes and condemns at the same time, those reasons are often left implicit. There is usually no pause given in which to consider the weight of the arguments behind the message of condemnation. Instead, the expansion of medical discourse into areas previously untouched by it is presented from the outset as a ‘foreign’ occupation, something everyone agrees is wrong. As a notion of moral condemnation, medicalisation is like ‘violence’ or ‘discrimination’: by referring to ‘facts’ that are wrong by definition, such ‘moral species terms’ serve as arguments that seem to need no further justification. This makes them extremely useful for rhetorical purposes.

The uses of ‘medicalisation’: descriptive, normative, and rhetorical
A nice illustration of the uses of ‘medicalisation’ can be found in a paper by Johanson et al., entitled “Has the medicalisation of childbirth gone too far?” The paper opens with a historical overview, stressing that the medical profession became involved in the area of labour and childbirth in the seventeenth century and that this involvement has intensified ever since. The description offers a good example of the type of development that medicalisation as a purely empirical claim would refer to. But it is only in one of the sub-headings that the term seems to be used in that sense. In the text of their paper, the authors typically refrain from using this term in connection with the historical development they describe. Nor do they argue that, on balance, that specific development should be considered as negative. On the contrary: the availability of adequate obstetric services means that, in case of complications, the lives of mothers and children can now be saved. That, they stress, is just a matter of good health care.
But the authors do speak of medicalisation where, in a more recent twist of things, uncomplicated pregnancies are increasingly subjected to medical interventions, the benefits of which the benefits for mother and child are doubtful at best. Their use of the term in connection with that practice clearly serves to convey a message of moral condemnation. The authors argue that three factors are behind this medicalisation of (British) obstetric practice: lack of teamwork, defensive medicine (‘medico legal pressures’) and inadequate participation of the pregnant women in question in the decision-making process. Their plea for ‘de-medicalisation’ would involve a quality-of-care policy aimed at reducing unnecessary interventions, based on a concept of birth - in the absence of complications - as a ‘normal physiological process’.

An example of the term’s rhetorical use can be found in the title of the paper, which presents us with a question to which the answer can only be ‘yes’. The medicalisation of childbirth has gone too far, yes of course it has, how could it not? Although the idea of medicalisation ‘going too far’ might, indeed, also be taken as implying a normatively neutral understanding of the term, that does not provide a very convincing interpretation of the phrase. As if one could perhaps also expect to be asked whether medicalisation is not going far enough, or just as far as it should go. The same holds for the standard use of the combined terms ‘unnecessary medicalisation’. Since one would have trouble finding instances of the opposite combination, this should not be taken as showing that “in some texts the concept of medicalisation is losing its pejorative meaning”. The adjective is better understood as a rhetorical underscoring of that very meaning, saying that in a particular area of life (sexuality, menopause, old age, the preconceptional period), there is simply no place for medical discourse, or the labels of health and illness. Unnecessary medicalisation, like medicalisation that ‘goes too far’, is close to a tautology.

**Medicalisation and medical ethics**

As an evaluative term, medicalisation refers to a whole range of negative consequences of medical expansion, both for those involved and for society as a whole. This includes unnecessary physical and mental burdens, iatrogenic health damage caused by unnecessary interventions, and unnecessary costs. No one would deny that these effects are highly unwanted. But by what criterion do we decide whether what medicine has to offer in any particular area is, indeed, unnecessary? The authors of the article on childbirth answer that question by referring to standards of ‘evidence-based practice’ and the requirement that obstetric care should focus on the real needs of the women involved. That seems to be a correct approach, also with regard to prevention and screening. In the
normative framework that is widely used to evaluate screening programmes, a central criterion is that for all concerned the benefits must clearly outweigh the harms. Since only a relatively small number of participants will test positive, and then be able to profit from any benefits of timely detection, the evaluation of the harms/benefit ratio of such programmes is often a very complex affair. But for addressing the relevant questions, classical medical ethical principles are more appropriate tools than the vague and ambiguous concept of medicalisation. In contrast to those principles, medicalisation does not help to spell out any concrete moral concerns. It is significant that in the summary of the Johanson et al. paper the term is not even mentioned. Their analysis of relevant issues (iatrogenic morbidity, improper informed consent, etc.) can do perfectly well without it.

Verweij comes to a similar conclusion where he writes that “obviously screening practices must be safe and effective, but such requirements are obscured rather than clarified if framed in terms of medicalisation”. Still, he thinks that the concept of medicalisation has something to add to the ethical analysis of preventive medicine and screening practices. That is to say: medicalisation as a descriptive concept, and not as an evaluative concept. By referring to “the phenomenon that healthy persons tend to adjust their life and life-style according to medical information, advice and procedures”, it would serve to highlight three moral problems that, as he claims, are often overlooked. This phenomenon of adjusting to medical discourse may (1) undermine peoples’ confidence in their own health, (2) undermine our shared beliefs regarding solidarity and responsibility for health, and (3) make it more difficult for people to develop views of life in which other values than health are most prominent.

As a purely empirical concept, medicalisation may refer to morally relevant facts, and thus be useful for ethical analysis. But given the hybrid nature of the term, the difficulty is how to keep description and evaluation separate. Verweij claims that his definition (healthy persons adjusting their lives to medical discourse) is relatively free of moral assumptions. I am not convinced that it is. The moral message that is implied is that the normal lives of healthy persons need no adjusting to medical information, advice and procedures; being healthy, they should not let their lives be governed by concerns about health and illness. Since that same message is behind each of Verweij’s moral problems, there is a smell of circularity here. It seems that what he presents as ‘the phenomenon’ of medicalisation is to be understood as a statement of fears rather than one of facts. There is nothing wrong with stating one’s fears, but
by backing them up with an apparently factual account of ‘the phenomenon of medicalisation’, Verweij only demonstrates the rhetorical utility of the term.

**Fears, not facts**

What about those fears? Taking Verweij’s three moral problems in reversed order, I find the third the least worrying. It is certainly true that prevention and screening practices convey the message that health is a very central value in human life. But does that necessarily mean that health is propagated as the single most important value, at the exclusion of world views implying a different hierarchy of values? Health is not an end in itself, but a condition for the realisation of whatever other ends people may want to pursue in their lives. Since, in that sense, health belongs to the ‘conditions of autonomy’, it is difficult to see how its promotion would be at odds with the principle of respect for personal autonomy.

Verweij’s second concern is that providing people with opportunities to reduce risk and avoid disease may lead to holding them responsible in a way that might eventually undermine societal solidarity. These are large steps. It cannot be denied that creating more options for choice also gives more scope for calling people to account for the consequences of their free and informed decisions. However, as Verweij acknowledges, in most cases people can at best be held partially responsible for their health, but given the contribution of genetic and environmental factors, it will generally not be easy to determine to what extent. On the basis of our shared beliefs about social justice, this is one good reason for not giving personal responsibility for health a central role in health benefit policies. Although it seems reasonable to expect that the proliferation of preventive opportunities may lead to further discussion about the precise implications of those beliefs, there is no reason to suppose that this debate can only have the bleak outcome Verweij suggests.

But what about forms of screening, such as prenatal screening for Down’s syndrome (DS) or CF carrier screening, where the attribution of responsibility would seem to be a fairly straightforward matter? Isn’t it quite reasonable to expect that, as a result of such programmes becoming (more) widespread, those who decline the opportunity of screening and then have a child with DS or CF will be left without much help from society when it comes to carrying the financial burdens resulting from their choice? Here again, I don’t think that is the only conceivable, or even the most reasonable outcome of any future debate on this issue. Precisely, if the aim of this type of screening is defined as providing prospective parents with meaningful opportunities for reproductive choice, rather than reducing the birth prevalence of the disorder, it is clear
that the practice could not be upheld if financial implications limit the scope for genuine choice. In other words, to the extent that, as a society, we find it important that prospective parents can make this type of decision, we should refrain from holding them financially responsible. A further argument is, of course, that doing so would unjustly deprive the children in question of the care they need.

Finally, Verweij says that prevention and screening practices may have harmful psychological effects, leading people to worry or be less confident about their health. This is an area which has been the subject of some research, also with regard to (preconceptional) CF carrier screening.

Among the findings summarised in a recent review is that where an initial positive result can lead to a surge in the level of anxiety, but that this drops again after a negative final test outcome. But residual psychological effects (anxiety, diminished self-image) have sometimes been found in some participants, as was the case in the Dutch preconceptional CF carrier screening pilot study. Whereas this is rightly seen as something that deserves to receive further attention, also in order to find out how such effects can be avoided, that is not Verweij’s point. As he says, his concern is not about the effects of any particular prevention or screening programme, but about what he supposes could be the accumulative effects of all such initiatives taken together. If people are constantly exposed to information about risk avoidance and health promotion, they might end up losing their basic confidence in their health. That sounds like a most serious concern, but it is also quite speculative. There is no empirical basis for the claim that this general undermining of people’s trust in the stability of their health is, indeed, what we have to expect as a result of the further proliferation of prevention and screening. That makes it hard to see how this ‘problem’ could be a reason for a policy of restraint regarding screening programmes with a clearly positive ratio of benefits and harms for those concerned, as seems to be the case with preconceptional CF carrier screening.

Conclusion

In the descriptive sense of the term, it is undoubtedly true that introducing preconceptional CF carrier screening in the Netherlands would lead to a further medicalisation of childbearing and pregnancy. But whether that renders it morally problematic is a separate question. Does the proposed screening imply that planning a pregnancy becomes unnecessarily burdened with medical concerns? That is certainly an important question, but not one that has been overlooked in the ethical analysis so far. In fact, it has been dealt with quite
extensively in the studies that have assessed the desirability and feasibility of introducing preconceptional CF screening in the Netherlands.\textsuperscript{14,15} It was concluded that, even though some aspects would require further attention, the screening does, in principle, fulfil the requirements of the normative framework that is internationally applied to the assessment of such programmes.\textsuperscript{6} It targets a severe, well-defined and incurable disease, a screening test is available, and if both partners test positive meaningful reproductive options are available as a consequence of timely detection. The pilot study showed that the target group can, indeed, be reached. Moreover, within that group, the researchers found a high degree of acceptance and a high level of satisfaction.

It cannot be maintained that the ethical analysis carried out in the context of this research has failed to take into account one important consideration, namely ‘medicalisation’, nor that including it would have led to changing the cautiously positive conclusion into a negative one. Insofar as the charge of medicalisation refers to any real disadvantages the screening may have for those involved, these have been accounted for in the analysis. The rest are fears, not facts.

Reference List


