# IMPLEMENTING CARRIER SCREENING IN A CHANGING LANDSCAPE

## Perspectives of public and professional stakeholders

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## SUMMARY

In the Netherlands, carrier screening for recessively inherited disorders, such as cystic fibrosis and sickle cell disease, is not current practice. Carrier testing is only available to those with an *a priori* increased risk due to a positive family history, or through some local initiatives where ancestry-based carrier screening is offered to specific high-risk populations. Carrier screening aims to identify couples facing an increased risk of having an affected child in order to facilitate informed reproductive choices. Screening is preferably done before pregnancy (preconception) as there is less of a time constraint, and it provides couples with a maximum number of reproductive options.

In recent years, technological developments such as Next Generation Sequencing (NGS) have altered the carrier screening landscape. Carrier screening panels have expanded and allow simultaneously screening for multiple disorders, genes or sequence variants. Moreover, the availability of these panels encourages a universal screening offer, i.e. regardless of ancestry. Alongside these developments, new ethical, societal and psychological issues arise. To ensure the successful and responsible implementation of carrier screening, it is necessary to fully understand the perspectives of all key stakeholder groups involved.

The studies in this thesis aimed to address the experiences with ancestry-based carrier screening for four specific Dutch high-risk populations. Furthermore, population-specific factors as well as general enabling and constraining ones for the implementation of carrier screening were identified. The results will provide lessons for the further implementation of carrier screening in a changing landscape in the Netherlands.

### PART I. EVALUATION OF ANCESTRY-BASED CARRIER SCREENING IN DUTCH HIGH-RISK GROUPS

In part one, four Dutch initiatives of ancestry-based carrier screening are studied: 1) carrier screening for sickle cell disease and thalassaemia (haemoglobinopathies); 2) carrier screening for cystic fibrosis; 3) carrier screening for disorders more common in a Dutch founder population; and 4) carrier screening for disorders more common in the Ashkenazi Jewish community.

**Chapter 2** explores how pregnant women at risk of being a haemoglobinopathy (HbP) carrier perceive an offer of HbP carrier screening by their midwife in the first trimester of their pregnancy. Testing during pregnancy reduces the number of reproductive options, but may inform the health professional about a coexistent anaemia due to the HbP carrier status. Women's experiences were studied through semi-structured interviews (n=26) preceded by the booking consultation where screening was offered alongside prenatal screening for Down syndrome. Generally, women perceived the HbP carrier screening offer as positive, and most women accepted screening (n=19). Seven women

declined testing; two of them already knew their carrier status. The possibility to obtain knowledge about their own carrier status and the health of their unborn child, and the ease of the procedure, were important reasons for women to accept screening. Reasons to decline included: the absence of a positive family history for HbP, having the feeling of not being a carrier, and a fear of needles. For many women decision-making seemed to be a multistep process as they did not give follow-up testing in case of a possible screen-positive result (e.g. sequential testing of their partner and prenatal diagnosis) much consideration before deciding on accepting or declining the screening test. Though some women expressed a need for more information, others experienced an information overload as the information came quite unexpectedly during the booking consultation. Women preferred receiving the information as well as the offer at different points in time, for example before the intake by means of a leaflet, or preconceptionally.

**Chapter 3** describes a six-year process evaluation of a direct-to-consumer (DTC) carrier screening offer for cystic fibrosis (CF) aimed at couples without CF family history through the website of a Dutch university hospital. It was shown that it is feasible to develop and offer screening by means of at-home buccal sampling kits. However, one-fifth of the initial analyses failed because insufficient DNA was recovered from the samples, or samples had been swapped. Moreover, higher uptake rates were expected. From December 2010 until December 2016, only 44 carrier tests were requested, partly by couples *with* an a priori increased risk due to a positive family history for CF, though they did not belong to the intended target group (couples *without* a positive family history). The lack of familiarity with CF and carrier screening might have impeded the implementation of the DTC CF carrier screening offer, besides lack of awareness of the offer itself. Users were generally positive about the offer, and requested testing because of the accessibility and the ease of the test, the feeling of anonymity, but also because of perceived shortcomings of regular healthcare (e.g. long waiting lists and excessive costs of screening). The low uptake, and the fact that the offer is not primarily used by the intended target group raise questions on its future existence in this particular format.

**Chapter 4** presents the results of a mixed-methods study (questionnaires and semi-structured interviews) which assessed the experiences with a preconception carrier screening outpatient clinic for four disorders in a Dutch founder population. Questionnaires were completed by 182 attendees before and after testing, and by 137 non-attendees. Semi-structured interviews were held with seven identified carrier couples. This study demonstrated that familiarity with genetic disorders was high. Attendees were mainly informed about the availability of screening by their friends/colleagues (49%), and by family members (44%). Non-attendees reported not being aware of the offer as the main reason for non-attendance. Attendees were very satisfied about the offer, did not regret testing, and would recommend it to others. Only 18% of the attendees accepted the offer of an additional standard preconception care consultation on e.g. health promotion and general risk factors. Knowledge after counselling increased significantly but a proportion (9%) of the attendees still wrongly mentioned being at

an increased risk of having an affected child if both partners are carriers of different disorders. Almost all attendees recalled their results correctly, but two couples reported being a carrier of another disorder than was reported to them. All carrier couples made reproductive decisions based on their screening results (e.g. prenatal diagnosis and selective termination of pregnancy, preimplantation genetic diagnosis, and refraining from having more children). With expanded carrier screening, adequately informing couples is of major importance, and counselling is preferred by the vast majority (94%) of the attendees. These findings can be helpful for the implementation of expanded carrier screening in other communities and settings.

In **Chapter 5,** the results of an online questionnaire completed by 145 individuals from the Dutch Jewish community are presented. The Ashkenazi Jewish (AJ) community is familiar with ancestry-based carrier screening for single disorders since the 1970s. As it is now feasible to screen for many more diseases, the question arose as to whether the AJ population prefers a limited ancestry-based offer or an offer that goes beyond the disorders that are frequent in their own population, and that is offered regardless of ancestry (i.e. expanded universal carrier screening (EUCS)). The questionnaire results showed that more than half of the respondents (65%) were aware of ancestry-based screening, and were generally positive about it. About half of the respondents (53.8%) preferred an EUCS offer because "everyone has a right to be tested", "fear of stigmatisation when offering ancestry-based screening", and "difficulties with identifying risk due to mixed backgrounds". "Preventing high healthcare costs" was the most important reason against EUCS among those in favour of ancestry-based screening. As costs of EUCS are most likely to drop in the near future, it is expected that these panels will receive more support in the future.

## PART II. IMPLEMENTATION OF CARRIER SCREENING IN A CHANGING LANDSCAPE

The studies in part II of this thesis reflect on the transition from ancestry-based carrier screening towards EUCS. The focus is on the enabling and constraining factors for the successful and responsible implementation of carrier screening, and the ethical issues related to the implementation of an expanded universal offer.

The studies in **Chapter 6** aimed to identify critical factors involved in the successful implementation of carrier screening from a user perspective, by learning from initiatives already implemented. A literature review and two case studies, studying the experiences with carrier screening in two high-risk communities (a Dutch founder population and the Ashkenazi Jewish community), including a survey among community members, enabled the identification of factors associated with successful implementation. The results showed that familiarity with (specific) genetic disorders and the availability of carrier screening, high perceived benefits of screening (e.g. screening avoids much suffering), acceptance of reproductive options, perceived risk of being a carrier, and low perceived social barriers (e.g. stigmatisation) were key factors in implementing carrier screening.

Furthermore, community support tended to play a role in implementation. In contrast to the Jewish community, the initial demand for screening in the Dutch founder population did not entirely come from the community itself. However, the high social cohesion of the community facilitated the implementation process after its introduction by healthcare professionals. To ensure successful implementation of EUCS, effort should be made to increase knowledge and create awareness about genetic disorders, facilitate public debate about the pros and cons of screening, and address personal benefits of screening in a non-directive way.

**Chapter 7** discusses the general and population-specific barriers and needs reflected by professional stakeholders regarding the implementation of carrier screening in the changing landscape. Semi-structured interviews were conducted with seventeen Dutch key professional stakeholders. The perceived barriers and needs were categorised into three levels (culture, structure and practice) by using a theoretical framework: *the constellation approach*. According to the stakeholders, important barriers on a cultural level included undecidedness about the desirability of carrier screening, and a lack of priority of screening in regular healthcare. A need for organisational structures in healthcare for embedding carrier screening was mentioned as an important barrier on a structural level. Although offering screening preconceptionally was preferred, stakeholders also indicated that screening could be offered prenatally, for example embedded in existing routinely performed blood tests during pregnancy, or between pregnancies (interconception care). A need for guidelines, financial structures, and practical tools for overcoming challenges during counselling, as well as a need for educating both the public and professionals were other barriers on a structural level. Finally, practical barriers were a lack of demand for screening by the public, and uncertainties or even disagreement about responsibilities. To address and overcome these barriers, stakeholders suggested that change agents should be formally acknowledged to strategically plan broadening of current initiatives and attune different stakeholders.

**Chapter 8** presents an ethical analysis regarding the twofold expansion of carrier screening programmes (expanded universal carrier screening, EUCS). It aims to provide a balanced picture of the potential advantages and disadvantages of EUCS by reflecting on the seventeen semi-structured interviews with key Dutch professional stakeholders regarding their perspectives on carrier screening, including a possible EUCS scenario, as described in Chapter 7. Though stakeholders acknowledged the potential benefits of EUCS, they also expressed a number of moral concerns. They questioned whether EUCS responds to an urgent problem or a population need, and wondered whether it was possible to provide couples with both understandable and sufficient information about EUCS. Other concerns were: how will societal views on “reproductive disability” change as a result of EUCS, and will EUCS lead to a lower level of care for high-risk populations? A final concern was whether EUCS will reinforce disability-based stigmatisation. Although EUCS potentially solves issues stemming from ancestry-based screening, it is expected that it will also raise moral concerns of its own.

## CONCLUDING REMARKS

Positive attitudes among (potential) key stakeholders towards ancestry-based screening have been shown, and the four local initiatives provided lessons for further implementation. However, compared to ancestry-based screening, critical factors for a successful and responsible implementation from a user perspective are less evident in the context of expanded universal carrier screening. Additionally, professional stakeholders identified several barriers that have to be overcome and needs that should be addressed when discussing further implementation of carrier screening. While EUCS potentially solves moral challenges emerging from ancestry-based screening (e.g. increase equity as it allows testing of all individuals regardless of ancestry, and potentially reduces the risk of stigmatisation), new challenges will also arise. This calls for more research and efforts to further develop and responsibly disseminate current screening initiatives, and a debate among all key stakeholders about the desirability and feasibility of carrier screening. Attention should furthermore be paid to how screening is preferably offered (i.e. in what settings, and the timing of the offer), how people are informed best about screening (e.g. what information strategies are acceptable) and how an offer is facilitated (e.g. development of guidelines). As multiple factors are involved in a successful and responsible implementation, technological advances alone should never be a reason to implement carrier screening. Facilitating informed reproductive decision-making should always be the primary aim.