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## Implementing carrier screening in a changing landscape

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General introduction and  
outline of the thesis

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In the Netherlands, carrier screening for recessive disorders is not current practice. Testing is only available to those with an a priori increased risk due to a positive family history, or via some local initiatives where ancestry-based carrier screening is offered to specific high-risk populations. In recent years, technological developments have altered the carrier screening landscape by making expanded universal carrier screening (EUCS) available. At the same time, new ethical, legal, societal and psychological issues have emerged as a result. This thesis addresses the experiences with ancestry-based carrier screening for four specific high-risk populations, and identifies population-specific factors as well as general enabling and constraining ones for its implementation. The results will provide lessons for the further implementation of carrier screening in a changing landscape in the Netherlands.

## **CARRIER SCREENING**

Most children with an autosomal recessive (AR) disorder, for example cystic fibrosis (CF), sickle cell disease or spinal muscular atrophy, are born in families with no family history for that specific disorder. Parents are then confronted for the first time with the fact that they are both carriers of the same disorder, and they often ask themselves whether they could have known this beforehand. Theoretically, this would have been possible, but as carrier screening is not offered in regular healthcare in many places in the world, the practical answer would be “no” [1].

It is estimated that there are more than 1300 recessively inherited disorders, both autosomal and X-linked disorders, with symptoms ranging from very mild to severe (early onset and lethal in childhood) [2]. The birth prevalence of recessive disorders is expected to be 30 per 10,000, implying that 1 to 2% of all couples in the general population will be at risk of having affected offspring [2, 3]. Carrier screening for AR disorders is defined here as the identification of carrier status of that particular disorder in healthy individuals with no a priori increased risk (i.e. without a positive family history) [4]. It allows couples to find out whether both partners are carriers of the same disorder, and thus face a 1 in 4 risk of having an affected child with that specific disorder in each pregnancy. Although the prevention of an affected child may be an explicit and well-accepted purpose of screening in some communities with a high disease burden [5, 6], the primary aim of carrier screening is to provide carrier couples with autonomous reproductive choice [2]. Screening is preferably done before pregnancy (preconception) as there is less of a time constraint, and it provides couples with the maximum number of reproductive options [5]. Available options include: refraining from having their own biological children, accepting the risk, prenatal diagnosis (PND) and selective termination of the pregnancy, preimplantation genetic diagnosis (PGD), use of donor gametes, adoption or, in some cultures, choosing a different partner. Although the preconception phase is considered to be the most favourable timing to offer carrier

screening, it is also found to be less practical and feasible to execute. Consequently, if offered at all, carrier screening is often offered prenatally when pregnant women come to the attention of healthcare professionals [2].

## **ANCESTRY-BASED CARRIER SCREENING**

In previous decades, carrier screening specifically addressed high-risk groups that have higher frequencies of severe AR disorders. Screening panels thus included the specific mutations corresponding with the disorders that are relatively common in those populations [7]. This type of screening has often been referred to as ethnicity-based or ancestry-based carrier screening. Well-known examples are carrier screening for single disorders such as  $\beta$ -thalassaemia, a severe form of haemoglobinopathy in, for example, Southern European and Middle Eastern countries [6, 8], and screening for CF in the United States (US) [9], parts of Italy [10], and Australia [11]. Another example concerns the Ashkenazi Jewish population, which is at increased risk of several severe AR disorders owing to genetic drift and a founder effect [12]. Over the years, carrier screening in this community has expanded from screening for one single disorder, Tay-Sachs disease (TSD), in the 1970s, to screening for multiple “Ashkenazi Jewish” disorders more common in this specific population [13]. As a result of common ancestral origin, certain severe AR disorder also occur more frequently in other populations with founder mutations than in the general population. Examples of these communities and their screening programmes, mainly in Israel, have been described in the literature [14].

Four specific examples of ancestry-based carrier screening that have also been offered in and around Amsterdam in the last decade are described in more detail below.

### *Carrier screening for haemoglobinopathies*

Haemoglobinopathies (HbPs) such as sickle cell disease (SCD) and  $\alpha$ - and  $\beta$ -thalassaemia are hereditary blood disorders characterised by severe anaemia, and variable but often high morbidity and shortened lifespan [15]. As a result of heterozygote advantage against malaria, HbPs are the most common monogenic disorders worldwide [16]. Though mostly occurring in Africa, the Caribbean, Asia, the Middle East, and the Mediterranean area, HbPs are becoming increasingly common in other parts of the world as well due to global population movements [8, 17]. In contrast to most genetic disorders, carriers of HbPs can be identified by means of haematological and biochemical tests too, rather than by DNA analysis alone [18]. As described by Traeger-Synodinos *et al.* [18], these relatively cheap methods should thus preferably be used for the identification of carriers. DNA analysis, which is currently far more expensive, should only be employed in complex haemoglobinopathy cases or when the haematological and/or biochemical methods are not able to distinguish between (rare) haemoglobin variants.

Carrier screening for HbPs has been available for many years, and is carried out in several countries in different settings [6]. Since the late 1970s,  $\beta$ -thalassaemia carrier screening programmes accompanied by intensive education campaigns have been introduced in Southern European countries including Italy, Greece and Cyprus [8]. With an estimated carrier frequency of 1 in 7, Cyprus has been described as having one of the highest carrier frequencies in the world, and screening is primarily aimed at reducing the frequency of thalassaemia [6]. After the introduction of carrier screening programmes, its birth prevalence indeed reduced substantially, and in some areas by more than 90% [6, 19]. Furthermore, Iran has a mandatory premarital carrier screening programme for  $\beta$ -thalassaemia [20]. Here, prospective couples are referred by marriage registrars for premarital screening. When a couple is identified as an at-risk couple, they will attend as many counselling sessions as are needed to make an informed decision. Those who marry after counselling are referred for follow-up until they have completed their family [20]. In the United Kingdom (UK), an antenatal sickle cell and thalassaemia carrier screening programme linked to the new-born screening was launched in 2004 [21]. For the delivery of the programme, the UK has been divided into “high prevalence” and “low prevalence” areas. All pregnant women living in the high prevalence areas are offered laboratory screening for both sickle cell and thalassaemia (full blood count (FBC) and High Performance Liquid Chromatography). In low prevalence areas, all pregnant women are offered screening for thalassaemia using FBC. Further laboratory testing is carried out among women with an abnormal FBC, those with high-risk family origin, and those who request screening [22]. A family origin questionnaire is used to determine which women to test for haemoglobin variants, and to interpret laboratory results [22].

Although these are existing examples of systematic carrier screening programmes, screening for HbPs is mostly offered on an ad hoc basis [23], despite the advice of the World Health Organization urging member states to pay attention to HbPs, and to design, implement and reinforce HbP screening programmes [24, 25]. In regular Dutch healthcare, people at increased risk can ask their general practitioner for an HbP test, and a few midwifery practices offer HbP screening during pregnancy.

#### *Carrier screening for cystic fibrosis*

Cystic fibrosis (CF) is the most common AR disorder among Caucasians, with an estimated birth prevalence of 1 in 2500-3600 [26]. Though there are milder forms of the disorder, most CF patients suffer from progressive respiratory and gastrointestinal problems, including persistent respiratory infections, liver disease and pancreatic dysfunction [4, 27]. Most affected children (>80%) are born in families where no children with CF were born before and thus without an a priori increased risk for CF [4, 26]. These children are either diagnosed during pregnancy or in infancy as a result of the development of symptoms or, nowadays more common, shortly after birth through new-born screening programmes [4].

Following the discovery of the *CFTR* gene responsible for CF in the late 1980s [28], several studies were done to explore the feasibility of population-based carrier screening [29]. Years after the discovery of the *CFTR* gene, in 2001, both the American College of Obstetricians and Gynaecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) recommended that CF carrier screening should be offered to non-Jewish Caucasians and Ashkenazi Jews, and should also be made available to other ethnic groups [30]. Furthermore, it was stated in 2011 that CF carrier screening should be offered universally (regardless of ancestry) as it had become increasingly difficult to assign a single ethnicity to individuals [9]. In 2017, the ACOG confirmed its 2011 statement by indicating that “*cystic fibrosis screening should be offered to all women who are considering pregnancy or are currently pregnant*” [31]. In contrast to the US statements, due to insufficient evidence from randomised controlled trials, the Society of Obstetricians and Gynaecologists of Canada does not recommend the routine screening of all pregnant women, the current grading of evidence being III D [32]. They therefore argued that CF screening should only be offered to those women who are at increased risk of having an affected child due, for example, to ethnic background or personal or family history [32]. A higher grade of evidence could in theory be generated in randomised controlled trials, which until recently have not been done for carrier screening programmes [33, 34]. The European Society of Cystic Fibrosis does not take a position in recommending whether or not to offer CF carrier screening and to whom, but provides a framework for the principles of screening, stating the importance of voluntary screening and sufficient pre- and post-test information [4].

Despite the diversity in international recommendations, CF carrier screening programmes have been established in a number of countries. For example, following the ACGM/ACOG statements, CF carrier screening was introduced into routine care in the US in 2001. In Italy and Australia, CF carrier screening is offered regionally [10, 11], and in Israel, population screening for CF is offered to all citizens [35]. In the Netherlands, the feasibility and desirability of CF carrier screening was studied in pilot projects [36, 37], and since 2010 screening has been available for people without a family history of CF via a university hospital website.

#### *Carrier screening in the Ashkenazi Jewish population*

As explained above, compared to other populations, the Ashkenazi Jewish (AJ) population is at increased risk for several AR disorders that are very rare among the general population [38]. Disorders sometimes referred to as “Jewish genetic disorders” range in birth prevalence from 1 in 900 to 1 in 40,000 in this community [39], according to literature. These numbers have, however, been questioned [40]. It has been argued that owing to the willingness of this community to participate in screening and research, researchers were able to identify many disease-related genes which did not necessarily mean that this community was at higher risk [40]. Though these disorders are generally rare, it is estimated that 1 in 5 Ashkenazi Jews is a carrier of at least one of these disorders (e.g. TSD, familial dysautonomia, and Canavan disease) [38, 39, 41].

Carrier screening was first implemented for TSD, a neurodegenerative disorder that presents in the first year of life and is lethal in early childhood [41]. TSD is caused by a deficient activity of the lysosomal isoenzyme  $\beta$ -hexosaminidase A (HEX A), and the measurement of its levels in serum or leukocytes can be used to identify carrier status [12, 42]. Shortly after this discovery in the late 1960s, screening was introduced from within the community itself [43, 44].

In the ultra-orthodox Jewish community, carrier screening is also performed via a premarital confidential carrier matching programme (Dor Yeshorim) [45]. Screening is performed worldwide without disclosure of individual test results; partners of a couple are therefore only told whether they are compatible or not. Additionally, screening is offered to high school students in, for example, Australia [46].

As a result of screening in the AJ community, the TSD birth prevalence decreased by more than 90% [41], and the vast majority of children born with TSD nowadays have non-Jewish parents [39]. Over the years, testing for disorders that are relatively more common in the AJ population has become more readily available, and carrier screening panels have expanded and included a wider range of disorders [13]. Following these developments, recommendations for testing and inclusion of certain disorders have also changed [41]. Practice guidelines from the ACOG and the ACMG now recommend that AJ individuals should be offered screening for four and nine diseases respectively [39, 42]. However, commercial carrier screening panels have expanded beyond these recommendations, and nineteen disorders are commonly included [47, 48]. The disorders included in these larger AJ carrier screening panels differ in their severity and treatability, resulting in discrepancies in addressing genetic screening criteria.

In the Netherlands, there are approximately 37,000–53,000 Jews, 90–95% of whom are of AJ descent [49]. Although carrier screening for AJ couples is available in the university hospitals in Amsterdam, very few couples actually request testing.

#### *Carrier screening in founder populations*

In several founder populations, certain severe AR disorders that are generally very rare are much more frequent due to the presence of specific founder mutations based on common ancestral origin. As described by Rosner *et al.* [14], carrier screening is widespread in Israel – an ethnically, religiously and culturally diverse country. Owing to this diversity, many groups live in closed “genetically isolated” communities, all with their own preserved genetic structures [14]. Examples are Muslim Arab, Druze and Bedouin populations, most of whom live in small towns and villages that have been settled by a small number of founders [14, 50]. These populations are characterized by close family relationships and, as described by Zlotogora [51], even though the major religions discourage consanguinity, intrafamilial marriages are highly prevalent in the region. In their study, Basel-Vanagaite *et al.* [52] describe carrier screening in a Muslim Israeli Arab village where screening is performed for non-syndromic mental retardation. They found a carrier frequency of about 1 in 11, which could partly be explained by



the founder effect due to the high prevalence of consanguinity in the village [52]. The high frequency of specific mutations in these villages make the establishment of carrier screening programmes possible, and screening is often well-known and well-accepted [14, 50-52]. In the Amsterdam region, carrier screening for a specific founder population is available. Screening was first developed for a severe neurodegenerative disorder of childhood, and included four lethal childhood disorders in 2015 [53].

### **Attitudes, preferences and experiences regarding carrier screening**

The attitudes, preferences and experiences among both the public and professionals regarding ancestry-based carrier screening have been well-studied and described in the literature.

#### *Public perspectives*

Research on carrier screening for HbPs, CF, the AJ community and several founder populations has shown positive attitudes among the general public [29, 54], and also among patients, parents of patients, and their relatives [46, 55, 56]. More specifically, positive attitudes among individuals at risk for being an HbP carrier towards different forms of carrier screening – premarital, preconceptional and prenatal – have been shown [56-58]. However, as described by Ahmed *et al.* [56], parents of affected patients are more positive than the general public, and are more likely to believe that it is important to know whether partners are thalassaemia carriers than relatives or lay adults. This might indicate that familiarity with genetic disorders plays a pivotal role in perceptions regarding reproductive genetic testing [59, 60]. Positive attitudes among the general population regarding carrier screening for CF have also been described. A systematic review by Ioannou *et al.* [29] showed that the vast majority of the public, 60-100%, felt that carrier screening for CF should be made available. A routine offer of CF carrier screening is supported by 80-96% of the public. In the AJ community, positive attitudes towards screening of adults [45, 61], but also of minors via high school carrier screening programmes, [46] have been shown since screening came available, and have remained positive when carrier screening panels have expanded to screen for multiple disorders simultaneously [13].

Besides the general positive attitudes, some concerns have been raised. For example, the impact of screening on psychological well-being [62, 63], perceptions of health [64], and the negative attitudes towards being identified as a carrier, and possibly be stigmatised because of it [56]. Additionally, although a study among CF patients and parents showed that more than 80% of all study participants were in favour of preconception carrier screening for CF, some were also concerned about potential negative consequences of a population-wide offer of CF screening [55]. This fear of potential negative consequences, for example stigmatisation, is an important barrier in the implementation of carrier screening programmes. In the early years (1970s) of HbP carrier screening in the US, many African-Americans were stigmatised because of their carrier status. For example, they were denied insurances, and had worse employment

opportunities than non-carriers [65, 66]. This labelling process was a result of poor knowledge and a lack of understanding of the complexities in offering carrier screening on a large scale [66]. Over the years, much has been learned from these experiences, and efforts have been made to ameliorate the stigmatising effects of carrier screening [65]. The improvement of community education, information and counselling has been suggested as one way to tackle the issue of stigmatisation [2]. Another solution has been demonstrated by the Dor Yeshorim programme for the orthodox AJ community. In order to prevent the stigmatisation of carriers and their families within this community, carrier screening results are not individually disclosed [67]. However, it is questionable whether this is a universal solution to diminish stigmatisation, as research indicates that individuals outside this population prefer the disclosure of their individual test results [68].

### *Professional perspectives*

Comparable to the public, professionals generally show positive attitudes towards carrier screening for individual disorders such as CF and HbPs. However, they also express concerns and challenges. In their review, Janssens *et al.* [69] describe major concerns reported in the literature. First of all, it has been discussed that, as there is already limited time for consultations, the provision of, for example, CF carrier screening is perceived as an extra burden among general practitioners and obstetricians [69]. The urgent need to educate professionals also is clear from previous studies. The literature shows that professionals struggle not only with the understanding of the epidemiology, the interpretation of positive screening tests, and a lack of familiarity with specific disorders, but also with genetics in general [70-72]. Another example of challenges described are professionals being unaware of existing guidelines [72]. As professionals are key to the success of carrier screening, it is vital that these barriers are overcome.

### **Current situation in the Netherlands**

Over the past fifteen years, four PhD theses on the topic of carrier screening for CF and HbPs and their implementation have been published in the Netherlands [36, 37, 73, 74], including pilot studies offering screening. These studies overall conclude that there are positive attitudes towards carrier screening among both the target group (i.e. couples planning a pregnancy) and professionals. Although it has been demonstrated that the target group is often difficult to reach, potential screening participants are generally positive about the offer [75]. It was concluded from these studies that there are no major moral objections, and fear of discrimination and stigmatisation does not seem to play a major role. However, correctly interpreting carrier test results remains a challenge.

Despite the positive findings of the previous studies, in the Netherlands, carrier screening is only available in regular healthcare for people with an a priori increased risk due to a positive family history. In 2007, the Health Council of the Netherlands recommended studying the feasibility and effectiveness of preconception carrier

screening for CF and HbPs in conjunction with other aspects of preconception care in a large-scale pilot study [76]. However, to date, this pilot study has not yet been realised. Although the minister of Health, Welfare and Sports of the Netherlands emphasised in 2014 the need for proper counselling and sufficient information, doubts were expressed about offering carrier screening structurally [77]. Fear of medicalisation of the pregnancy was one of the comments raised. Despite the absence of a structural offer of carrier screening, several local initiatives did succeed in implementing carrier screening within healthcare in the Netherlands.

CF carrier screening has been offered by the Clinical Genetics Department of VU University Medical Center through their website ([www.vumc.nl/CFtest](http://www.vumc.nl/CFtest)) since 2010. This test is aimed at couples planning a pregnancy without a positive family history for CF, and is directly offered to consumers [78]. Furthermore, there are a number of communities in the Netherlands in which certain AR disorders and endogamy are more prevalent [79]. In one of these genetically isolated communities, carrier screening for a number of AR disorders has been offered via a preconception outpatient clinic since 2012 [53]. Examples of disorders more common in this community than in the general population, and for which screening is available, are: pontocerebellar hypoplasia type 2 (PCH2), foetal akinesia deformation sequence (FADS), rhizomelic chondrodysplasia punctate type 1 (RCDP1), and osteogenesis imperfecta (OI) type IIB/III. Affected children suffer from significant morbidity, and have a severely reduced lifespan [53]. A first-year evaluation of the clinic showed that 1 in 3 of all individuals tested were identified as being carriers of at least one disorder [53]. Additionally, carrier screening for the AJ community in the Netherlands is available via at least two university hospitals, and is often reimbursed by the health insurance. Furthermore, in 2015, a carrier screening panel for nine disorders (plus a tenth optional disorder) targeting this community has been developed. Screening is offered for TSD, familial dysautonomia, Canavan disease, Bloom syndrome, Fanconi Anaemia group C, Glycogen Storage disease type 1 a, Mucopolysaccharidosis type IV, Niemann-Pick type A, CF and Gaucher (optional) [80]. Although Gaucher is the most common disorder among Ashkenazi Jews, the age of onset and severity are variable, it can have a very mild form, and treatment is available [42]. Therefore, screening for Gaucher has been questioned in the literature [81]. Finally, some primary care midwives working in areas with a relatively large population at risk for HbPs offer prenatal HbP carrier screening on an ad hoc basis (i.e. on their own initiative in the absence of a structural offer).

Although ancestry-based carrier screening is available in these specific niches, little is known about how these offers are perceived by the public and the professionals, nor what population-specific enabling factors and challenges are encountered.

## **A CHANGING LANDSCAPE**

Technological developments have altered the screening landscape over the past few years, and have triggered a two-fold transition in carrier screening. First, with the introduction of high-throughput genotyping and sequencing approaches (Next Generation Sequencing (NGS)) it is now possible to screen for many disorders, genes or sequence variants simultaneously at a faster turnaround time, and without significantly increasing costs [2, 82, 83]. Carrier screening panels have thus “expanded” to include many more disorders. Second, the availability of these expanded panels encourage the transition of an ancestry-based offer towards screening, regardless of ancestry or geographical origin, and thus offering screening “universally” [84].

Expanded universal carrier screening (EUCS) panels now often include over 100 disorders, and are increasingly offered by commercial laboratories in the US, Australia and Europe [85]. Since 2016, Dutch clinical genetic centres of two university hospitals have initiated the development and availability of EUCS. The offer of University Medical Center Groningen involves screening for 50 disorders via participating general practitioners within a research setting [86], whereas Academic Medical Center Amsterdam, in collaboration with VU University Medical Center Amsterdam, offer EUCS via the Clinical Genetics Department of the hospital [87]. The latter is not reimbursed for the general public, but will be (partly) reimbursed by insurance companies if the couple has an increased risk based on a positive family history, on ancestry, or when there is a consanguineous relationship.

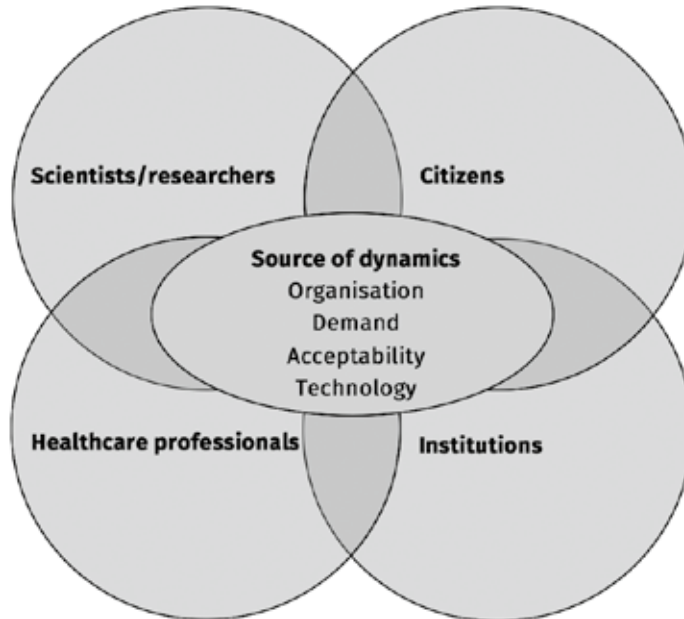
The advantages of EUCS have been highlighted in the literature, several opinion statements, and reports. Advantages mentioned include the increase of equity and the potential decrease of risk of stigmatisation of ethnic groups [2, 84]. However, medical professionals, including genetics professionals, are also critical of these developments. Concerns include difficulties with selecting specific mutations that should be included in a panel, and challenges with counselling and pre- and post-test information [88]. With regard to this discussion, it is essential to identify factors for the successful and responsible implementation of EUCS [89, 90]. Lessons can be learned from existing carrier screening initiatives, both ancestry-based and EUCS.

## **IMPLEMENTATION OF CARRIER SCREENING**

Many different theoretical frameworks, originating from several disciplines (e.g. psychology, sociology, and implementation science), have been developed to better understand the determinants involved in implementation, to enhance implementation of new practices, and to evaluate them in terms of, for example, availability, continuation and institutionalisation [91-93]. In order to successfully implement new practices, changes are needed in the three main elements of a larger societal system: the culture, the structure and the practice [94].

In the implementation of carrier screening, either ancestry-based or EUCS, many different parties are involved. According to the Network of Actors model by Achterbergh *et al.* [95] (figure 1), one group of stakeholders involved is the scientists and researchers (including laboratory scientists) developing the carrier screening tests. Citizens (e.g. the target population, i.e. couples planning a pregnancy without an a priori increased risk, or patient organisations) are included in this model as they might have a demand for carrier screening. The implementation of carrier screening will furthermore require adaptations in the daily practices and organisation of healthcare professionals. Finally, the perspectives of institutions (e.g. regulatory and advisory agencies, policy makers) need to be taken into account as it is they that develop policy and regulations regarding an offer of carrier screening.

The recent technological developments in EUCS have made the current situation in carrier screening susceptible to change, and might result in a transition moving beyond ancestry-based screening. However, considering these advances and transition in the screening landscape, it is important to consider not only the technological perspectives, but also to investigate and focus on the translation from bench to bedside [96, 97]. Furthermore, the perspectives of all stakeholders need to be understood and taken into account in order to successfully and responsibly implement carrier screening.



**Figure 1.** Stakeholders involved in the implementation of carrier screening grouped according to the Network of Actors model (based on [95, 96])

## AIM AND RESEARCH QUESTIONS

As technological advances have caused the carrier screening landscape to change over the past years, the main aim of this thesis is to gain insight into the responsible implementation of carrier screening with respect to this change, by exploring the views of various stakeholders, both professionals and the public. In Part I, ancestry-based carrier screening initiatives in four Dutch high-risk groups is studied, while Part II reflects on the transition from ancestry-based carrier screening towards expanded universal carrier screening. In this thesis, the following research questions will be addressed:

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

1. **What are the attitudes, preferences and experiences regarding carrier screening of:**
  - a. Populations at risk of having affected offspring with haemoglobinopathies (Chapter 2) or cystic fibrosis (Chapter 3)?
  - b. People at risk of having affected offspring with several severe childhood-onset recessive disorders in a genetically isolated Dutch community (e.g. PCH2) (Chapter 4) or in the Ashkenazi Jewish community (e.g. TSD) (Chapter 5)?

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

2. **What are the enabling and constraining factors for the successful and responsible implementation of carrier screening?**
  - a. What can be learned from existing carrier screening initiatives when looking at the implementation of expanded universal carrier screening? (Chapter 6)
  - b. What are general and population-specific barriers and needs reflected by stakeholders regarding the implementation of carrier screening? (Chapter 7)
3. **What are ethical issues when implementing expanded universal carrier screening?**
  - a. What are the advantages and challenges of a transition from ancestry-based carrier screening towards expanded carrier screening, according to stakeholders? (Chapter 8)
  - b. What are prerequisites for a responsible offer of carrier screening? (Chapters 7 and 8)

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