## Implementing carrier screening in a changing landscape

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2017

***document version***
Publisher's PDF, also known as Version of record

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# General discussion

In recent years, technological developments such as Next Generation Sequencing (NGS) have led to changes in the carrier screening landscape. Carrier tests have now expanded from screening one single disorder to NGS panels enabling the detection of a much larger set of sequence variants, but also to simultaneously screen for many more disorders [1]. In this way screening can be offered more universally, regardless of ancestry or geographic origin, which in this respect increases equity and potentially reduces the risk of stigmatisation of high-risk groups [1]. The universal offer of these panels is encouraged by its availability as well as by findings that show that expanded testing panels can identify more carrier couples at risk for severe or profound phenotypes in their offspring than testing based on current screening guidelines [2, 3]. Considering this transition in the screening landscape, and the responsible implementation of carrier screening, it is necessary to fully understand the perspectives regarding carrier screening of all key stakeholder groups. It furthermore requires attuning stakeholders involved in the implementation process.

This thesis is divided into two parts: 1) the evaluation of ancestry-based carrier screening in four high risk groups (i.e. populations at risk of having affected offspring with haemoglobinopathies (HbPs) and cystic fibrosis (CF), and people in a genetically isolated Dutch community and in the Ashkenazi Jewish (AJ) community); and 2) the implementation of carrier screening in a changing landscape, by reflecting on the existing ancestry-based carrier screening initiatives, the enabling and constraining factors for successful and responsible implementation, and the ethical issues involved.

The general discussion of this thesis briefly addresses the main findings which will then be discussed in the context of the scientific literature. This is followed by the reflections on the methodologies used, implications for practice, and recommendations for further research. The chapter ends with the conclusions.

## DISCUSSION OF MAIN FINDINGS

### Attitudes towards, and experiences with, ancestry-based carrier screening

The results of the studies described in this thesis generally showed positive attitudes - from a user perspective - towards an offer of ancestry-based carrier screening, which is confirmed by other studies [4-8]. HbP carrier screening in early pregnancy, as described in chapter 2, was perceived as positive by pregnant women, and many accepted the offer. This willingness of women to be screened is in accordance with the literature [9-12]. Additionally, reasons to accept screening show parallels with reasons described by others, e.g. the perceived relevance for future children, and obtaining information or reassurance [13, 14]. The possibility of CF carrier screening direct-to-consumers (DTC CF carrier screening) through the website of a Dutch university hospital was also seen as positive by its users (chapter 3), although very few people requested testing. Attendees of an outpatient clinic in a Dutch founder population were positive about,

and highly satisfied with, the offer of carrier screening for four disorders common in their community, and would recommend screening to others (chapter 4). No feelings of stigmatisation were reported, and all carrier couples that were identified made reproductive decisions based on their test results. Similar to the findings in this founder population, few members of the Dutch Jewish community feared stigmatisation, and there was an overall acceptance of screening aimed at this population (chapter 5). Stigmatisation of (presumed) carriers (and their families) within, for example, the orthodox AJ community has previously been described [15]. Encouragingly, recent studies have revealed no predominant feeling of stigma among carriers [1] Moreover, as described by de Wert *et al*. [16], much seems to depend on how screening is offered and what information is provided.

In addition to these positive attitudes, the studies also showed challenges when offering carrier screening. As appeared from chapter 2, many pregnant women experienced information overload and preferred receiving the information at a different moment (e.g. prior to the booking appointment by means of a leaflet, or preconceptionally), as the screening was offered at a time when they are already receiving a lot of new information. Although the preconception phase is generally considered to be the most favourable timing, as more reproductive options are available besides prenatal diagnosis [16], it is also considered quite challenging to reach the target population (couples planning a pregnancy) [10, 11]. Moreover, some women expressed a need for more information on the topic of HbP. This has also been described by others [4, 17], and a lack of information and thus suboptimal knowledge might hamper the informed decision-making process. A multistep process of decision-making was observed as many pregnant women did not give follow-up testing in case of a screen-positive result (e.g. sequential testing of their partner and prenatal diagnosis) much consideration when deciding on accepting or declining the HbP carrier screening test. It has been shown that when women do not think about possible consequences and follow-up testing when making their initial decision on, for example, prenatal screening, suboptimal informed decision-making might be the consequence [18]. Efforts to improve this, for example by providing information (in writing) prior to the booking appointment, and to safeguard informed decision-making would therefore seem important.

Despite the positive attitudes on CF carrier screening reported in many other studies [11, 19-21], only 44 DTC carrier tests had been requested through the website in six years (chapter 3). A study among users of DTC personal genomic testing showed that only one-third of the respondents were interested in obtaining carrier status information, and it was argued that this information may not have been viewed as being personally relevant. A Belgian study among CF patients and parents furthermore revealed that respondents were generally unfamiliar with DTC genetic testing [22]. Although they indicated that people have the right to request commercial DTC genetic testing, a proportion of the respondents also felt that it should be forbidden by law to offer genetic testing via a commercial company (40%), or through a hospital website (31%) [22]. The limited use

of our offer can also be caused by a reticent attitude towards screening unless it is either actively offered by a healthcare professional [23, 24], or if people have a positive family history for CF [24]. The latter might also explain why many participants did have a positive family history for CF while they actually did not belong to the intended target group (i.e. couples planning a pregnancy *without* a positive family history for CF).

A lack of knowledge of genetics among the lay public has been a major concern among professionals with regard to the implementation of carrier screening [25]. The study in the Dutch founder population showed that people were highly familiar with genetic disorders and carrier testing. However, while knowledge after counselling increased and remained high afterwards, some people continued to think that they are at risk of having affected offspring when both partners were carriers of different autosomal recessive (AR) disorders (chapter 4). This might call for more emphasis on this particular topic during counselling, especially if screening is expanded to include more disorders.

Finally, the questionnaire study among the Dutch Jewish community showed that despite positive attitudes towards screening, few people made use of the Dutch offer, and often went abroad for screening (chapter 5). This limited use raises a number of questions, for example, about the awareness regarding the availability of screening, and the demand for screening. In the 1970s, the development of screening for Tay-Sachs disease, initiated from within the AJ community, seemed to be a response to an urgent problem (i.e. children dying from Tay-Sachs disease) [26]. However, does this also apply to the Netherlands? Discussing carrier screening with key figures within the Dutch Jewish community showed that this might indeed not be perceived as an urgent problem here, as one of the rabbis argued that he did not know any affected children (personal communication, 2014). Do mixed marriages in certain sections of the Dutch Jewish community result in the absence of these disorders? Are the diagnoses not widely shared? Or does the offer not respond to a demand due to the availability of screening elsewhere? In the United Kingdom, the AJ community can request screening via, for example, a walk-in clinic at Guy's Hospital in London [27]. A needs assessment report by the PHG foundation in 2009 concluded that "the rarity of the condition and the relatively small size of the AJ population in the UK mean that a screening programme should be viewed not as solving a major public health problem in disease [prevalence] but as putting in place a service for a community that is identified and sees itself as high-risk" [28].



**Widening the scope – expanded universal carrier screening**

Reflecting on the ongoing technological advances, a change in the carrier screening landscape has been identified (see figure 1). On the one hand, carrier screening tests have become more extensive; instead of screening for one single disorder (e.g. Tay-Sachs disease), they have expanded to include multiple disorders (e.g. panels for the AJ community and for a Dutch founder population) (arrow A in figure 1). It has been described that communities support developments to screen for more disorders for

which they face an increased risk [29, 30]. A shift away from ancestry-based carrier screening towards a more universal offer of screening is also observed. An example here is CF carrier screening. Whereas in the US CF screening was initially only recommended to be offered to Caucasian couples (including AJ couples) planning a pregnancy or seeking prenatal care [31], it is now advised to offer CF screening regardless of ancestry, thus universally, as it is increasingly difficult to assign a single ethnicity to individuals [32, 33] (arrow B in figure 1).

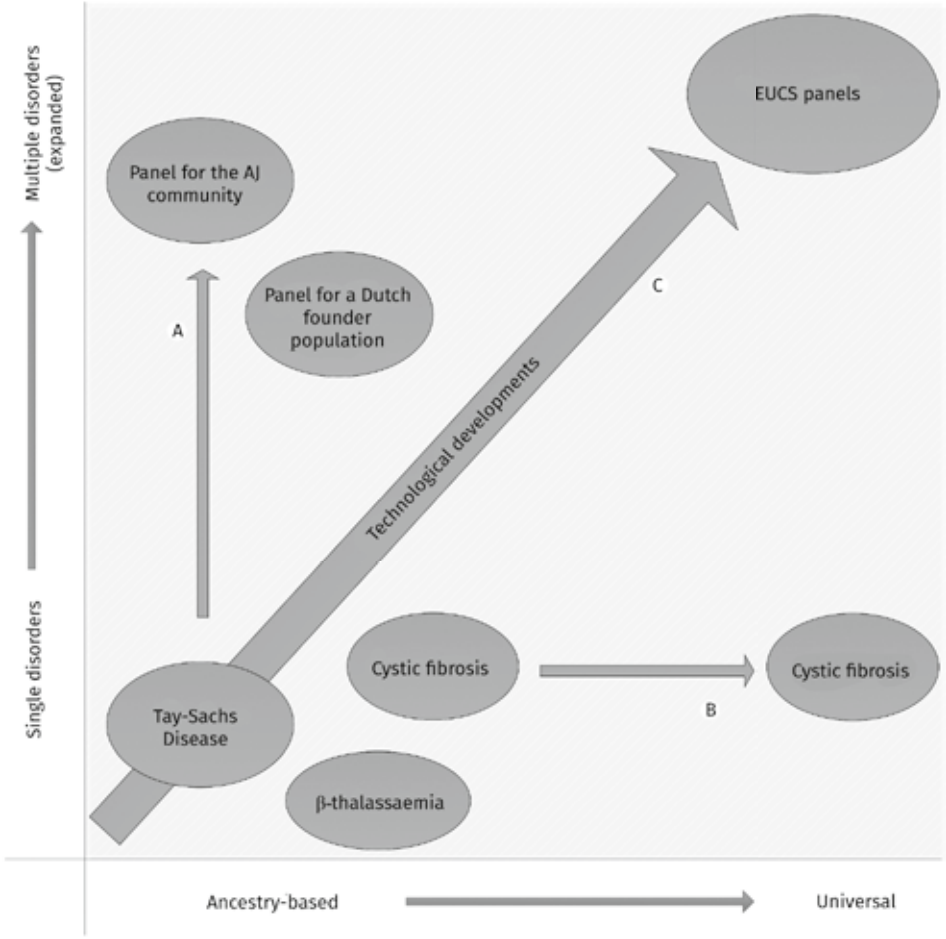


**Figure 1.** The changing landscape of carrier screening

A combination of these two shifts resulted in the development of expanded universal carrier screening (EUCS) panels. These developments are mainly due to advances in high-throughput genotyping and sequencing approaches and decreasing costs [3, 34]. In the past, there was increasing interest in expanding screening beyond, for example, Tay-Sachs disease to include other severe and debilitating recessive disorders as well.

However, expansion was limited by either the fact that disease genes were unknown, or by the lack of accurate detection methods [35]. Nowadays, although it has been well-acknowledged that multiple factors are of importance in the successful and responsible implementation of carrier screening [36], the technical developments seem to be the main driver for the development of EUCS (arrow C in figure 1), as there are doubts about the demand for screening and its acceptability [37, 38], and the adjustments needed in the organisation of healthcare, at least in some countries. Furthermore, though EUCS potentially solves issues stemming from ancestry-based screening, it is expected that it will also raise moral concerns of its own such as how to provide couples with both understandable and sufficient information about EUCS, and whether EUCS will lead to a lower level of care for high-risk populations (chapter 8).

**Successful and responsible implementation – learning from existing initiatives**

*The demand for screening*

Although the prevention of the birth of an affected child is a well-accepted aim of screening in some communities with a high-disease burden [16, 39], the main aim of carrier screening is to provide couples planning a pregnancy with meaningful options for autonomous reproductive choice [16]. It has been widely accepted that this should also be the aim of expanded universal carrier screening [1]. Successful and responsible implementation of carrier screening should thus comply with this.

This thesis identified enabling and critical factors for the implementation of carrier screening from a user perspective (chapter 6), and important population-specific and general barriers and needs reflected by other stakeholders (chapter 7). From a user perspective, among other things, the familiarity with the genetic disorders included in the screening test and the availability of carrier screening, but also the perceived personal benefits of screening and perceived risk seemed to be important factors in the implementation of screening, as they might influence a demand for screening (chapter 6). However, the presence of these factors in the general population is less evident. Stakeholders interviewed in chapter 7 questioned whether or not there is an actual demand for screening as it is not often requested in daily practice. Since the development of EUCS panels is mainly technology-driven, it is important to attune to the actual demand for screening.

A questionnaire study among Dutch respondents of reproductive age regarding offering population-based carrier screening for fifty severe, early onset AR disorders showed that approximately one-third would consider screening when offered [40]. Additionally, in a Dutch survey in 2015 among 803 participants, 63% believed that screening should be offered universal, regardless of ancestry [41]. A recent Belgian survey study indicated that slightly more than half of the respondents expressed willingness to have carrier screening [42]. These findings seem to support the notion that there is some demand for (expanded universal) carrier screening but as these studies measure attitudes rather than actual behaviour, the intention-behaviour gap should be taken into account [43].

In the USA, opting out of a recent offer of expanded carrier screening was mainly due to logistical issues (e.g. time or travel limitations) rather than opposing the rationale for testing [44]. Nevertheless, a lack of demand does not necessary imply that screening should not be offered. An offer of carrier screening can possibly generate familiarity with screening and therefore generate a demand. Offering carrier screening shows similarities to offering prenatal screening for Down syndrome. The target population in the Netherlands (i.e. women in the first trimester of pregnancy) is highly aware of this type of screening, also because it is offered despite the fact that the majority of women refrain from testing (the uptake ~30%) [45]. Considering the primary aim of screening (i.e. facilitating informed reproductive decision-making), a high uptake rate of screening should not be a criterion for success, as is also not the case with prenatal screening [46]. Moreover, it is important to realise that, although individually rare, it is estimated that 1 in 150 couples are at risk of having affected offspring due to recessively inherited disorders [1]. As described by Ropers [47], this number is comparable to the risk of having a child with Down syndrome at the age of 37, for which we do offer screening.

*The desirability and acceptance of screening*

Internationally, ancestry-based carrier screening is generally well-accepted and found to be desirable by both the public [5, 11] and professionals [26, 48]. Regarding the desirability and acceptance of EUCS, however, results are less straightforward. A slight majority of the respondents from the Dutch Jewish community and from the Dutch founder population preferred EUCS over an ancestry-based offer. As costs of EUCS are likely to drop even further in the future, these panels might gain in popularity (chapter 6). Professional stakeholders on the other hand, found the desirability and acceptance of EUCS to be less obvious and cited both practical and moral concerns (chapter 7 and 8) [38, 49, 50].

One of the concerns mentioned was related to the composition of a panel; what disorders should be included in a screening test? Stakeholders argued that a clear set of inclusion criteria should be determined by a multidisciplinary team. Lazarin *et al.* [51] proposed a classification of disease severity for the inclusion of disorders in EUCS based on the opinions of healthcare professionals, whereas Korngiebel *et al.* [52] selected disorders based on the significance of the impact on a person's life in terms of the need for medical treatment and management. These methods therefore differ. Additionally, participants of an international workshop on preconception expanded carrier screening in Glasgow in 2015 felt that "severe" disorders should be included in carrier screening, but they also recognised that there is no clear, consensus definition of what "severe" actually is [53]. For the responsible implementation of carrier screening, this discussion should be addressed.

As argued by proponents of EUCS, it has the potential to reduce the risk of stigmatisation of ethnic groups, as screening is not offered based on ancestry [1]. In addition, by addressing the entire population and screening for multiple disorders, it will show that

being a carrier is not exceptional. However, it has also been argued that EUCS might reinforce stigmatisation of affected individuals and their families (i.e. disability-based stigmatisation) (chapter 8, [54]).

It has been observed that EUCS might increase equity of access due to the possibility of screening for a larger number of disorders enabling *universal* screening. Nevertheless, stakeholders in this thesis (chapter 8) and elsewhere [55] have argued that it might also hinder equity. Edwards *et al.* [3] suggested that because EUCS can provide information about carrier status beyond population estimates, it eliminates the need for ancestry-based screening. However, when designing EUCS panels, specific founder mutations might not be included, causing screening to be less suitable for particular high-risk groups. It was therefore argued that EUCS should not replace ancestry-based screening (chapter 8). Focusing on population-specific founder mutations can be replaced by universal sequencing of the entire genes involved. This will result in missing less true pathogenic mutations, irrespective of ancestry, but will introduce the identification of variants of unknown significance (VUS) as well [56]. The reproductive options for carrier couples where VUS results are involved are not straightforward. A solution for the time being could be to report only proven pathogenic variants in preconception and prenatal carrier screening.

*Infrastructure*

The findings of this thesis also indicate the need for developing well-organised infrastructures when considering the further implementation of carrier screening in the Netherlands. Nowadays, carrier screening is mainly available, and (partly) reimbursed for those with an a priori increased risk due to a positive family history or based on ancestry or consanguinity, or through a few local initiatives. However, there is no clear structure within regular healthcare to embed carrier screening. In the absence of a solid structure, stakeholders proposed different options of how and when screening could be offered. The argument concerning where to embed carrier screening was often accompanied by a discussion about preconception care. The potential of preconception care has been widely discussed, but as it also encounters many barriers, e.g. a lack of knowledge among both healthcare professionals and the target group, and a lack of funding (chapter 7, [57, 58]), to date, it has not been as successful as hoped for [57]. Moreover, interconception care, i.e. care provided between pregnancies, might also be suitable to address carrier screening as child healthcare has a unique position in reaching mothers and has an expertise in preventive healthcare [59]. However, for some this might come too late as parents have already been confronted with the birth of an affected child without being aware of their increased risk. At other moments in time, however, carrier screening is often not considered to be urgent enough. In order to take the implementation of carrier screening one step further, other structures could be considered, including a model where screening is offered at different moments in time by several healthcare providers. This would create a safety net for those who have not been offered screening before [60].

### Commercialisation of carrier screening

While discussing the responsible and successful implementation of carrier screening within regular healthcare, the commercial developments and offers of carrier screening cannot be ignored. Recently, Chokoshvili *et al.* [61] described the growing complexity of carrier screening and a highly fragmented carrier screening landscape due to the variety of ways in which commercial companies offer carrier screening. They and others have described a diversity among these different companies in terms of clinical characteristics, pre-test information and post-test counselling practices [1, 61, 62]. Though stakeholders in this thesis perceived these developments as inevitable, they also expressed concerns regarding, for example, the provision of pre- and post-test counselling, the quality of the test, and increasing inequality due to high costs (chapter 8). A national health services system as, for example, the healthcare system in the UK, might guarantee equity of access to healthcare services (e.g. carrier screening). However, in many countries, healthcare is often not completely public, but also includes privatised elements, including commercial influences. In these structures, it is conceivable that commercial companies, or at least a direct-to-consumer offer, could play a role in the provision of carrier screening, and can initiate an innovation curve. Nevertheless, as a purely commercial structure might contribute to socio-economic inequalities [63], proper monitoring and evaluation is needed [64]. Companies should furthermore be transparent about their goals, and autonomy should be safeguarded [1].

### Taking responsibility

Currently, stakeholders point to each other when discussing who is responsible for implementing carrier screening or even preconception care in general. To move forward, it is crucial to effectuate a new division of responsibilities and attune the involved key stakeholders accordingly. One way to organise this is by having governments adopt an active role in discussing implementation and organising a public debate [1, 65]. Additionally, so-called change agents (i.e. key stakeholders) might take the lead in their own initiative, and strategically plan implementation [66]. The development of initiatives on either ancestry-based screening or EUCS by professionals might serve as a blueprint here for taking responsibility.

## REFLECTIONS ON METHODOLOGY

To provide a balanced answer to the research questions posed in this thesis, quantitative and qualitative research methods, or a combination of these two, were used. While the (online) questionnaires used in chapters 4, 5 and 6 allowed the study of larger data samples and the evaluation of screening over different moments in time, the semi-structured interviews enabled the in-depth exploration of key stakeholders' perspectives on the different initiatives of ancestry-based carrier screening, and on the changing screening landscape. The interviews furthermore facilitated the collection of data in a private environment, especially when conducting interviews with women at

risk of being a HbP carrier (chapter 2), and with carrier couples (chapter 4). Despite the different methods used, other methods would have been appropriate as well and thus might be used in follow-up studies. Focus groups, for example, can be used to trigger a lively discussion among participants, and to explore and collect data on group norms [67]. Additionally, observation of counselling sessions might provide insight into the practical procedures of healthcare professionals, and allow guidance for improvement to be developed.

Another strength of this thesis is the use of theoretical frameworks and models (e.g. the Network of Actors model, and the constellation approach (chapter 7)) to support both the presentation of the findings, and the definition and recruitment of involved stakeholders. As a result, all stakeholder groups involved in the implementation of carrier screening were included in this thesis. However, this also directly entails a limitation, as the inclusion of stakeholders was not exhaustively carried out. Some professionals, for example gynaecologists and fertility specialists, but also some professional organisations, did not respond to invitations and were thus not included. Furthermore, although representatives of patient organisations were included in the stakeholder interviews, the perspective of patients and their family members themselves, but also of consanguineous couples, is lacking in this thesis. This provides opportunities for future research. Additionally, the study among women at risk of being a HbP carrier focused on experiences with *prenatal* HbP carrier screening as some primary care midwives offer screening to them on their own initiative in the absence of national policy support [68], thus on an ad hoc basis. However, as the *preconception* stage is considered the most favourable timing to offer screening, future research should further focus on reaching the women in the high risk population for HbPs before pregnancy.

As is often the case with participants in scientific research [69], study participants were mostly highly educated (with the exception of the study population described in chapter 2). The analysis on non-completers on the AJ questionnaire furthermore showed that respondents who had completed the questionnaire were more likely to be familiar with screening than non-completers. This might have resulted in biased findings as people with a lower level of education or familiarity with screening might have different views on the topic.

The studies in part II of this thesis provide insight into the perspectives of both the public and professionals regarding the changing carrier screening landscape. The studies among AJ community members and inhabitants of a Dutch founder population were the first to actively ask community members to make their preference known. Until then, only professionals - mostly geneticists – had been asked about their considerations, or the focus had been on the technical developments in screening. Second, the combination of experiences in two communities familiar with ancestry-based carrier screening provided a unique insight into possible critical factors for the implementation of screening on a population-level. Finally, the study in chapter 8 is,

to our knowledge, the first to explore perspectives of (health) policy professionals and patient organisations on EUCS, with an explicit focus on its ethical dimension.

EUCS is not widely available in the Netherlands. In 2016, two initiatives on offering EUCS were initiated: 1) screening was offered via general practitioners in a research setting in Groningen [40], and 2) non-reimbursed carrier screening has been available via the genetics department of a university hospital in Amsterdam [70]. The research findings on the evaluation of both initiatives (also including questionnaire studies among participants) are expected soon. These may guide the discussion on the further implementation of EUCS in the Netherlands.

## IMPLICATIONS FOR PRACTICE

The carrier screening landscape is currently subject to change due to technological advances which, in return, offer opportunities but also challenges for implementation. In the studies conducted, it was found that although key stakeholders are positive about offering carrier screening, a number of critical factors, barriers and needs regarding its implementation were expressed. Further discussion about the desirability of offering carrier screening, either ancestry-based or expanded universal, with representatives from all involved stakeholders groups should thus take place. Additionally, it requires attuning the four main stakeholder groups (i.e. scientists/researchers, citizens, healthcare professionals, and institutions). This is crucial to realise further implementation or at least to take the discussion one step further. To facilitate this process, and to avoid stakeholders continuously pointing to each other, so-called “change agents” should be formally acknowledged by the government, or take professional responsibility on their own initiative. When the further implementation of carrier screening in regular healthcare, in any form, is found to be desirable, adjustments to current structures and practices is required. First, it should be carefully considered who offers screening, and when screening is preferably offered. Suggestions stemming from this thesis include offering screening during preconception care by midwives or general practitioners, embedding screening in routinely performed blood tests during pregnancy, or between pregnancies (interconception care) in well-baby clinics, or during the follow-up appointment with the midwife. Furthermore, a role might be assigned to gynaecologists and fertility clinics. Second, attention should be paid to how an offer is facilitated (e.g. taking care of costs and reimbursement, development of guidelines) as well as how people are informed about screening. As shown in this thesis, the education and training of both professionals and the public on the topic of carrier screening is found to be inadequate, and requires improvement. Education of professionals could be improved by assigning a leading role to this topic in the curricula of medicine students, and in postgraduate education. Awareness and knowledge on a public level might be created by incorporating information in secondary education or by developing a mass media campaign using different information channels, e.g. traditional media

(television and newspapers) and social media. Specific roles seem to be reserved for, for example, clinical geneticists, patient organisations or non-commercial organisations like the Erfocentrum in the Netherlands (www.benikdrager.nl). However, as providing couples with meaningful options for autonomous reproductive choice is considered the primary aim of screening, information should comply with this and should therefore be non-directive.

## RECOMMENDATIONS FOR FUTURE RESEARCH

Given the ongoing changes in the carrier screening landscape and the questions that arise from this thesis, the following recommendations for research can be formulated:

- In many studies, attitude and intention towards screening are measured instead of actual behaviour, resulting in discrepancies between expectations on the desirability and demand for screening and, for example, actual demand. More research is needed here, and ongoing studies among users of EUCS initiatives provide insight into this. The execution of these studies is thus encouraged.
- The impact of EUCS on users in terms of, for example, the consequences of knowing their carrier status, but also the impact of its implementation on regular healthcare, in terms of, for example, subsequent costs, waiting lists, input from professionals within healthcare should be studied further.
- The criteria that disorders have to meet in order to be included in a screening panel currently differ across providers, resulting in different compositions of panels. Criteria should therefore be discussed, studied, and attuned by multidisciplinary teams including all key stakeholders.

## CONCLUSION

The studies on the four initiatives of ancestry-based carrier screening showed positive attitudes towards carrier screening, and provided lessons for further implementation. However, it was also argued that the critical factors for successful implementation from a user perspective are less evident when it comes to EUCS compared to ancestry-based screening. Additionally, barriers have to be overcome and needs addressed when discussing further implementation. While EUCS potentially solves moral challenges emerging from ancestry-based screening (e.g. stigmatisation), new challenges will also arise. To address the critical factors from a user perspective, and the discussed barriers and needs by professionals, more research is needed, and efforts should be made to further develop and responsibly disseminate current carrier screening initiatives. A debate among all key stakeholders about the desirability and feasibility of carrier screening should be organised. This discussion should also focus on, for example, how screening is offered (i.e. in what settings), how people are informed about screening (e.g. what information strategies are acceptable), and how an offer is facilitated (e.g. development of guidelines). Furthermore, since multiple factors are involved in a successful and responsible implementation, technological advances alone should never be a reason to implement carrier screening. Facilitating reproductive decision-making should always be the primary aim.

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