Superior Health Council

ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9240

Expanded carrier screening in a reproductive context. Towards a responsible implementation in the healthcare system

In this advisory report, the Superior Health Council of Belgium provides recommendations on the criteria that need to be applied in preconceptual genetic testing for severe autosomal and X-linked recessive diseases for couples planning a pregnancy.

This report aims at providing healthcare authorities and healthcare professionals with specific recommendations on the scientific and ethical issues that need to be considered in view of a responsible implementation of preconceptual genetic testing in a reproductive context. The report specifically discusses the framework underpinning the appropriate introduction of such testing and suggests inclusion criteria for diseases that could be targeted by the screening process: (i) severity, (ii) age of onset, (iii) prevalence, (iv) selection of mutations based on clinical significance and (v) treatability.

This version was validated by the Board on February 2017[1]

I INTRODUCTION AND ISSUE

Population based screening aims at identifying “healthy” carriers of a recessive disease who have no a priori increased risk based on family history. Their risk of being a carrier is linked to the prevalence of the disease in the population. An autosomal recessive disease will occur early or later in life, when the two copies (alleles) of a particular gene are mutated. Carriers of one such mutated allele are healthy. As long as there is no family history and no testing performed, they do not know that they carry a mutation. When two carriers with a mutation in the same gene want to reproduce, they have a ¼ risk of having an affected child and when their child is born healthy, the child has a 2/3 risk of being a carrier.

An X-linked recessive disease is typically seen in boys or men while women are usually healthy carriers. This is explained by the fact that men have only one X chromosome and thus only one copy (allele) of each X-linked gene. Women have two X-chromosomes and therefore two copies (alleles) of each X-linked gene. In most cases, when a woman is a carrier of one mutated allele, she will be healthy, but there are exceptions. However, being a carrier, the risk of her sons being affected is ½. Moreover, and assuming the partner is healthy, the risk of her daughters being carriers is also ½.

[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

The reasons why some female carriers may be symptomatic, often at an older age, are variable and therefore the observational facts have to be taken into account when screening is offered.

Altogether, over 1300 mild or severe recessive diseases are known today affecting 2 to 3 children /1000 and leading to 1 to 2 % of couples being at risk. In a recent study of an ethnically diverse sample of 23 453 individuals, 24 % were identified as carriers for at least one of 108 different monogenic disorders (Lazarin et al., 2012).

Keywords and MeSH *descriptor terms*[2]

MeSH terms*	**Keywords**	**Sleutelwoorden**	**Mots clés**	**Schlüsselwörter**
Genetic Testing / Genetic screening	Genetic Testing / Genetic screening	Erfelijkheidstests/ Erfelijkheidsonderzoek	Test génétique / Screening génétique	Gentests/ genetisches Screening
Reproductive Medicine	Reproductive Medicine	Reproductieve geneeskunde	Médecine de la reproduction	Reproduktionsmedizin
Reproductive Rights	Reproductive Rights	Reproductieve rechten	Droits de la reproduction	reproduktive Rechte
Delivery of Health Care	Delivery of Health Care	Aanbieden van gezondheidszorg	Prestation de soins de santé	Bereitstellung von Gesundheitsdienstleistungen
Genetic Diseases, Inborn	Genetic Diseases, Inborn	Erfelijke aandoeningen, aangeboren	Maladie génétique, innée	Genetische Krankheit, angeboren
Bioethics	Bioethics	Bio-ethiek	Bioéthique	Bioethik
Genetic screening	Public Health Genomics	Genomica voor de volksgezondheid	Génomique en santé publique	Genomik im Gesundheitswesen

MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed http://www.ncbi.nlm.nih.gov/mesh.

[2] The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

II CONCLUSIONS AND RECOMMENDATIONS

Firstly, the Superior Health Council (SHC) considers that knowledge of a person's carrier status can provide benefit in a reproductive context. Knowledge of a person's carrier status provides the opportunity to identify reproductive risks in couples that have no a priori known family risks of autosomal recessive or X-linked conditions, and allows increasing reproductive choices.

Identifying a person's carrier status with the goal to learn about reproductive risks and potentially make reproductive decisions is most valuable within a setting in which both reproductive partners are being screened for carrier status. Couples that are being followed up in a tertiary care setting for fertility problems or for a known genetic condition could also benefit from detecting other genetic risks that might affect their offspring.

The Council recognizes that identifying the carrier status of a healthy individual may encompass important ethical and legal issues which need to be considered within the broader context of the application of genomic/genetic data with respect to personal and population health. The Council recommends a request for advice from the Council of Bio-ethics.

Secondly, the SHC considers that expanded carrier screening should be offered preconceptionally as this allows more reproductive options, and has less time constraints, resulting in less emotional distress than if the test were performed during the pregnancy. Nevertheless, this does not mean that carrier screening should be excluded during pregnancy, but this falls outside the scope of this report.

Thirdly, the SHC considers that carrier screening panels should include disorders and mutations based on specific criteria (I. severity, II. age of onset, III. prevalence, IV. selection of mutations based on clinical significance, V. treatability). As the main aim of offering carrier screening to couples is enhancing reproductive autonomy, the SHC believes that carrier screening should be performed for conditions that are severe enough to warrant altering reproductive plans. The SHC advances that expanded carrier screening should focus on conditions that manifest in early childhood rather than in adulthood; and recommends limiting carrier screening to the conditions whose natural history can be ascertained by reliable and a sufficiently high number of clinical case reports in the literature.

Considering the important reproductive implications of carrier screening, the SHC states that priority should be given to pathogenic mutations with high penetrance and low variable expressivity in order to minimize uncertainty in counseling carrier couples. The SHC believes that expanded carrier screening panels should also include serious disorders for which therapeutic interventions exist, where the treatment may incur high physical, emotional, or financial burden.

Fourthly, considering the role of professionals such as gynecologists and general practitioners in guiding pregnant women or in guiding families planning a pregnancy, these professionals are well placed to inform about carrier screening or to follow up requests for carrier screening. Couples with a positive test (either both are carriers for the same autosomal recessive disorder or the female partner is a carrier of an X-linked disorder) should be referred to a Center for Medical Genetics for genetic counseling and follow-up.

Fifthly, the SHC believes that the most affordable strategy for identifying at-risk couples is screening both partners. Samples are collected at the same time from both partners. To limit costs, initially the sample provided by the female partner could be analysed for all autosomal and X-linked recessive disorders included in the screening panel. The sample of the male partner will only be analysed if a disorder causing mutation is identified in the female partner.

Sixthly, as for any medical intervention, participation in carrier screening implies an informed and voluntary participation. As an expanded carrier screening panel includes a broad range of conditions, pre-test information and informed consent should explain the goal, concept and implications of carrier screening, as well as its advantages and disadvantages. Information about the individual disorders should be available. As the focus of a screening offer would be on carrier couples, the SHC recommends focusing the reporting of information that is of relevance for reproductive decision-making of the couple.

Seventhly, the SHC also recognizes that stakeholder involvement about carrier screening should take place. Citizens' panels on the subject (such as those organized by the King Baudouin Foundation[3]) can assist in having a public debate on carrier screening.

Finally, the SHC recommends a stepwise introduction of the carrier screening as the implementation of carrier screening as a reproductive choice may imply considerable adaptation of current services and practices or even require novel types of services. A pilot-study is the best option as the initial step in the stepwise introduction in which the first step should be addressing the ethical and legal aspects related to the carrier screening offer seeking embedding the topic in a broader context of the use of genomic/genetic information at personal and public health level. The pilot study should (1) be managed centrally and foresee a population-wide registration including the possibility for (long-term) outcome analysis; (2) involve all key stakeholders including but not limited, to the genetic centers, responsible officials, and patient organisations; (3) develop technical guidelines for next-generation sequencing (NGS) in expanded carrier screening, including a blueprint for data management, data storage and accessibility for various purposes including research; (4) develop a carrier screening panel based on the criteria set out above; (5) develop information materials and educational sessions for healthcare professionals involved in the pilot study; (6) develop laboratory protocols and counseling strategies for carriers and carrier couples; (7) study the immediate and downstream costs related to the test offer, and the psychological and social impact of a carrier screening offer.

The pilot study should allow addressing the following issues: How to deal with the legal, ethical and privacy issues? What are the disorders of most interest to be included in the carrier screening? What is the interest and participation rate of the target population? How can (pre) counseling be organized in the best way (who informs who on what, when)? What are the minimal performance requirements for running NGS tests at general population scale? What are optimal models for such a population wide initiative? What will be the economic impact?

[3] The statutes of the King Baudouin Foundation published for the first time in the annexes to the " *Moniteur belge - Belgisch Staatsblad* " of December 31, 1975

III METHODOLOGY

After analysing the project of own initiative, the Board and the Chair of the area Public Health Genomics identified the necessary fields of expertise. An *ad hoc* working group was then set up which included experts in biomedical ethics, human and medical genetics, medicine, epidemiology, Public Health Genomics, *in vitro* diagnostics. The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.

Once the advisory report was endorsed by the working group, it was ultimately validated by the Board.

IV ELABORATION AND ARGUMENTATION

List of abbreviations used

ACCE	Analytical validity, Clinical validity, Clinical utility, Ethical, legal and social implications of genetic testing (model)
CF	Cystic fibrosis
DMD	Duchenne muscular dystrophy gene
FMR1	Fragile X mental retardation 1 gene
HbPs	Hemoglobinopathies
IVF	*In vitro* fertilisation
NGS	Next-generation sequencing
NHS	National Health Service (UK)
PGD	Pre-implantation genetic diagnosis
PKU	Phenylketonuria
PPV	Positive Predictive Value
SHC	Superior Health Council

1 Why carrier screening?

The main purpose of preconceptual carrier screening is to identify couples who are carriers of autosomal recessive or X-linked recessive disorders. This knowledge of genetic risks can provide the couples with various reproductive options such as prenatal diagnosis followed (or not) by termination of pregnancy or accepting the risk of the child being affected, but also deciding to refrain from having children, opt for adoption, using donor sperm or eggs, or chose for embryo selection using *in vitro* fertilisation (IVF) with pre-implantation genetic diagnosis (PGD). Moreover, carrier screening cannot only be of interest to couples planning a pregnancy or being pregnant, it can also be used to screen individuals or gamete donors in the context of reproductive care.

Carrier screening has been recommended for some single-gene conditions (so-called Mendelian disorders) by professional societies such as the American College of Medical Genetics and the American College of Obstetricians and Gynaecologists (Grody et al., 2001), but carrier screening panels have rarely been elaborated outside certain communities (Angastiniotis & Hadjiminas, 1981 ; Angastiniotis et al., 1988 ; Zeesman et al., 1984 ; Scriver, 2006 ; Raz & Vizner, 2008). Nevertheless, carrier screening for couples without knowledge of an increased risk for heritable disorders has been studied extensively for CF-cystic fibrosis (Axwortht et al., 1996 ; Bekker et al., 1993-1994 ; Payne et al., 1997 ; Henneman et al., 2002 ; Poppelaars et al., 2003-2004abcd) and HbPs-hemoglobinopathies (Keskin et al., 2000 ; Lena-Russo et al., 2002 ; Giordano et al., 2006 ; Lakeman et al., 2006-2008-2009). HbPs such as thalassemia syndromes and sickle cell disorders are serious autosomal recessive disorders endemic in the Mediterranean, African and Asian regions. Due to migration flows, systematic neonatal screening in Brussels and Liège has shown that one neonate in 1600 has a sickle cell disorder (Gulbis et al., 2009). Beta thalassemia is very rare with 0,001 affected births/1000 live births.

According to the UK National Health Service (NHS) sickle cell & Thalassemia screening programme, preconception counseling and carrier testing should be available to all women who are identified as being at high risk of HbPs by their family origin (NHS, 2011).

Various carrier screening studies reported positive attitudes from care providers (Janssens et al., 2014-2015), patients and their relatives (Poppelaars et al., 2003 ; Janssens et al., 2015), and the general population (Poppelaars et al., 2004). Healthcare services have been hesitant to implement carrier screening programs for all couples planning a pregnancy, but various companies have recently started to promote these inside or outside the healthcare system (Borry et al., 2011). This development has sparked various challenges and questions that also motivated the development of this report.

Also, in the past carrier screening was performed for a relatively small number of prevalent, recessive conditions with significant morbidity and reduced life-expectancy. Today, the technology allows analyzing a much larger set of conditions and variants, in a much faster and cheaper way than before. Various (commercial) panels have been described to analyze more than 100 conditions at a time. Moreover, while carrier screening offered in the past was mainly ethnicity-based, some test panels are currently been offered to individuals regardless of ethnic background.

The focus of carrier screening in this document is on both autosomal recessive and X-linked recessive disorders. We believe that we cannot exclude the latter group of disorders, even though for some X-linked disorders such as fragile X syndrome, female carriers may show mild symptoms. However, the majority of females who are carrier of an X-linked recessive disorder are healthy and not aware of the fact that they have an increased risk for having an affected son. In this way they do not differ from carriers of autosomal recessive disorders and meet therefore the criteria for carrier screening.

We want to emphasize that we do not consider in this document autosomal dominant disorders, including particular rare cancer syndromes, since “carriers” or heterozygotes are (or may become) by definition affected and symptomatic. Also, predictive testing for late-onset disorders is based on different criteria and concerns than carrier screening and therefore not the subject of this document.

The goal of this report is to provide a basis for discussions about carrier screening in Belgium and to facilitate a responsible implementation of expanded carrier screening within the healthcare system. In particular, this report aims to provide recommendations on (a) the desirability to develop carrier screening panels; (b) the way carrier screening panels should be offered; (c) the development of criteria that could guide the inclusion of diseases and sequence variants in carrier screening panels.

2 Carrier testing and screening: a definition

At the start of this document, it is important to clearly distinguish between cascade carrier testing and carrier screening. Cascade carrier testing is hereby defined as a genetic test that is offered to blood relatives and partners of an individual with a mutation for a particular recessive disorder.

In this context a carrier test is being offered because of an *a priori* known increased risk of transmitting a recessive genetic condition to the offspring. Concretely, blood relatives may be tested for a particular familial mutation; or partners (partner carrier testing) may be tested for any mutation in the gene for the particular disorder under analysis.

In contrast, carrier screening is the detection of carrier status in persons, who do not have an *a priori* increased risk of having a child with a certain disease based on their or their partners' personal or family history (Henneman et al., 2016). It is relevant to mention that carrier screening can be done in the context of gamete donation in which carrier status of the donors and recipients are being analyzed, and which could lead to identifying at risk matches between the two parties.

3 Carrier screening: ethical considerations

Although the primary focus of the present document is not on the societal and ethical questions related to the provision of carrier screening, the SHC deems some of those issues highly important and would like to address them in this chapter.

Firstly, the provision of carrier screening creates tensions with regard to the underlying objective of a screening offer. Various programs in public health settings (e.g. breast cancer screening, neonatal screening, etc.) have clearly as objective to improve the overall health of society. Such screening programs are set up to provide individual preventive or therapeutic options (GR, 2008). Here, the primary goal of a carrier screening offer is to provide information which may have an impact on the choice of reproductive options. Speaking of prevention in the context of reproductive decision-making is inappropriate or at least controversial, as the objective is not as such the prevention of certain conditions, but the provision of genetic risk information, informed choice and reproductive options. The final outcome based on the parent's choice may however be the prevention of the birth of an affected child.

The participation of governmental agencies to test offers (whether it is in reimbursement of a test or the provision of material conditions that enables a test to take place) that lead to reproductive choices is a very sensitive topic. According to some commentators, such test offers are never neutral. It might create societal, political and medical pressure to prevent the birth of individuals with certain conditions.

Debates about prenatal screening for Down syndrome for example have already shown these sensitivities. The term "eugenics" has often been used in this context. Using the term eugenics, however, is inappropriate, as the term refers to a context where certain reproductive options on individuals and couples are imposed. From an ethical perspective, a carrier screening test (and the potential follow up given to a test) should never be imposed. The provision of a test offer should provide couples with quality information to enable them to decide whether or not to undergo a test, and take the potential following decisions without external coercion or pressure. The integration of certain conditions on a test panel doesn't imply at all that individuals living with such conditions have less dignity, should have no right to appropriate management nor that they should not have been born.

The SHC recognizes this difficult balance. In the context of carrier screening we have seen that offers have been developed with the goal to reduce birth rates of affected children, as illustrated by carrier screening for Ashkenazi Jewish disorders (Grinzaid et al., 2015 ; Langlois & Wilson, 2006 ; Zlotogora et al., 2015) and pre-marital screening for thalassemia in the Mediterranean (Cousens et al., 2010). Screening offers in the context of reproductive medicine should however be addressed very cautiously, as the issues surrounding reproductive decision-making are very personal. Therefore, carrier screening should aim to inform couples about their genetic risks and to enable reproductive decision making in accordance with their values (Henneman et al., 2016 ; De Wert et al., 2012).

Secondly, carrier screening will lead to opportunities but might also lead to difficult decisions in the domain of reproduction in general and in the domains of pre-implantation genetic diagnosis and of prenatal diagnosis and termination of pregnancy in particular. Therefore, it is crucial that couples are properly informed on the aims of carrier screening, and the potential risks and benefits of the test. Any carrier screening offer will have to be supported by adequate mechanisms of appropriate and qualitative pre- and post-test information and counseling (Borry et al., 2008). Finally, couples need to be made aware that a normal test result greatly reduces, but does not fully eliminate, the probability of having an affected child. They have to be informed that due to this residual risk and other existing pregnancy risks, normal test results do not guarantee a “healthy child” (Cho et al., 2013).

Thirdly, the social impact of carrier screening is a potential area of concern. Studies have shown that the generalized access to carrier screening could lead to stigmatization and discrimination of identified carriers within some “traditional” communities (Raz & Vizner, 2008 ; Raz, 2009). Public education, appropriate information and counseling about the meaning of carrier status may be required to alleviate this (McAllister et al., 2016). Moreover, the fact that carrier screening could lead to changing the partner as a way to “remediate” an identified defect is a potentially contentious issue and requires further ethical reflection (Markel, 1992).

4 Technological approaches for carrier screening: “Next generation sequencing” opens possibility to massively-parallel analysis of multiple genes

The method used for carrier screening should be reliable, affordable and enable screening of many samples in a short period of time. The newest technology of next (second)-generation sequencing meets these criteria. NGS applies to genome DNA sequencing, transcript RNA profiling, epigenome characterization, etc. In all these cases, millions or more simultaneous (parallel) sequencing analyses are performed producing thousands or millions of DNA sequences (so-called reads) concurrently. This first part is performed on the laboratory bench and is often designated as the “wet lab” part.

These large amounts of sequence information are then assembled into contiguous genome information either *de novo* or through comparison with a reference human genome. This assembly process is driven by a set of algorithms serially organized into so-called pipelines. The genetic variation within the generated sequences compared to a comparator (reference) sequence is determined in the “variant calling” process. Both assembly and variant calling are bioinformatics processes often designated as the “dry lab” part.

To avoid or minimize incidental findings and the identification of variants of unknown or questionable pathogenicity, we recommend in the “wet lab” the use of mutation-based targeted gene panels rather than the use of whole exome sequencing. The latter would also involve an important issue on data storage, if data are to be stored. The targeted gene panels should be designed in such a way that only the regions of the genome containing the particular mutation(s) are captured and sequenced. After the sequencing effort, bio-informatic tools within the “dry lab” should be used to filter and focus the analysis only on the sequencing data related to the mutations the panel is designed for. Depending on the nature of the mutations that have to be analyzed, different approaches may be necessary. For example, the detection of triplet repeat expansions in the FMR1 gene (Fragile X mental retardation 1 gene - Fragile X syndrome) or intragenic deletions in the DMD (Duchenne muscular dystrophy) gene will require a different technology than mutation-based targeted gene panels. Finally, the panels used for carrier screening should be flexible. Based on the latest information on the pathogenicity of (eventually new) sequence alterations in the studied genes, the panels should include these novel findings.

For many unique and novel mutations, there is no clinical evidence to ascertain pathogenicity or predict the clinical phenotype of an affected offspring. Although bio-informatical tools can be used to estimate the clinical significance of a novel mutation, such predictions are probabilistic by nature and are often prone to error. In line with the goal of enhancing reproductive autonomy of carrier couples, the SHC believes that prospective parents should be provided with accurate, non-questionable and actionable results. To this end, NGS-based carrier screening should be aimed at minimizing the probability of false-positive results or results with unclear clinical significance. As a general approach, we recommend that only clearly pathogenic mutations (Plon et al., 2008 ; Richards et al., 2015) should be routinely identified and reported to patients (class 5 variants - See Table 1). Variants of unknown significance should not be reported and we believe it is more prudent to apply stringent filtering protocols, so that likely pathogenic mutations and variants of unknown significance are not identified. Communication of likely pathogenic mutations should be conditional on the possibility of obtaining evidence to confirm pathogenicity.

Table 1. *Proposed Classification System for Sequence Variants Identified by Genetic Testing (Richards et al., 2015)*

Class	Description	Probability of being pathogenic
5	Definitely pathogenic	>0.99
4	Likely pathogenic	0.95– 0.99
3	Uncertain	0.05– 0.949
2	Likely Not Pathogenic or of Little Clinical Significance	0.001– 0.049
1	Not Pathogenic or of No Clinical Significance	< 0.001

5 Carrier screening: panel development

Carrier screening has been recommended by professional associations in the past for a limited number of conditions. For example, the offer of carrier screening for CF to all women of reproductive age was recommended by the American College of Medical Genetics (Watson et al., 2004), the American College of Obstetricians and Gynaecologists (ACOG, 2011) and the National Society of Genetic Counselors (Langfelder et al., 2014). Additionally, ethnicity-based carrier screening has been recommended in certain populations, such as HbPs in couples of African ancestry (ACOG, 2007) and conditions prevalent among Ashkenazi Jewish population among the Jewish community (Gross et al., 2008 ; ACOG, 2009).

As mentioned by Edwards et al. (2015) “traditional methods of carrier screening generally have focused on conditions that significantly affect quality of life as a result of cognitive or physical disabilities or a requirement for lifelong medical therapies and have a fetal, neonatal, or early childhood-onset and well-defined phenotype”. The development of commercial offers of expanded carrier screening panels has challenged somewhat this point of departure (Borry et al., 2011). Firstly, conditions that have a significant variation in severity, age of onset, expressivity and penetrance were integrated in panels. Secondly, the list of screened disorders considerably varies from company to company, which illustrates the lack of coherent criteria at the moment (Henneman et al., 2016). Thirdly, some conditions for which carrier screening had been actively discouraged for various practical and ethical reasons have been integrated into expanded carrier screening panels. The issues outlined above indicate the need for developing more concrete criteria for the inclusion of disorders in carrier screening, which was also recommended by American College of Medical Genomics: “the proper selection of appropriate disease-causing targets for general population basis carrier screening (i.e. absence of a family history of the disorders) should be developed using clear criteria rather than simply including as many disorders as possible” (Grody et al., 2013).

In order to address the current important heterogeneity of carrier screening panels, and to assist the development of those panels, the SHC started to list criteria that should guide the inclusion of conditions in expanded carrier screening panels. We will discuss hereby (i) severity, (ii) age of onset, (iii) prevalence, (iv) selection of mutations based on clinical significance; (v) treatability.

The SHC also recognizes that stakeholder involvement about those criteria and their potential interpretation is important. As the interpretation of benefits and harms of screening for certain conditions might differ amongst stakeholders, an open interaction between patients and their representatives, as well as with the general public is important.

These criteria are discussed in the following sub-sections.

5.1 Severity

As the main aim of offering carrier screening to couples is enhancing reproductive autonomy, the SHC believes that carrier screening should be performed for conditions that are severe enough to have an impact on reproductive plans. As disorders can vary in clinical expression (clinical variability), this criterion should also be included together with the criterion that aims at integrating mutations with a high pathogenicity and a low variability in expression (see below). This is in line with the following recommendation from the American College of Medical Genomics: “disorders should be of a nature most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction” (Grody et al., 2013). The European Society of Human Genetics also recommended focusing on severe disorders, by giving priority to **“**carrier screening panels that include (a comprehensive set of) severe childhood-onset disorders. Tests should be designed to achieve high clinical validity (clinical sensitivity, negative and positive predictive values) and should have established clinical utility” (Henneman et al., 2016). In a recent joint statement, the American College of Medical Genetics and Genomics, the American College of Obstetricians and Gynecologists, the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine recommended to screen for conditions that are “a health problem that encompasses one or more of the following: (a) cognitive disability, (b) need for surgical or medical intervention, (c) effect on quality of life” (Edwards et al., 2015). Although the SHC recognizes difficulties with defining a “serious condition” (Wertz & Knoppers, 2002), experience shows that at least for some conditions, consensus can be achieved among medical professionals (Lazarin et al., 2014).

The SHC also acknowledges that routine identification of carriers of disorders that are not associated with severe health disability would undermine the goal of carrier screening by putting carrier couples in a position where making the “right” choice is considerably more difficult (Leib et al., 2005). A systematic screening offer for a relatively mild condition such as hemochromatosis (Powell et al., 2016) would from this perspective not be recommended.

5.2 Age of onset

The SHC proposes that expanded carrier screening should focus on conditions that manifest in childhood rather than in adulthood. This recommendation is grounded in the concern that screening for adult-onset recessive conditions will occasionally identify individuals with two mutations who are at risk of developing the disorder themselves (e.g. alfa-1-antitrypsin deficiency).

Although pre-symptomatic identification of individuals who could develop the disorder may offer medical benefits in certain cases, this would represent a significant deviation from the scope of expanded carrier screening (i.e. identification of at-risk couples) and introduce an extra layer of complexity into the process. Furthermore, in those cases where a carrier couple chooses not to alter their reproductive plans and has an affected child, carrier screening for adult-onset disorders becomes presymptomatic testing in children, a practice that has been viewed highly controversial due to the possible violation of the minor's autonomy and the right to self-determination (Borry et al., 2006).

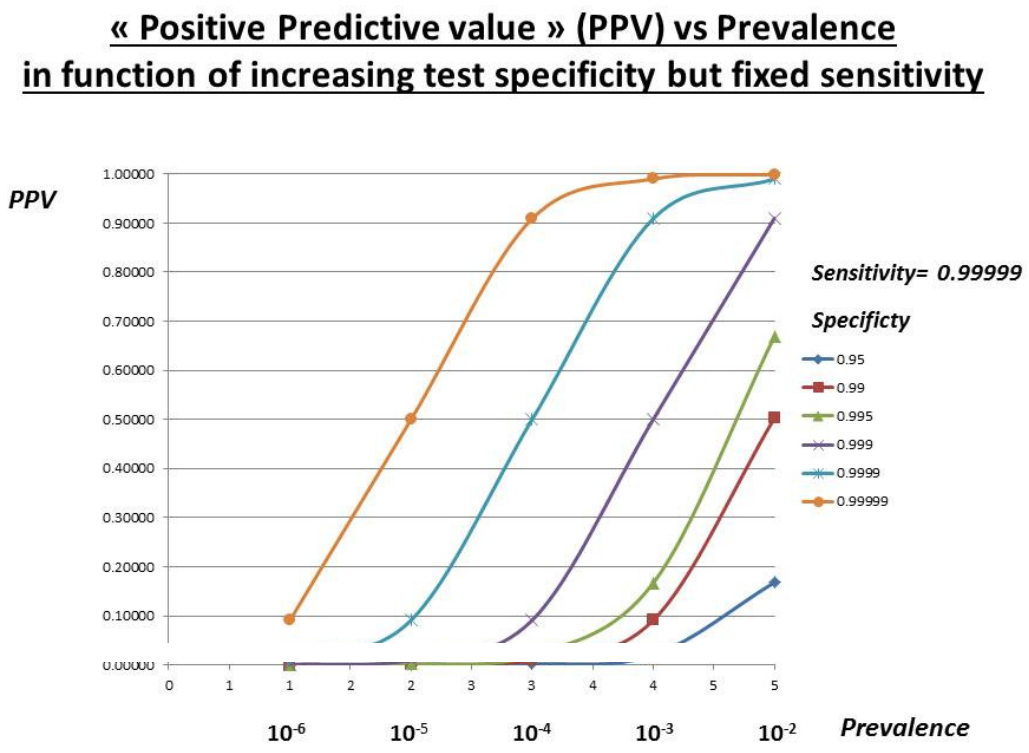
Consequently, the SHC suggests that expanded carrier screening, at the current stage, should be limited to conditions where clinical symptoms appear in childhood. This recommendation is in line with the recent statements from American and European professional organizations, which also discourage screening for disorders predominantly manifesting in adulthood.

5.3 Prevalence

Given a recent report that each person harbors on average 2.8 recessive mutations, there is theoretical utility of voluntary carrier testing in the general populations (Kingsmore, 2012). The broad rationale is the success of general population testing for carrier status of cystic fibrosis [https://www.omim.org/entry/219700 – consulted 24/01/2017].

With the improvements in carrier screening technology such as the use of NGS, it is becoming increasingly simple and inexpensive to integrate additional disorders into screening panels (Lazarin et al., 2012 ; Bell et al., 2011 ; Tanner et al., 2014). Therefore, from a technical point of view, the prevalence *in se* generally should not play a decisive role for its inclusion in a screening panel. Even though the probability of identifying a couple in which both members carry a mutation in a gene for a very rare disorder is extremely low, a population-wide screening for multiple rare disorders may lead to positive test-results in some couples. Especially the specificity of the test and the prevalence of the marker have a major impact on the Positive Predictive Value (PPV), being the proportion of persons with a positive result that is carrier of the disorder. Even slightly lower test specificity results in an increase of the number of false positives, when the mutation is rare in the population. Furthermore, the simultaneous testing of a large number of markers adds to the risk of false positive findings. In figure 1, it is shown that at low prevalence, the PPV of the test with a very high sensitivity and very high specificity drops dramatically when the specificity is somewhat lower.

Figure 1 :



Legend: Demonstration of the impact of the specificity of a test on the Positive Predictive value (PPV) of the test for diseases with different prevalence in a population, when the sensitivity is set at a fixed value (here sensitivity = 0.99999). Prevalence of the disease ranges between 1/100 to 1/ 000 000.

It may be advisable to exclude disorders from the screening when, due to the extremely low prevalence of the disorder, there is insufficient clinical data available on the disorder and its natural history is not well-understood. As Lyman & Moses (2016) clearly state “ideally, the identification of a specific marker of disease vulnerability, such as a molecular or genetic biomarker, would be matched with a specific therapeutic intervention that targets that vulnerability”. There is a strong need to increase the reliability and precision of both the target assay and outcome in order to increase the PPV of the test and the outcome causality when applied in population-based screening. Establishing clinical utility fundamentally depends upon the analytic and clinical validity of the biomarker requiring full documentation of adequate test performance in the laboratory and accurate association of the assay result with the clinical outcomes of interest (Lyman & Moses, 2016).

Establishing clinical utility is still contentious though. Point of discussion are 1°) the degree to which analytic and clinical validity have been established, 2°) what outcomes and improvement in those outcomes constitute meaningful clinical benefit, 3°) what should constitute the comparator setting, and 4°) what level of evidence is needed to establish clinical utility with acceptable analytic and clinical validity” (Lyman & Moses, 2016).

Although randomized controlled trials may establish that an intervention can work in a specific setting, real-world data are often needed to establish that an intervention actually does work and to determine if it has greater value compared with other approaches (Lyman & Moses, 2016).

The impact is particularly pronounced for newly discovered rare disorders, where first patients are only now being identified. Understanding the natural history of a disorder is necessary to ensure that carrier couples can make informed reproductive decisions, based on the disorder's perceived severity and impact on the family.

Therefore, the SHC recommends limiting carrier screening to the conditions whose natural history can be ascertained by reliable and a sufficiently high number of clinical case reports in the literature. In line with ACCE recommendations on Analytic validity, Clinical validity, Clinical utility and associated Ethical, legal and social implications (Burke et al., 2002), it is absolutely necessary to establish an acceptable evidence base about the selection of conditions when offering carrier screening.

5.4 Selection of mutations based on clinical significance

Considering the important reproductive implications of carrier screening, priority should be given to pathogenic mutations with high penetrance and low variable expressivity in order to minimize uncertainty in counseling carrier couples. Moreover, it is important to ensure that the criteria for the selection of mutations reflect the criteria used for the inclusion of disorders. It is essential that for all mutations included in screening, a clearly established genotype-phenotype correlation exists based on multiple clinical case reports, as recommended by professional organizations (Edwards et al., 2015). As genomic knowledge continues to increase rapidly, it is expected that future studies will lend more solid evidence to ascertain pathogenicity and clinical significance of many mutations. As a consequence, some mutations previously thought to be pathogenic can later be reclassified as benign polymorphisms, as has already been the case with some CF-related variants (Rohlfs et al., 2011). In an expanded carrier screening platform for 448 severe recessive disorders, Bell et al. (2011) found that a considerable proportion of purportedly pathogenic mutations in the literature can be common polymorphisms or misannotations. Furthermore, owing to the complex interplay of genetic and environmental factors, it is also possible that some disease-causing mutations may not be pathogenic in certain populations, as also reported by American professional organizations (Golovleva et al., 2010).

Thus as indicated already above, NGS-based carrier screening should minimize the probability of false-positive results or results with unclear clinical significance. Only clearly pathogenic mutations are routinely identified and should be reported to patients (class 5 variants - See Table 1). Variants of unknown significance should not be reported, and communication of likely pathogenic mutations should be conditional on the possibility of obtaining evidence to confirm pathogenicity (Plon et al., 2008 ; Richards et al., 2015).

5.5 Treatability

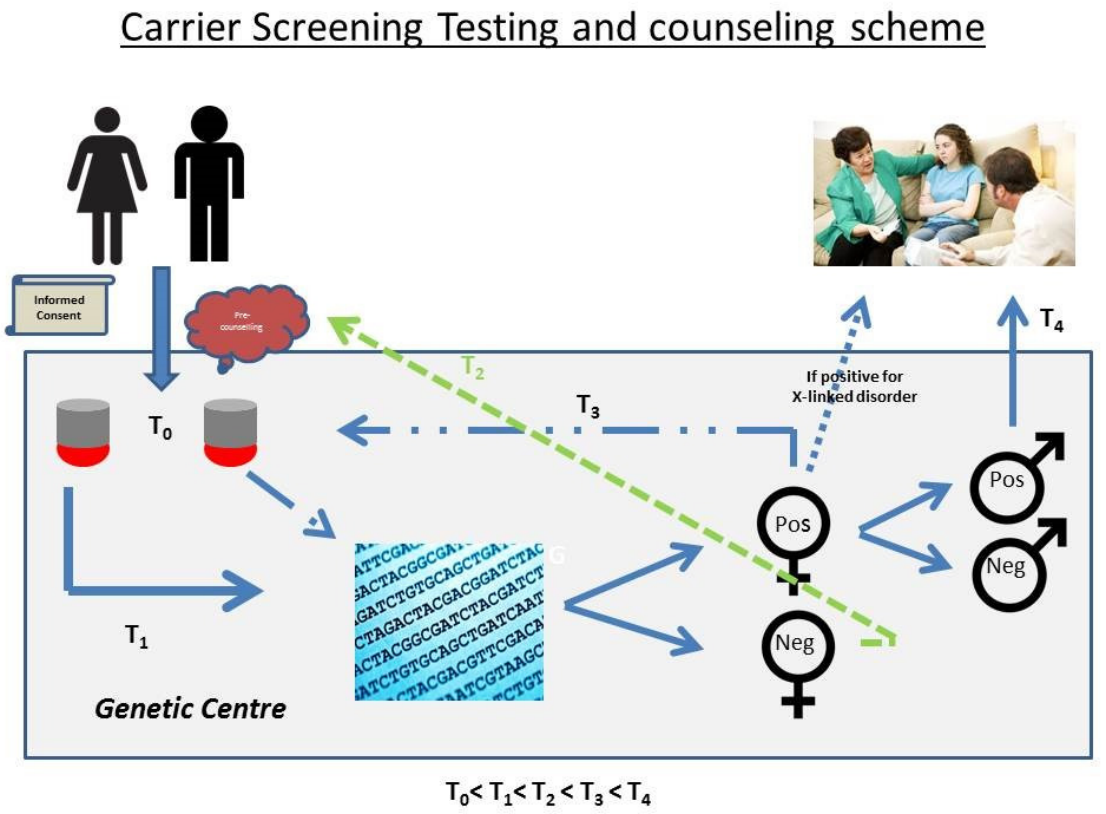
The SHC believes that expanded carrier screening panels should also include serious disorders for which therapeutic interventions exist. An illustrative example is phenylketonuria (PKU), an autosomal recessive metabolic disorder which has a good clinical prognosis, provided that dietary interventions and medical monitoring are initiated during the first weeks of life (MacDonald & Asplin, 2006). Despite the availability of a treatment for PKU, some prospective parents may find the life with an affected child overly burdensome or want to avoid lifelong dietary restriction to their child, and choose to alter their reproductive plans. Furthermore, even when carrier couples accept the possibility of having an affected child with a treatable disorder, awareness of their carrier status may still provide medical benefits, as this could improve the prognosis if the diagnosis can be made earlier. In particular, at-risk couples may undergo prenatal diagnosis and, should an affected pregnancy be identified, make necessary logistical arrangements to prepare for the birth of a child with special health needs (Edwards et al., 2015). The SHC recognizes the particular counseling challenges of carrier screening for serious conditions that might be treatable, as this might generate a mixed message to couples.

6 How to offer carrier screening?

The SHC believes that the most affordable strategy for identifying at-risk couples is sequential screening of both partners. Although at the level of sample collection samples can be collected at the same time from both partners, in this approach, in the lab, initially the sample provided by the female partner will be screened for all autosomal and X-linked recessive disorders included on the screening panel (Edwards et al., 2015).

This would reduce the workload for the diagnostic laboratory as well as minimize costs associated with screening. Reasonably accurate estimates of expected carrier detection rates can be drawn from the study of Lazarin et al. (2012), where an expanded panel of 108 recessive disorders identified 24 % of individuals as carriers in a large ethnically diverse sample of 23 453 individuals. A carrier screening panel developed based on our recommendations would exclude some conditions that were included in the above mentioned offer, resulting in a lower cumulative carrier detection rates. Therefore, if adopting this sequential approach, screening of samples provided by both reproductive partners would be required in a quarter of the cases.

Figure 2:



Legend: Schematic flow of proposed carrier screening testing (T_0 = intake of interested couple; T_1 = CS test of female partner; T_2 = reporting of absence of any carrier mutations in the female partner; T_3 = CS test of male partner; T_4 = reporting of carrier mutation status to the couple).

Ideally, carrier screening should be targeted at couples planning a pregnancy. In order to effectively reach out to this demographic group, the screening program should actively collaborate with healthcare providers, such as gynecologists, fertility centers and general practitioners, who could inform their patients about the carrier screening offer (Nazareth et al., 2015). The SHC recommends that carrier screening should however not be limited to an offer before the pregnancy. This would ensure that those couples who did not have an opportunity to access carrier screening in the preconception period are still given a possibility to determine the potential risks for their child (Edwards et al., 2015 ; Langlois et al., 2015).

As we discuss in this document carrier screening within a reproductive context, the identification of carrier status with the goal to learn about reproductive risks and potentially make reproductive decisions is most valuable within a setting in which both partners are being screened for carrier status. Individual requests for identification of carrier status are from this perspective less useful and do therefore not fall under the present proposal.

To facilitate informed and voluntary participation in carrier screening, all couples and individuals undergoing the procedure should provide a signed informed consent.

As the focus of a screening offer would be on carrier couples, the SHC recommends focusing the reporting of information that is of relevance for reproductive decision-making of the couple. When screening couples, informed consent should indicate that, by default, only carrier status for the same autosomal recessive disorders present in both partners will be communicated. However, as some prospective parents may wish to access their individual test results (Henneman & Ten Kate, 2002), we believe this option should be made available, if explicitly requested. Couples choosing to receive individual results should be explained that screening of the male partner will be performed only in a minority of cases, where the female member is found to be the carrier of an autosomal recessive condition. Therefore, it should be made clear that a negative couple test result does not imply that the male partner is not a carrier of any of the pathogenic variants included on the screening panel.

Couples that are both carriers for the same conditions or the female partner is carrier of an X-linked disorder should be sent to a Center for Medical Genetics for further genetic counseling and follow up.

V REFERENCES

ACOG - American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 78: hemoglobinopathies in pregnancy. Obstetrics and gynecology 2007;109(1):229-37.

ACOG - American College of Obstetricians and Gynecologists. Genetics ACo. ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. Obstetrics and gynecology 2009;114(4):950-53.

ACOG - American College of Obstetricians and Gynecologists. ACOG Committee Opinion No 486: Update on carrier screening for cystic fibrosis. Obstetrics and gynecology 2011;117(4):1028-31.

Angastiniotis MA, Hadjiminas MG. Prevention of thalassaemia in Cyprus. Lancet 1981;1(8216):369-71.

Angastiniotis M, Kyriakidou S, Hadjiminas M. The Cyprus Thalassemia Control Program. Birth Defects Orig Artic Ser 1988;23(5B):417-32.

Axworthy D, Brock DJ, Bobrow M, Marteau TM. Psychological impact of population-based carrier testing for cystic fibrosis: 3-year follow-up. UK Cystic Fibrosis Follow-Up Study Group. Lancet 1996;347(9013):1443-6.

Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, et al. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? BMJ 1993;306(6892):1584-6.

Bekker H, Denniss G, Modell M, Bobrow M, Marteau T. The impact of population based screening for carriers of cystic fibrosis. J Med Genet 1994;31(5):364-8.

Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Sci Transl Med 2011;3(65):65ra4.

Borry P, Stultiens L, Nys H, Cassiman JJ, Dierickx K. Presymptomatic and predictive genetic testing in minors: a systematic review of guidelines and position papers. Clin Genet 2006;70(5):374-81.

Borry P, Clarke A, Dierickx K. Look before you leap. Carrier screening for type 1 Gaucher disease: difficult questions. Eur J Hum Genet 2008;16(2):139-40.

Borry P, Henneman L, Lakeman P, ten Kate LP, Cornel MC, Howard HC. Preconceptional genetic carrier testing and the commercial offer directly-to-consumers. Hum Reprod 2011;26(5):972-7.

Burke W, Atkins D, Gwinn M, Guttmacher A, Haddow J, Lau J, et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. Am J Epidemiol 2002;156(4):311-8.

Cho D, McGowan ML, Metcalfe J, Sharp RR. Expanded carrier screening in reproductive healthcare: perspectives from genetics professionals. Hum Reprod 2013;28(6):1725-30.

Cousens NE, Gaff CL, Metcalfe SA, Delatycki MB. Carrier screening for beta-thalassaemia: a review of international practice. Eur J Hum Genet 2010;18(10):1077-83.

De Wert GM, Dondorp WJ, Knoppers BM. Preconception care and genetic risk: ethical issues. J Community Genet 2012;3(3):221-8.

Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol 2015;125(3):653-62.

Giordano PC, Plancke A, Van Meir CA, Janssen CA, Kok PJ, Van Rooijen-Nijdam IH, et al. Carrier diagnostics and prevention of hemoglobinopathies in early pregnancy in The Netherlands: a pilot study. Prenat Diagn 2006;26(8):719-24.

Golovleva I, Kohn L, Burstedt M, Daiger S, Sandgren O. Mutation spectra in autosomal dominant and recessive retinitis pigmentosa in northern Sweden. Adv Exp Med Biol 2010;664:255-62.

Grinzaid KA, Page PZ, Denton JJ, Ginsberg J. Creation of a National, At-home Model for Ashkenazi Jewish Carrier Screening. J Genet Couns 2015;24(3):381-7.

Grody WW, Cutting GR, Klinger KW, Richards CS, Watson MS, Desnick RJ. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Genet Med 2001;3(2):149-54.

Grody WW, Thompson BH, Gregg AR, Bean LH, Monaghan KG, Schneider A, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med 2013;15(6):482-3.

Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. Genet Med 2008;10(1):54-6.

Gulbis B, Cotton F, Ferster A, Ketelslegers O, Dresse MF, Ronge-Collard E, et al. Neonatal haemoglobinopathy screening in Belgium. J Clin Pathol 2009;62(1):49-52.

Health Council of the Netherlands. Screening: between hope and hype. Hague, the Netherlands 2008.

Henneman L, Ten Kate LP. Preconceptional couple screening for cystic fibrosis carrier status: couples prefer full disclosure of test results. J Med Genet 2002;39(5):E26.

Henneman L, Poppelaars FA, ten Kate LP. Evaluation of cystic fibrosis carrier screening programs according to genetic screening criteria. Genet Med 2002;4(4):241-9.

Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. Eur J Hum Genet 2016;24(6):e1-e12.

Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening: Summary and recommendations of the European Society of Human Genetics. Eur J Hum Genet 2016;24(6):781–783.

Janssens S, De Paepe A, Borry P. Attitudes of health care professionals toward carrier screening for cystic fibrosis. A review of the literature. J Community Genet 2014;5(1):13-29.

Janssens S, Kalokairinou L, Chokoshvili D, et al. Attitudes of cystic fibrosis patients and their parents towards direct-to-consumer genetic testing for carrier status. Personalized Medicine 2015;12(2):99-107.

Keskin A, Turk T, Polat A, Koyuncu H, Saracoglu B. Premarital screening of beta-thalassemia trait in the province of Denizli, Turkey. Acta Haematol 2000;104(1):31-3.

Kingsmore S. Comprehensive carrier screening and molecular diagnostic testing for recessive childhood diseases. PLoS Curr 2012:e4f9877ab8ffa9.

Lakeman P, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society. Genet Med 2006;8(8):502-9.

Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med 2008;10(11):820-30.

Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Preconceptional ancestry-based carrier couple screening for cystic fibrosis and haemoglobinopathies: what determines the intention to participate or not and actual participation? Eur J Hum Genet 2009;17(8):999-1009.

Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med 2013;15(3):178-86.

Langfelder-Schwind E, Karczeski B, Strecker MN, Redman J, Sugarman EA, Zaleski C, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns 2014;23(1):5-15.

Langlois S, Wilson RD. Carrier screening for genetic disorders in individuals of Ashkenazi Jewish descent. J Obstet Gynaecol Can 2006;28(4):324-43.

Langlois S, Benn P, Wilkins-Haug L. Current controversies in prenatal diagnosis 4: pre-conception expanded carrier screening should replace all current prenatal screening for specific single gene disorders. Prenat Diagn 2015;35(1):23-8.

Leib JR, Gollust SE, Hull SC, Wilfond BS. Carrier screening panels for Ashkenazi Jews: is more better? Genet Med 2005;7(3):185-90.

Lena-Russo D, Badens C, Aubinaud M, Merono F, Paolasso C, Martini N, et al. Outcome of a school screening programme for carriers of haemoglobin disease. J Med Screen 2002;9(2):67-9.

Lyman GH, Moses HL. Biomarker Tests for Molecularly Targeted Therapies: Laying the Foundation and Fulfilling the Dream. J Clin Oncol 2016;34(17):2061-6.

MacDonald A, Asplin D. Phenylketonuria: practical dietary management. J Fam Health Care 2006;16(3):83-5.

Markel H. The stigma of disease: implications of genetic screening. Am J Med 1992;93(2):209-15.

McAllister M, Moldovan R, Paneque M, Skirton H. The need to develop an evidence base for genetic counselling in Europe. Eur J Hum Genet 2016;24(4):504-5.

Nazareth SB, Lazarin GA, Goldberg JD. Changing trends in carrier screening for genetic disease in the United States. Prenat Diagn 2015;35(10):931-5.

NHS - National Health Service. NHS Sickle Cell &Thalassaemia Screening Programme. Standards for the linked Antenatal and Newborn Screening Programme 2011. Internet: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/402208/Standards2ndEdition__1_.pdf

Payne Y, Williams M, Cheadle J, Stott NC, Rowlands M, Shickle D, et al. Carrier screening for cystic fibrosis in primary care: evaluation of a project in South Wales. The South Wales Cystic Fibrosis Carrier Screening Research Team. Clin Genet 1997;51(3):153-63.

Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat 2008;29(11):1282-91.

Poppelaars FA, Henneman L, Ader HJ, Cornel MC, Hermens RP, van der Wal G, et al. How should preconceptional cystic fibrosis carrier screening be provided? Opinions of potential providers and the target population. Community Genet 2003;6(3):157-65.

Poppelaars FA, van der Wal G, Braspenning JC, Cornel MC, Henneman L, Langendam MW, et al. Possibilities and barriers in the implementation of a preconceptional screening programme for cystic fibrosis carriers: a focus group study. Public Health 2003;117(6):396-403.

Poppelaars FA, Ader HJ, Cornel MC, Henneman L, Hermens RP, van der Wal G, et al. Attitudes of potential providers towards preconceptional cystic fibrosis carrier screening. J Genet Couns 2004;13(1):31-44.

Poppelaars FA, Henneman L, Ader HJ, Cornel MC, Hermens RP, van der Wal G, et al. Preconceptional cystic fibrosis carrier screening: attitudes and intentions of the target population. Genet Test 2004;8(2):80-9.

Poppelaars FA, Cornel MC, Ten Kate LP. Current practice and future interest of GPs and prospective parents in pre-conception care in The Netherlands. Fam Pract 2004;21(3):307-9.

Powell LW, Seckington RC, Deugnier Y. Haemochromatosis. Lancet 2016;388(10045):706-16.

Raz AE, Vizner Y. Carrier matching and collective socialization in community genetics: Dor Yeshorim and the reinforcement of stigma. Soc Sci Med 2008;67(9):1361-9.
Raz AE. Can population-based carrier screening be left to the community? J Genet Couns 2009;18(2):114-8.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-24.

Rohlfs EM, Zhou Z, Heim RA, Nagan N, Rosenblum LS, Flynn K, et al. Cystic fibrosis carrier testing in an ethnically diverse US population. Clin Chem 2011;57(6):841-8.

Scriver CR. Community genetics and dignity in diversity in the Quebec Network of Genetic Medicine. Community Genet 2006;9(3):142-52.

Tanner AK, Valencia CA, Rhodenizer D, Espirages M, Da Silva C, Borsuk L, et al. Development and performance of a comprehensive targeted sequencing assay for pan-ethnic screening of carrier status. J Mol Diagn 2014;16(3):350-60.

Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med 2004;6(5):387-91.

Wertz DC, Knoppers BM. Serious genetic disorders: can or should they be defined? Am J Med Genet 2002;108(1):29-35.

Zeesman S, Clow CL, Cartier L, Scriver CR. A private view of heterozygosity: eight-year follow-up study on carriers of the Tay-Sachs gene detected by high school screening in Montreal. Am J Med Genet 1984;18(4):769-78.

Zlotogora J, Meiner V. Ashkenazi carrier screening for reproductive planning: is this what we planned for? Genet Med 2016;18(5):529.

VI COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Herman VAN OYEN**.

BORRY Pascal	Biomedical Ethics	KULeuven
CASSIMAN Jean-Jacques	Human genetics	KULeuven
HULSTAERT Frank	Medecine	KCE
LIEBAERS Ingeborg	Medical genetics	VUB
MORTIER Geert	Medical genetics	UZA
PEETERS Hilde	Medical genetics	UZLeuven
VAN DEN BULCKE Marc	Epidemiology, Public Health Genomics	WIV-ISP
VAN NEROM Anne	in vitro diagnostics	WIV-ISP
VAN OYEN Herman	Epidemiology	WIV-ISP
VERELLEN-DUMOULIN Christine	Medical genetics	IPG

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 40 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.shc-belgium.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.belgium.be.