



AVIS DU CONSEIL SUPERIEUR DE LA SANTE N° 9240

Dépistage génétique généralisé en contexte de procréation. Vers une mise en œuvre responsable dans le système des soins de santé

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.

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I INTRODUCTION ET QUESTION

Le dépistage en population vise à identifier les porteurs « en bonne santé » d'une maladie récessive alors qu'à priori, ceux-ci ne présentent aucun risque accru sur la base de leurs antécédents familiaux. Leur risque d'être porteur est lié à la prévalence de la maladie dans la population. Une maladie autosomique récessive se manifestera à un âge précoce ou plus avancé en cas de mutation des deux copies (allèles) d'un gène particulier. Les porteurs d'un tel allèle muté sont en bonne santé. En l'absence d'antécédents familiaux et de tests, ces personnes ignorent qu'elles sont porteuses d'une mutation. Lorsque deux porteurs d'une mutation du même gène désirent une grossesse, le risque que leur enfant soit atteint s'élève à 1/4 et si l'enfant naît en bonne santé, le risque qu'il soit porteur est de 2/3.

Une maladie récessive liée à l'X est typiquement observée chez les garçons ou les hommes, tandis que les femmes sont généralement des porteuses saines. Cette situation s'explique par le fait que les hommes ne possèdent qu'un seul chromosome X et, par conséquent, une seule copie (allèle) de chaque gène lié à l'X. Les femmes possèdent deux chromosomes X et donc deux copies (allèles) de chaque gène lié à l'X.

¹ Le Conseil se réserve le droit de pouvoir apporter, à tout moment, des corrections typographiques mineures à ce document. Par contre, les corrections de sens sont d'office reprises dans un erratum et donnent lieu à une nouvelle version de l'avis.

Lorsqu'une femme est porteuse d'un allèle muté, elle sera généralement en bonne santé, bien que des exceptions existent. En revanche, le fait qu'elle soit porteuse signifie que le risque que ses fils soient atteints s'élève à 1/2. De plus, et dans l'hypothèse où son conjoint est en bonne santé, le risque que ses filles soient elles-aussi porteuses s'élève également à 1/2. Les raisons pour lesquelles certaines femmes porteuses peuvent être symptomatiques, souvent à un âge plus avancé, sont variables et les faits observables doivent dès lors être pris en compte lorsqu'un dépistage est proposé.

Au total, plus de 1 300 maladies récessives légères ou graves sont connues à l'heure actuelle. Elles affectent 2 à 3 enfants/1 000 et signifient que 1 à 2 % des couples sont à risque. Dans une étude récente qui portait sur un échantillon diversifié sur le plan ethnique et composé de 23 453 individus, 24 % de ces derniers se sont avérés être porteurs d'au moins une parmi 108 différentes maladies monogéniques (Lazarin et al., 2012).

Mots clés et MeSH *descriptor terms*²

MeSH terms*	Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Genetic Testing / Genetic screening	Genetic Testing / Genetic screening	Erfelijkheidstests/Erfelijkheids onderzoek	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

² Le Conseil tient à préciser que les termes MeSH et mots-clés sont utilisés à des fins de référencement et de définition aisés du scope de l'avis. Pour de plus amples informations, voir le chapitre « méthodologie ».

II CONCLUSION ET RECOMMANDATIONS

Tout d'abord, le Conseil supérieur de la santé (CSS) considère qu'il peut être avantageux de connaître le statut de porteur d'une personne dans un contexte de procréation. Cette connaissance permet d'identifier les risques liés à la procréation chez des couples pour lesquels il n'existe à priori aucun risque familial connu de maladies autosomiques récessives ou liées à l'X, ce qui permet d'accroître les options en matière de procréation.

L'identification du statut de porteur dans le but de connaître les risques liés à la procréation et, le cas échéant, de prendre des décisions en matière de procréation, est particulièrement utile dans un contexte dans lequel un dépistage est réalisé chez les deux conjoints pour déterminer s'ils sont porteurs d'une telle maladie. Les couples qui sont suivis dans un milieu de soins tertiaires pour des problèmes de fertilité ou pour une maladie génétique connue pourraient également bénéficier de l'identification d'autres risques génétiques susceptibles d'affecter leurs enfants.

Le Conseil est conscient que l'identification du statut de porteur d'un individu en bonne santé peut impliquer des questions éthiques et juridiques importantes qui doivent être envisagées dans le contexte plus large de l'utilisation de données génomiques/génétiques dans le cadre de la santé individuelle et publique. Le Conseil supérieur de la santé recommande de solliciter l'avis du Comité consultatif de bioéthique.

Deuxièmement, le CSS considère que le dépistage génétique généralisé devrait être proposé avant la conception. En effet, une telle démarche permet d'accroître les options en matière de procréation alors que les contraintes temporelles sont moindres, ce qui génère moins de détresse émotionnelle que lorsque le test est réalisé en cours de grossesse. Néanmoins, cela ne signifie pas que le dépistage génétique doit être exclu pendant la grossesse, mais ce point sort du cadre du présent avis.

Troisièmement, le CSS considère que les mutations et troubles repris dans les panels de dépistage génétique devraient être sélectionnés sur la base de critères spécifiques (I. gravité, II. âge à l'apparition de la maladie, III. prévalence, IV. sélection de mutations sur la base de leur importance clinique, V. existence d'un traitement). Étant donné que l'objectif principal de proposer un dépistage génétique aux couples est de renforcer leur autonomie en matière de procréation, le CSS estime que le dépistage génétique doit être réalisé pour des troubles suffisamment graves pour justifier une adaptation des projets en matière de procréation. Le CSS avance que le dépistage génétique généralisé devrait se concentrer sur les troubles qui se manifestent dans la petite enfance plutôt qu'à l'âge adulte. Il recommande par ailleurs de limiter le dépistage génétique aux troubles dont l'évolution naturelle est étayée par des rapports de cas cliniques fiables et disponibles en nombre suffisamment élevé dans la littérature

Compte tenu des importantes implications du dépistage génétique en termes de procréation, le CSS estime que la priorité doit être accordée aux mutations pathogènes à forte pénétrance et à faible expression variable afin de réduire à un minimum les incertitudes lors de l'accompagnement des couples porteurs. Selon le CSS, les panels de dépistage génétique généralisé devraient également comprendre des troubles graves pour lesquels des interventions thérapeutiques existent, lorsque le traitement peut générer une importante charge physique, émotionnelle ou financière.

Quatrièmement, les professionnels de la santé tels que les gynécologues et les médecins généralistes, compte tenu de leur rôle dans l'orientation des femmes enceintes ou des familles ayant un projet de grossesse, occupent une place privilégiée pour les informer quant au dépistage génétique ou assurer le suivi des demandes de dépistage génétique. Les couples dont le test s'est avéré positif (soit les deux sont porteurs du même trouble autosomique récessif ou la conjointe est porteuse d'un trouble lié à l'X) doivent être orientés vers un Centre de génétique médicale pour un conseil génétique et un suivi.

Cinquièmement, le CSS estime que la stratégie la plus abordable pour identifier les couples à risque consiste à réaliser le dépistage chez les deux conjoints. Les échantillons sont prélevés chez les deux conjoints en même temps. Afin de limiter les coûts, l'échantillon fourni par la conjointe pourrait être analysé dans un premier temps, afin de dépister tous les troubles autosomiques et liés à l'X récessifs inclus dans le panel de dépistage. L'échantillon du conjoint ne devra être analysé que si une mutation responsable d'une maladie est identifiée chez sa conjointe.

Sixièmement, le dépistage génétique implique une information des personnes chez lesquelles il est réalisé, ainsi que leur consentement, comme toute autre intervention médicale. Étant donné que les panels de dépistage génétique généralisés comprennent un large éventail d'affections, les informations préalables au dépistage et le consentement éclairé doivent expliquer l'objectif, le concept et les implications du dépistage génétique, ainsi que ses avantages et inconvénients. Des informations sur les différents troubles doivent être disponibles. Compte tenu du fait que l'offre de dépistage génétique se concentrerait sur les couples porteurs, le CSS recommande de cibler le rapportage des informations sur les éléments pertinents pour la prise de décision du couple en matière de procréation.

Un septième point est que le CSS est également conscient de la nécessité d'impliquer les parties concernées par le dépistage génétique. Des forums citoyens sur le sujet (à l'instar de ceux organisés par la Fondation Roi Baudouin³) peuvent contribuer à un débat public sur le dépistage génétique.

Enfin, le CSS recommande une mise en œuvre par étapes du dépistage génétique, car l'instauration du dépistage génétique à titre de choix en matière de procréation peut impliquer une adaptation non négligeable des pratiques et services actuels, voire même nécessiter des services d'un type nouveau. Une étude pilote constitue le meilleur choix pour la première étape de cette mise en œuvre, dans laquelle devraient, dans un premier temps, être abordés les aspects éthiques et juridiques liés à l'offre de dépistage génétique, tout en cherchant à intégrer le sujet dans un contexte plus large de l'utilisation des informations génomiques/génétiques au niveau de la santé individuelle et publique.

³ Les statuts de la Fondation Roi Baudouin ont été publiés pour la première fois dans les annexes du *Moniteur belge - Belgisch Staatsblad* du 31 décembre 1975.

L'étude pilote devrait : 1) être gérée de manière centralisée et prévoir un enregistrement à l'échelle de la population, y compris la possibilité d'une analyse des résultats (à long terme) ; (2) impliquer toutes les principales parties concernées, y compris, mais pas seulement, les centres de génétique, les autorités responsables et les organisations de patients ; (3) élaborer des lignes directrices techniques pour le séquençage de prochaine génération (NGS) dans le cadre du dépistage génétique généralisé, y compris un plan directeur pour la gestion des données, le stockage des données et l'accessibilité à diverses fins, y compris la recherche ; (4) mettre au point un panel de dépistage génétique sur la base des critères développés ci-dessus ; (5) élaborer des documents d'information et des séances d'information pour les professionnels de la santé impliqués dans le projet pilote ; (6) formuler des protocoles de laboratoire et des stratégies d'accompagnement pour les porteurs et les couples porteurs ; (7) étudier les coûts immédiats et en aval liés à l'offre de dépistage, ainsi que l'impact psychologique et social d'une offre de dépistage génétique.

L'étude pilote devrait permettre d'aborder les questions suivantes : Comment traiter les questions juridiques, éthiques et de vie privée ? Quels sont les troubles les plus opportuns à inclure dans le dépistage génétique ? Quel est le niveau d'intérêt et de participation de la population cible ? Quelle est la meilleure façon d'organiser le conseil préconceptionnel (qui informe qui, sur quoi, quand) ? Quelles sont les exigences de performance minimales pour réaliser des tests NGS au niveau de la population générale ? Quels sont les modèles optimaux pour une telle initiative à l'échelle de la population ? Quel sera l'impact économique ?

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	<i>In vitro</i> 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 & Hadjiminias, 1981 ; Angastiniotis et al., 1988 ; Zeesman et al., 1984 ; Sriver, 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 (Axworth 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 being 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.

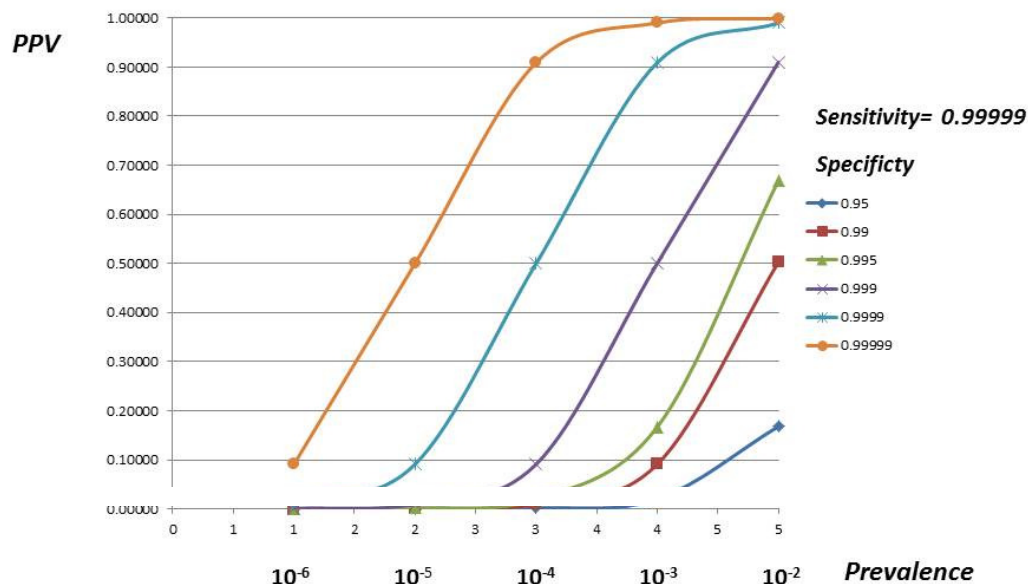
5.3 Prevalence

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 :

« Positive Predictive value » (PPV) vs Prevalence
in function of increasing test specificity but fixed sensitivity



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 (Rohlf's 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.

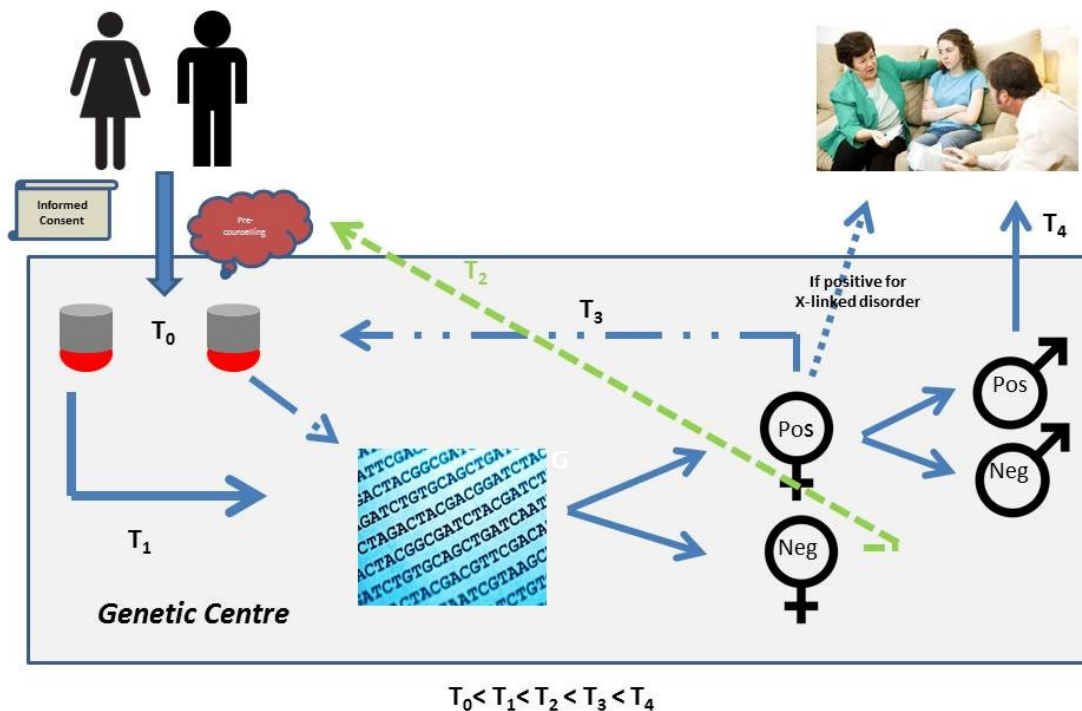
6 How to offer carrier screening?

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:

Carrier Screening Testing and counseling scheme



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.

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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

Au sujet du Conseil Supérieur de la Santé (CSS)

Le Conseil Supérieur de la Santé est un organe d'avis fédéral dont le secrétariat est assuré par le Service Fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement. Il a été fondé en 1849 et rend des avis scientifiques relatifs à la santé publique aux ministres de la Santé publique et de l'Environnement, à leurs administrations et à quelques agences. Ces avis sont émis sur demande ou d'initiative. Le CSS s'efforce d'indiquer aux décideurs politiques la voie à suivre en matière de santé publique sur base des connaissances scientifiques les plus récentes.

Outre son secrétariat interne composé d'environ 25 collaborateurs, le Conseil fait appel à un large réseau de plus de 500 experts (professeurs d'université, collaborateurs d'institutions scientifiques, acteurs de terrain, etc.), parmi lesquels 300 sont nommés par arrêté royal au titre d'expert du Conseil. Les experts se réunissent au sein de groupes de travail pluridisciplinaires afin d'élaborer les avis.

En tant qu'organe officiel, le Conseil Supérieur de la Santé estime fondamental de garantir la neutralité et l'impartialité des avis scientifiques qu'il délivre. A cette fin, il s'est doté d'une structure, de règles et de procédures permettant de répondre efficacement à ces besoins et ce, à chaque étape du cheminement des avis. Les étapes clé dans cette matière sont l'analyse préalable de la demande, la désignation des experts au sein des groupes de travail, l'application d'un système de gestion des conflits d'intérêts potentiels (reposant sur des déclarations d'intérêt, un examen des conflits possibles, et une Commission de Déontologie) et la validation finale des avis par le Collège (organe décisionnel du CSS, constitué de 40 membres issus du pool des experts nommés). Cet ensemble cohérent doit permettre la délivrance d'avis basés sur l'expertise scientifique la plus pointue disponible et ce, dans la plus grande impartialité possible.

Après validation par le Collège, les avis sont transmis au requérant et au ministre de la Santé publique et sont rendus publics sur le site internet (www.css-hgr.be). Un certain nombre d'entre eux sont en outre communiqués à la presse et aux groupes cibles concernés (professionnels du secteur des soins de santé, universités, monde politique, associations de consommateurs, etc.).

Si vous souhaitez rester informé des activités et publications du CSS, vous pouvez envoyer un mail à l'adresse suivante : info.hgr-css@health.belgium.be.