Editorial

A higher impact of less specific preconception carrier screening: a plea for a "one size fits all" approach?

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Introduction

When an autosomal recessive disorder is diagnosed in a child, this is often the first moment that parents find out that both of them are carriers of the same disorder. If they ask: "Could we have known beforehand that both of us are carriers of this disorder?", the theoretical answer is "yes", but the practical answer is often "no", since carrier screening is not offered in the health care system in many places around the world. Yet, although these disorders are hereditary, most children with autosomal recessive disorders are born in families with a negative family history of the disease, and carrier screening would be the only effective strategy to inform couples of their risk before the birth of an affected child.

Implementation of carrier screening in the last decades, where available, often was ancestry based, such as Tay-Sachs carrier screening in Ashkenazi Jewish populations, and haemoglobinopathy (thalassemia and sickle cell disease) screening in people of Mediterranean or African descent (1,2). Initially, cheap testing of one enzyme or one protein was feasible (hexosaminidase in Tay Sachs disease, hemoglobin in sickle cell disease and thalassemia). Thus, carrier screening of large numbers of parents-to-be became possible, but in these early days screening was ancestry based. Target groups were "high risk" groups. Technical developments increasingly made it possible to investigate DNA for a larger number of diseases for a reasonable price. Currently carrier screening is commercially available independent of ancestry (expanded, panethnic, universal). If the same test is offered to all couples, independent of ancestry, a "one size fits all" offer may apply: all clients are tested for a large number of disorders, without tailoring the test to the specific risk of the population. While technical possibilities increased, and prices of DNA testing dropped, some professional organizations, especially in the United States of America, developed guidelines on carrier testing, often starting from ancestry-based testing, and gradually increasing the target group and simultaneously increasing the number of conditions to screen for.

The aim

When both partners are identified as carriers of the same autosomal recessive disease, they have a one in four risk in each pregnancy of having a child affected by this disease. In each pregnancy the chance to have a healthy child is 0.75. Couples often choose to have more than one child. The chance that N children of a carrier couple are healthy is 0.75^N. The chance that a couple with N children has at least one affected child is $1–0.75^N$. For a couple with for example three children the risk that at least one of the three children is affected is 58%.

If partners know that they both are carriers of the same autosomal recessive disorder before getting pregnant, several reproductive choices are available. The first choice is whether or not to accept the risk. If the couple wants to avoid the risk, the second choice is whether or not to avoid pregnancy (and either to have no children or to adopt children). However, if they want to have a child

that is biologically related to at least one of them, and at the same time want avoid the birth of an affected infant, they can choose to undergo prenatal testing and terminate the pregnancy if the foetus would be affected, they can get pregnant using preimplantation genetic diagnosis and embryo selection, or they can use donor gametes of a non-carrier donor. In some cultures, the choice of a partner may be altered to avoid the marriage of a carrier couple. All of these choices imply ethically sensitive issues, for which values may differ between individuals and between cultures. Because of this, in most Western countries there is consensus that the aim of reproductive screening, including carrier screening, should be to enhance reproductive autonomy and enable meaningful reproductive choices (3). From a public health perspective one could argue that reducing the burden of disease is the aim, which is reflected in scientific literature reporting the success of carrier screening programs by describing the reduced disease prevalence. Conversely, interventions to enhance informed choices in screening programs are rarely reported (4). If enhanced informed choice is the aim, the reduced prevalence can be the consequence. The risk of defining the reduced prevalence as the primary aim is that couples may be forced or may feel forced to make choices that are not in line with their values.

A higher impact of less specific preconception carrier screening

In the *JAMA* of August 16th, 2016, Haque and colleagues present a retrospective modelling study of results from 346,790 expanded carrier screenings (5). Five of the six authors belong to the staff of Counsyl™, a commercial company that offers carrier screening, including over 90 serious conditions. The authors have calculated the potential impact of their panethnic expanded carrier screening, the FamilyPrepScreen, in terms of the proportion of foetuses that would be affected by one of the single gene disorders on their panel (5). They compare the impact of their panel to the proportion of foetuses affected by disorders in professional USA guidelines-based screening panels. Out of 430,584 patients screened, a total of 346,790 individuals underwent carrier screening for routine reasons in 2012–2015. People with a positive family history (n=11,052), consanguinity (n=741) or fertility problems (n=28,716) were excluded from this number. These participating individuals self-reported their ancestry or ethnicity.

For couples with the same racial/ethnic category, the probability of a hypothetical foetus being affected and homozygous or compound heterozygous for pathogenic variants for a given condition was calculated and presented. African or African-American couples were predicted to have a severe haemoglobinopathy risk of 305.9 in 100,000 pregnancies. Ashkenazi Jewish couples would have a 131 in 100,000 pregnancies risk for one of the diseases recommended for them by the American College of Medical Genetics. Including the >90 disorders on the panel would identify more hypothetical foetuses at risk for severe or profound phenotypes than did testing based on current screening guidelines. The difference was relatively small for African or African-American couples, but for couples of other ethnicities, the cumulative risk of severe and profound conditions outside the guideline recommendations was greater than the risk identified by guideline based panels. In epidemiological terms, the population attributable fraction (PAF) of the expanded screening test was more than double the PAF for guideline based panels for most ethnic groups. Thus a "one size fits all" approach would have a higher impact than tailored testing offers according to current guidelines.

What does this article not tell us?

Having developed a test that identifies a high number of hypothetical foetuses at risk for severe or profound phenotypes is a major achievement. Also other companies and institutions have developed expanded carrier screening offers, and research studies are ongoing. The higher impact is likely to apply for many expanded universal tests. When offering carrier screening to a target population in a screening program, it is however only one element that is relevant for responsible implementation. Questions that remain include whether the couples tested felt that they had made informed decisions, which groups have been tested and for which couples the test was not accessible, why expanded carrier screening is not available in many health care systems globally, and how the cost of expanded carrier screening relates to other health care expenditure.

Is more better?

Whether or not an expanded universal test is best for a specific couple depends on their specific risk factors. If founder mutations from their ancestral population are not part of the panel, especially if they are consanguineous, other tests may be more appropriate. For many couples however,

expanded tests indeed seem to have a high detection rate. Partners considering to start a family and to optimize their information to be prepared to make reproductive choices probably want to be informed about risks for severe foetal conditions in a broad sense. As compared to single gene screening or guideline based panels, an expanded universal carrier test would maximise opportunities for autonomous reproductive choice by informing prospective parents about a much wider array of reproductive risks (6). It could provide equity of access to carrier testing services, also for couples of mixed ancestry or from minority populations less covered by guidelines. Finally it could reduce the risk of stigmatization, since in the end all of us will turn out to be carriers of some disorder. Concerns also exist however. Stakeholders in the Netherlands argued that it should not be taken for granted that people without an a priori increased carrier risk are open to the idea of expanded carrier screening (6). These couples do not feel urgency. Part of the problem may be the lack of information available to the general public as well as health care professionals. Genetic education and information, including the diversity of diseases on the expanded panel, is needed. However, the provision of more genetic risk information does not automatically translate into more opportunities for meaningful reproductive choice. Information overload may undermine informed choices as much as too little information. We need to understand better how couples make informed reproductive decisions, and what level of detail is needed for them. Layered information may help each couple to find their own way in deciding what they want to know—starting from a general explanation of severe childhood conditions and carrier screening, adding possibilities to find more information or get more counseling where needed. Finally the societal aspect of "reproductive responsibility", the care for people with a disability and the possibility to reinforce disability-based stigmatization need attention. Would expanded carrier screening lead to a world that risks solidarity or a world where at the same time care for affected individuals and tolerance is guaranteed? A free choice of prospective parents is only possible if the future care of affected individuals is not at stake.

Conclusions

Expanded universal panethnic preconception carrier testing may identify a higher proportion of couples at risk of serious autosomal recessive conditions than tailored testing offers, following professional guidelines. Whether this leads to enhanced reproductive autonomy and will enable meaningful reproductive choices, thus contributing to the aim of preconception carrier screening, is an issue for further research.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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