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Opinion

Responsible Implementation of Expanded Screening Programs for Genetic Diseases at the Beginning of Life

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Abstract:

Technology makes it possible to expand many of the current screening programs. Initiatives for preconception screening of carrier status of recessive diseases, prenatal screening of aneuploidies and neonatal screening were initially undertaken by targeting one or at most, a few, conditions. Tandem mass spectrometry and genomic technologies, such as sequencing and panel testing, make it possible to increase the scope of these programs to include more disorders or markers. While inclusion of a larger number of conditions with similar characteristics may lead to greater success in the goal of screening, the inclusion of non-similar conditions raises new questions. Informed decision-making requires adequate and relevant information, which may be a challenge if many more conditions are added, especially for non-similar conditions. The goals of offering health benefits and greater reproductive choice may become blurred; thus, clear communication of the aims of screening is imperative. Screening for more conditions risks increasing the number of false positives. Evaluation of the pros and cons of screening programs, including the cost-effectiveness, is needed to ascertain the potential of expanded screening. Targeted analysis

based on careful evaluation of these pros and cons combined with the availability of new technologies represents an important opportunity to devise expanded screening programs.

Keywords
Expanded screening; panel; prenatal screening; neonatal screening; preconception carrier screening; pre-implantation genetic screening

1. Introduction

While many patients seek healthcare for a specific reason, screening is typically organized as an invitation-only program implemented by healthcare professionals. The objective of such initiatives is to identify the group of "at risk" individuals among the invited population for subsequent diagnostic testing to confirm, or exclude, the existence of the target condition. All couples who could become pregnant or are planning a pregnancy are the target group in preconception carrier screening, while all pregnant women are the target group in prenatal screening and all newborns are the target group in neonatal screening. In cases of fertility problems or high genetic risk, a couple receiving in vitro fertilization treatment can also be offered pre-implantation genetic screening (PGS), where embryos are investigated to exclude aneuploidy before choosing the embryo(s) for implantation. The aims of screening can be two-fold: on the one hand, the aim is to identify treatable conditions early, thus avoiding irreparable damage to health, while on the other hand, the aim is to enable women or couples to make informed reproductive choices. These different aims may influence the protocols used to invite participants and organize the informed consent. While prenatal screening for Rhesus blood groups and neonatal screening are performed almost routinely, prenatal screening for aneuploidies where the option to terminate a pregnancy may be at stake, demands more extensive counseling to allow informed decision-making.

The rapid technological developments that have occurred in these fields over the last decade have led to the expansion of several screening programs. This has advantages (identification of a greater number of treatable conditions) but also disadvantages (a potential for less informed decision-making). In this opinion article, we will discuss issues that require careful balancing of pros of cons by policy makers. Similar issues associated with the implementation of screening programs can also be encountered when healthy people are invited to buy a product to assess their risk or to participate in a risk assessment on an individual basis; these settings will not be discussed in this article. Instead, we focus on expanded population screening programs in the beginning of life. Some issues relevant for responsible implementation appear in more than one screening program setting. In this article, we follow the experience of a couple during pregnancy, starting from preconception carrier screening, moving via pre-implantation genetic diagnosis (PGD) and prenatal screening to neonatal screening. No ethics approval was sought for this work, as we do not report any original research, but only provide the opinion of the author on current developments with reference to earlier publications.

2. Preconception Carrier Screening

When a child is born with a serious autosomal recessive disorder, parents often ask whether they could have avoided this situation. Often the practical answer is "no", since preconception carrier screening is not routinely offered in many healthcare settings. However, such conditions can indeed be identified if preconception carrier testing is offered, and parents-to-be can be tested for carrier status. Early examples of carrier screening programs include testing for thalassemias in some Mediterranean regions [1] and testing for Tay Sachs disease in populations of Ashkenazi Jewish ancestry [2, 3]. If both partners are carriers of the same autosomal recessive disorder, then each pregnancy is associated with a 25% risk of an affected infant. Since many couples plan to have more than one child, the risk of a couple having at least one child affected with the condition is $1-(0.75)^N$, where N is the number of pregnancies. For two pregnancies, the risk of at least one affected pregnancy is 44%, and 58% for three pregnancies. There are, in theory, several options for family planning available to carrier couples: accept the risk, avoid pregnancy, adopt children, use prenatal diagnosis and selective termination of pregnancy, use embryo selection after in-vitro-fertilization (pre-implantation genetic diagnosis, PGD), use a donor sperm, or find another partner. Different people choose different options. The Dor Yeshorim program for orthodox Jewish people tests potential partners before they have a relationship, so that a carrier couple can be avoided [2]. In Cyprus, couples are required to undergo carrier testing before marriage, but can choose how they proceed with their plans to have a family [1].

After these early preconception carrier screening programs, techniques became available to screen for a larger number of disorders. A panel test for four severe childhood conditions was developed in a specific Dutch founder population [4] and panel tests designed for Jewish populations now include more than 10 disorders. Commercial providers have started offering panel tests for more than 100 diseases [5]. Expanded carrier tests offer the advantage that a larger proportion of potentially affected fetuses can be recognized [5, 6]. A disadvantage, however, is that the person tested does not know the conditions that they can be tested for; therefore, the perceived sense of urgency may be limited and informed decision-making more difficult [7, 8]. Furthermore, founder mutations that occur in a specific population may not be included in the expanded test [9]. In obstetrics, especially in fertility clinics where people are seen before a pregnancy, the question is whether and what to offer in terms of carrier testing. Several versions of the Guidelines of the American College of Obstetricians and Gynecologists have been published, starting from ancestry-based testing of a small number of genes, to more recent guidelines recommending that (preconception) carrier screening should not be limited to people of certain ancestry, especially for cystic fibrosis, spinal muscular atrophy and hemoglobinopathies [10]. In Europe, it is has been advised that "governments and public health authorities should adopt an active role in discussing the responsible introduction of expanded carrier screening" [8]. In many countries, no guidelines have yet been published, leaving professionals to decide for themselves whether or not they inform couples they see before a pregnancy about the availability of carrier screening. In the absence of a professional stance, many obstetric care providers decline to inform couples of this service. However, identification of a carrier couple before pregnancy automatically raises the question of reproductive options, such as whether the couple wants to start a family and the availability of testing that may help to avoid the birth of infants affected by these serious

conditions. If a risk of a specific monogenic disorder has been recognized, the couple could use PGD, or prenatal testing for that specific disorder to help in their decision-making.

3. Pre-implantation Genetic Screening (PGS)

A couple with a 25% risk of having an infant with serious recessive disorder can apply for *diagnostic* testing, for instance, in the pre-implantation embryo. Some authors and companies advocate more than diagnostic testing of the embryo. If all embryos were tested for aneuploidy, one could speculate that pregnancy outcomes would improve. However, 11 randomized controlled trials of screening using this technique showed no improvement in in vitro fertilization delivery rates [11]. Subsequent trials assessed different techniques,, so the potential of PGS for aneuploidies to contribute to better pregnancy outcomes is still open for debate. It may become possible to expand screening in this pre-implantation setting, especially by screening one cell of the embryo for many conditions, a new approach that has been found to show promise in single cell sequencing trials [12]. Expanded pre-implantation screening is also conceivable in terms of including monogenic conditions. This raises issues that are similar to those we have highlighted already in that the couples involved may not always know the conditions for which the embryo is tested and therefore, may not be able to make an informed decision regarding their options. Furthermore, the phenomenon of genetic mosaicism raises the issue of the positive and negative predictive value of anomalies found (or not found) in the embryo. For the moment, expanded pre-implantation genetic screening is only relevant in research settings.

4. Prenatal Screening

Prenatal screening is performed for blood groups and Rhesus factors, infections and ultrasound anomalies. Improved techniques have led to gradual expansion of these tests, although recent discussions have focused predominantly on non-invasive prenatal testing (NIPT) [13]. Using maternal serum, free fetal DNA can be used to test for aneuploidies in the fetus, or actually, in the placenta [14]. If no anomalies are found, the negative predictive value is greater than 99%. However, if an aneuploidy is detected, the positive predictive value may be around 50% or higher, depending on maternal age and ultrasound findings. In contrast, this figure may be only a few percent when a combined testing approach is used. After a positive NIPT result, diagnostic testing by amniocentesis or chorionic villus sampling is needed, although the number of invasive tests has decreased greatly since the introduction of NIPT.

As the entire fetal DNA is present in maternal blood, one can imagine testing for more than just aneuploidies. Some companies have also started offering tests based on what is technically feasible in terms of identifying microdeletions. It is conceivable that NIPT could be expanded to include monogenic disorders (such as Duchenne muscular dystrophy, cystic fibrosis or congenital adrenal hyperplasia) or new mutations that are not present in the parents and might cause serious developmental delay. However, both costs and ethical issues should be considered. Furthermore, the number of false positives could increase, which may undermine the main achievement of NIPT: the significant reduction in the proportion of people undergoing invasive testing [13]. If the goal of reproductive screening is to help couples make an informed decision about their reproductive choices, it is imperative that we take care to ensure that the they are sufficiently “informed” if a screening test is expanded to include many conditions about which the couple have no knowledge.

The goal of prenatal screening is two-fold: apart from enabling couples to make informed reproductive choices, the objective is also to identify treatable infections and avoidable conditions, such as rhesus antagonism. Moreover, expanded prenatal screening might include more conditions that require prenatal treatment, such as congenital adrenal hyperplasia, or treatment soon after birth, before the result of neonatal screening is known. Thus, the prenatal counseling should be offered taking into account the dual goal of prenatal screening.

5. Neonatal Screening

Screening for phenylketoruria (PKU) screening in newborns was first implemented more than 50 years ago [15]. If the disorder was recognized, severe developmental delay in the newborn could be avoided by dietary intervention. PKU screening is now offered in many countries around the world. For PKU, a program was set up to register all newborns and screen them using just one laboratory test, to inform the parents and pediatricians of the result and initiate treatment. Thus, it was relatively simple to add a second and third laboratory test or condition to expand the screening program. Congenital hypothyroidism (CHT) has now been added in the programs of many countries around the world [15] and while PKU is treated by metabolic pediatricians, endocrine pediatricians manage CHT. Programs have expanded from one to two conditions to over 50 different conditions [15]. The recent expansions were driven mainly by advances in tandem mass spectrometry (MS/MS), where one test could be used to screen for several metabolic diseases. Another driver of expansions was the development of treatments, such as stem cell transplantation and enzyme replacement therapy. Countries have made different decisions regarding expansion of their neonatal screening programs and further expansions are ongoing. In Europe in 2012 one country (Albania) did not yet screen newborn infants, while other European countries screened between one and more than 40 conditions, and some American states screened for more than 50 conditions [15].

A potential future driver of expansions is sequencing techniques, either whole genome sequencing, whole exome sequencing or targeted panels [16]. For the moment, the cost is much higher than that for regular neonatal screening programs, and the test properties, such as sensitivity and positive predictive value, are insufficiently characterized; however, it is conceivable that these technologies will be used in the near future as a second tier test to limit the number of false positives.

Continuing technical developments repeatedly raise the question of the “target” conditions for inclusion in screens [17]. If more disorders can be diagnosed, a decision must be made regarding the benefits, or whether the targets should remain those where a clear health benefit can be achieved by earlier diagnosis [16]. Some have argued that earlier diagnosis of “untreatable” conditions is beneficial by avoiding a long diagnostic odyssey. Furthermore, this approach would inform the parents of a potential reproductive risk before the next pregnancy, thus allowing for informed reproductive choices. If one child has a serious condition, it may be beneficial for the family not to have a second child that also needs special care. So far neonatal screening is focused on those conditions where the benefit of the index patient is scientifically proven [17].

6. Discussion and Conclusion: Is Better?

Technological developments make it possible to expand many of our current screening programs. This may be a positive development, if a greater number of similar conditions can be recognized at the same cost, and thus the aim would be better achieved. However, often possibilities to expand screening will also generate more costs, more false positives, and may make informed decision-making more difficult. Whether or not screening criteria are (still) met, whether or not quality and cost increase and the value of the expanded screening program to the recipients needs to be investigated for each potential expansion. Overall, screening will be improved by the application of available technologies combined with a targeted analysis based on careful evaluation of the associated pros and cons.

Author Contributions

MC drafted and revised the manuscript.

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Competing Interests

The author is employed by a University Medical Center that offers expanded carrier screening and prenatal screening as part of its services. The author is Chair of the Netherlands Program Committee Neonatal Heelprick Screening and a member of the Health Council Committee on Population Screening.

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