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Reproductive autonomy in expanded carrier screening: more than meets the eye?

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Expanded carrier screening (ECS), which screens prospective parents for the carrier status of a large number of recessive disorders have recently become offered more widely [1]. Many prospective parents undergo ECS each year to learn about their risk of having a child affected by a disease [2]. The most commonly discussed benefit of ECS is its potential to enhance reproductive autonomy of prospective parents by allowing them to make informed reproductive decisions in line with their values [3–5]. This is particularly pertinent to couples found to be at risk of having an affected child (i.e. 'carrier couples'), who may choose to alter their reproductive plans. If identified preconceptionally, a carrier couple's options include *in vitro* fertilization through pre-implantation genetic diagnosis to select against embryos with the condition they carry, using donor gametes, or foregoing pregnancy, pursuing instead adoption, or deciding against having children. If already pregnant, a carrier couple could choose to undergo prenatal genetic diagnosis for the disorder and, should the fetus be affected, subsequently elect to terminate the pregnancy. Alternatively, a carrier couple may decide not to alter their reproductive plans and accept the possibility of having an affected child [2]. This is particularly relevant to recessive disorders for which effective therapeutic interventions exist, where a couple's carrier status information can be used to monitor the at-risk pregnancy and, if the fetus is found to be affected, prepare for initiating a treatment during the newborn period. Consequently, ECS can be viewed as allowing carrier couples to make reproductive decisions based on their personal values, such as their perception of the moral status of the fetus/embryo.

Despite these autonomy-enhancing qualities of ECS, the relationship between reproductive autonomy and ECS may be complex. Imagine, for example, that a pregnant couple is identified as being carriers of a recessive disorder, such as cystic fibrosis (CF), and a follow-up prenatal genetic diagnosis confirms that their fetus is affected. Consequently, the couple is provided with the choice between pregnancy termination and carrying the affected pregnancy to term. Given the significance of this choice, the couple seeks to gain comprehensive information about CF, in order to make an informed decision. They learn about the clinical characteristics of CF, form an opinion regarding the severity of the disorder, and decide that the prospect of caring for an affected child is manageable for their family. Furthermore, the couple also becomes aware that the recently developed ivacaftor therapy is

highly effective in patients with the same CFTR mutations affecting their fetus. Although the cost of the therapy is estimated at \$300 000 per patient per year [6], the couple learns that their national healthcare system fully subsidizes patients' access to the therapy and that their future child will be eligible to access it. Based on these considerations, the couple feels that termination of pregnancy is not warranted and decides to carry the affected pregnancy to term.

In this example, the couple has clearly made an autonomous reproductive decision, factoring in all the relevant information and taking into account their personal values. Yet, it is plausible that the couple's decision could be viewed as morally objectionable by others. Some might argue, for example, that despite recent advances in CF treatments, CF remains a severe condition and that by knowingly having a child with CF, the parents are effectively condemning their child to an 'inferior' quality of life. Therefore, the couple's decision to forego pregnancy termination can be viewed by some as irresponsible toward their future offspring [7]. Others may criticize the couple's decision on the grounds that it imposes a significant financial burden on the society, given that providing treatment to their affected child will be extremely costly [8]. Disapproval may also come from the pregnant couple's family members or healthcare providers, which may place pressure on the couple to undergo pregnancy termination. Furthermore, the couple may be concerned that their future child will be stigmatized, with some viewing the child's very existence as wrongful. This could, in turn, be detrimental to the child's interactions with others and may even affect the society's willingness to provide costly life-saving treatments. It is conceivable that these external factors could motivate the couple to subsequently reconsider their initial decision in favor of pregnancy termination.

Although the final say in reproductive matters remains with the couple, the example above shows that reproductive autonomy does not exist in a vacuum and reproductive decision-making takes place in a context where external factors could play an important role. In some cases, such external factors may conflict with the values and preferences of a couple, leading to a situation where, somewhat paradoxically, ECS ultimately limits, rather than promotes, a couple's reproductive autonomy.

Traditionally, the costs associated with implementing a population carrier screening program were higher than economic gains

from reducing the birth prevalence of recessive disorders. However, with the continuous progress in molecular genetics, ECS may have recently passed the cost-effectiveness threshold as a population screening intervention. In 2018, Beauchamp et al. demonstrated that it would be cost-effective to screen the US population using a commercial 176-disease ECS panel, assuming reproductive outcomes previously observed among at-risk couples. The ECS test used by the authors would identify 1.2% of couples in the general population as being at risk, an approximately 10-fold increase in the yield of carrier couples compared to screening for CF alone [9].

We believe the cost-effectiveness of ECS will become even more pronounced in the near future due to the following factors. First, the diminishing cost of DNA sequencing is likely to drive the price of commercial ECS tests down. Second, as the molecular basis of more rare recessive diseases is elucidated, additional disorders may be included on ECS panels, further increasing the yield of carrier couples. Third, the emergence of novel expensive therapies means that the total costs associated with the treatment of patients with rare recessive diseases will keep rising in the foreseeable future. Owing to these considerations, it is highly probable that both public health authorities and private insurance companies will acknowledge the potential cost savings offered by ECS, prompting greater interest in its implementation. Therefore, ECS may soon be offered routinely in a population screening setting, much like the prenatal screening tests that are currently offered to pregnant women. However, it may be challenging to create a routine offer of ECS that is value-free, and there is a risk that prospective parents may interpret such an offer as carrying with it a moral responsibility to participate in screening. For example, one could speak of a couple's culpability where the couple declines the offer and subsequently has a child with a severe (or financially burdensome) recessive disease, whose birth could have been prevented through ECS.

In conclusion, the potential impact of ECS on the reproductive autonomy of future parents can be best described as ambivalent. On the one hand, if ECS becomes widely accessible, it can be expected that a large number of couples will be interested in such an offer, and many couples found to be at risk will choose a reproductive option that would be deemed medically appropriate and/or socially responsible. Such couples would indeed have their reproductive autonomy enhanced through ECS, as the availability of the test would enable them to make reproductive decisions in line with their personal values. On the other hand, some couples may not be interested in ECS, or they may hold divergent views on what constitutes an appropriate reproductive decision for a given ECS test result. There is a possibility that ECS may limit the reproductive autonomy of such couples, potentially pressuring them into decisions that conflict with their personal values. As we move toward a population-wide ECS offer, it is crucial for this complex relationship between reproductive autonomy and ECS to receive greater attention and for any routine offer of ECS to include measures to protect and promote prospective parents' ability to make truly autonomous decisions. In carrier couples, additional education and counseling should be provided regarding the potential residual uncertainty of ECS test results in order to allow prospective parents to incorporate this into their reproductive decision-making process.

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Declaration of interest

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One reviewer is an employee of a commercial laboratory that performs expanded carrier screening. The rest of the peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

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