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Attitudes of European Geneticists Regarding Expanded Carrier Screening

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ABSTRACT

Objective: To explore attitudes of clinical and molecular geneticists about the implementation of multi-disease or expanded carrier screening (ECS) for monogenic recessive disorders.

Design: Qualitative; semistructured interviews.

Setting: In person or via Skype. Interviews were audiorecorded and transcribed verbatim.

Participants: European clinical and molecular geneticists with expertise in carrier screening ($N = 16$).

Methods: Inductive content analysis was used to identify common content categories in the data.

Results: Participants recognized important benefits of ECS, but they also identified major challenges, including limited benefit of ECS for most couples in the general population, lack of knowledge on carrier screening among nongenetic health care providers and the general public, potential negative implications of ECS for society, and limited economic resources. Participants favored an evidence-based approach to the implementation of population-wide ECS and were reluctant to actively offer ECS in the absence of demonstrable benefits. However, there was a consensus among the participants that ECS should be made available to couples who request the test. In addition, they believed ECS could be routinely offered to all people who use assisted reproduction.

Conclusion: Although a limited ECS offer is practical, it also raises concerns over equality in access to screening. A comprehensive risk–benefit analysis is needed to determine the desirability of systematic population-wide ECS.

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The purpose of carrier screening is to identify couples at risk of conceiving a child with a monogenic recessive disorder. This risk is present when both reproductive partners carry a mutation associated with the same autosomal recessive disorder or when the woman is a carrier of an X-linked disorder (Wienke, Brown, Farmer, & Strange, 2014).

Because of the recessive pattern of inheritance, many carriers of these disorders have no family history suggestive of the condition. Once identified, at-risk couples have the option to act on this information and may alter their reproductive plans (Ropers, 2012).

In some countries and ethnic communities with a high birth prevalence of severe recessive disorders, carrier screening programs were introduced as early as the 1970s. Notable examples of the first screening programs include Tay-Sachs carrier screening in the Ashkenazi Jewish community (Kaback, 2000) and premarital screening of couples for beta-thalassemia in the Mediterranean region (Cousens, Gaff, Metcalfe, & Delatycki, 2010). Subsequently, carrier screening became available in some countries for conditions such as cystic fibrosis (CF), fragile X syndrome, and spinal muscular atrophy (Metcalfe, 2012).

Because of largely technical limitations, most tests for carrier screening have traditionally been used to target a limited set of pathogenic mutations associated with a single disorder or a small panel of monogenic disorders (Bajaj & Gross, 2014). However, recent advances in molecular diagnostics have resulted in the development of expanded carrier screening (ECS) panels capable of identifying hundreds of mutations implicated in a large number of recessive conditions (Bell et al., 2011; Kingsmore, 2012; Tanner et al., 2014). ECS products are currently available at a price comparable to that of carrier screening for single conditions (Higgins, Flanagan, Von Wald, & Hansen, 2015; Langlois,

Health care providers with expertise in carrier screening are well-positioned to discuss the perceived advantages and disadvantages of a population expanded carrier screening program.

Benn, & Wilkins-Haug, 2015; McGowan, Cho, & Sharp, 2013). The capacity to screen for more disorders for a similar price and the ability to identify carriers regardless of ethnicity constitute major appeals of ECS (Cho, McGowan, Metcalfe, & Sharp, 2013; Lazarin et al., 2012; Ready, Haque, Srinivasan, & Marshall, 2012; Srinivasan et al., 2010). These advantages over traditional forms of carrier screening suggest ECS has the potential for wide implementation in reproductive health care (McGowan et al., 2013). Results of a survey conducted in the United States in 2012 suggested that ECS is already routinely offered by some obstetricians and gynecologists (Benn et al., 2014).

Widespread adoption of ECS will profoundly influence reproductive health care practices and is likely to be associated with significant practical and ethical challenges that will require special consideration. Valuable insights can be gained from exploring the opinions of genetic professionals who have extensive experience with diverse forms of genetic testing (Cho et al., 2013). Here, we report the results of an interview-based study with European clinical and molecular geneticists and present the issues that surround the implementation of ECS in reproductive medicine.

Methods

Because of the explorative nature of our research question, we conducted key informant interviews with clinical and molecular geneticists to investigate their views about the implementation of ECS in reproductive health care (Popay, Rogers, & Williams, 1998). Participants were eligible for inclusion if they were practicing clinical or molecular geneticists based in the European Economic Area and had demonstrable expert knowledge in carrier screening, such as authorship of relevant scientific publications or conference abstracts. Potential participants were identified by members of our research team and invited to participate via e-mail. Additional respondents were recruited by snowball sampling, where we asked our participants to identify colleagues with expertise in carrier screening.

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Interviews were conducted using a semi-structured interview guide, which allowed for in-depth exploration of issues related to implementation of ECS (Liamputtong & Ezzy, 2005). Interviews took place between April and September 2014 and were audiorecorded and transcribed verbatim to enable coding and analysis.

Inductive content analysis was used to identify common content categories from the interviews, rather than coding using a predetermined coding scheme (Downe-Wamboldt, 1992; Graneheim & Lundman, 2004; Schamber, 2000). The data were coded into broad categories before sections of the data within these categories were compared and more specific content categories were developed. Coding was performed by DC using the qualitative data management software QSR Nvivo; data were reviewed by all members of the research team for validation. This study was approved by the institutional ethics committee of the University Hospital Ghent.

Results

The group of participants included 16 genetics professionals from eight member states of the European Economic Area. The group included 13 clinical geneticists (CGs), 2 molecular geneticists (MGs), and 1 medical geneticist with expertise in clinical and molecular genetics (CMG). At the time of the interviews, all participants were affiliated with an academic institution, and 12 geneticists (9 CGs, 2 MGs, 1 CMG) had more than 20 years of professional experience in clinical or diagnostic practice. Eleven participants were female, and five were male.

Thirteen interviews took place in person, and three were conducted via Skype. Three categories relevant to the implementation of large-scale ECS programs were identified from the data: *Potential benefits of ECS, Challenges of population-wide carrier screening using expanded panels,* and *Models for provision of ECS*. These categories and their subcategories are described below and are accompanied by illustrative quotes from the participants.

Category 1: *Potential Benefits of ECS*

All participants believed that systematically offering preconception ECS to prospective parents would result in significant potential benefits, such as reduced cost of ECS and greater access to testing. Overall, there was agreement that

provision of ECS to the general population was desirable because currently many at-risk couples have no possibility of learning about their reproductive risks. For example, one participant commented, "At the moment, we have a situation where most people with most conditions only have the possibility of making informed decisions about reproduction when they already have an affected child and that is … not good" (CG).

Furthermore, several participants highlighted the ability of ECS to identify carriers in the general population, regardless of ethnicity. For some participants, this meant that ethnicity-based testing would soon fall out of favor, a development they welcomed:

> People don't want to have themselves registered in a hospital based on [their] ethnicity. If you make one panel, and … the technique is progressing and it's becoming more and more easy to put a lot of mutations on one panel for a relatively low price. I think you should put it all on one panel to prevent discrimination issues. (CG)

Category 2: *Challenges of Population Carrier Screening Using Expanded Panels*

Despite the potential benefits of ECS, participants identified several major challenges associated with systematic implementation of ECS.

Subcategory 2.1: *Limited utility of ECS for the general population.* Some participants noted that the yield of carrier couples from population-wide ECS would be low. This was partly attributed to the inability of current ECS products to identify many carrier couples because ECS panels would not include all disease-associated mutations. According to participants, the incomplete coverage of pathogenic mutations would make it impossible to completely exclude the risk of having an affected child. Consequently, several participants were particularly concerned that many couples in which only one partner is identified as a carrier would experience excessive anxiety over this residual risk:

> [I have seen a couple where the husband] had a family history of cystic fibrosis and he was screened positive for the most frequent mutations and then we screened the wife [and] she was screened negative. But it was a rare mutation and they experienced the disease. If you screen for many diseases, you will find many [couples where] one member of the couple will be a carrier and for the other one you won't be able to lower the risk enough to reassure completely them. So I think this gap is problematic for [couples] because many will be anxious and not much will be really reassured, and very few will be really at risk. (CG)

In the case of multidisease panels, several participants believed that because both members of a couple may carry novel or private mutations in genes associated with recessive disorders, the couple's residual risk of having an affected child would be quite high. The probability of identifying couples with confirmed high risk, on the other hand, was perceived to be low (estimated at 1%–3% by several participants). Because of this, participants believed that population-wide ECS would benefit only a small minority of participating couples and that for the remainder of couples, testing would be an unnecessary intervention that could potentially lead to psychological distress: "All this testing, anxiousness, maybe finding something which you don't know what the meaning is… [this] is stirring up everything and for most people it's not relevant, but we do it for those few couples" (CG).

Similarly, another participant discussed the absence of any immediate medical benefit for most couples and referred to the possibility of experiencing undue anxiety as the "collateral damage" (CMG) of population-wide ECS.

Subcategory 2.2: *Lack of public education on carrier screening.* To promote informed decision making about screening, participants believed it would be necessary to ensure that all prospective parents undergoing ECS understood the aims and implications of the test. However, all participants expressed doubt regarding the general public's ability to comprehend issues surrounding preconception carrier screening. In particular, they were concerned that prospective parents may have difficulty understanding the meaning of being a carrier: "I think for the general public['s] understanding of what it means to be a carrier it is perhaps not yet good enough to be able to distinguish between carrier and affected status" (CG).

Most participants believed the poor genetic literacy among the lay public would pose significant challenges to large-scale implementation of ECS.

Therefore, participants suggested that implementation of population-wide ECS should be preceded by public education efforts to ensure "that people would understand the issue. Would understand what is at stake, including the uncertainty there is" (CMG).

Subcategory 2.3: *Lack of genetic education and counseling expertise among health care providers.* All participants believed a successful population-wide carrier screening program would require active involvement of nongenetic health care professionals to inform and educate prospective parents about ECS. However, some participants were concerned that health care providers often lack sufficient genetic knowledge to be able to provide adequate counseling: "I think at the moment many colleagues are not capable to counsel people about genetics. It's completely out of their understanding, I would say" (CG). Consequently, participants emphasized the importance of educated counselors and stressed that ECS should not be offered to the general population without taking preparatory measures.

> If you test for a lot of disorders, then the probability you find that carrier couple is there. So you must be very prepared, know these disorders; you have to be able to explain that very well.… This [ECS] could be very interesting, but we need time to plan this kind of stuff. To educate ourselves, to make good counseling, and [to devise good practice guidelines]. (MG)

Subcategory 2.4: *Possible negative societal implications of ECS.* Some participants argued that offering ECS to the general public would result in a lower birth prevalence of children affected with recessive disorders: "If we imagine that there will be systematic carrier screening in the population, probably the disease[s] will really decrease and most of those patients will never be born" (MG). One participant articulated concerns that a widespread offer of ECS would result in discontent among some members of the general public: "[Some people fear that] we [geneticists] want to make a perfect population, so then there will be no chance for these children to [be born]… I mean, these extreme groups always see this as some form of eugenics" (CG). Another participant believed that implementation of ECS could be particularly controversial for people currently living with the disorders: "[T]hose people with the disease will feel, well, not at ease or embarrassed with it, saying that 'What is the legitimacy if you now avoid the birth of additional people with conditions we have?'" (CMG).

Recognizing the possible controversy of ECS among people with recessive diseases, participants called for more extensive discussion on the far-reaching societal effects of ECS: "So a part of the whole discussion would need to be about what it would be about to live in a society that had very few cases of … most recessive conditions. Would that be a good thing or not?" (CG).

Category 3: *Proposed Models for Providing ECS*

Participants discussed the following possible models for large-scale implementation of ECS: systematically offering screening to all reproductive-age couples, providing ECS upon request from prospective parents, and incorporating ECS into artificial reproduction services for people who undergo fertility treatment.

Subcategory 3.1: *Systematic screening of all reproductive-age couples.* Most participants believed that ideally, ECS would be implemented in such a way that ensures equal access to carrier screening for all prospective parents: "It will be important to make sure that all sections of society have ready access to it. So it would be bad if only the wealthy had access to it. Sure, it needs to be available generally" (CG). Some believed the significant improvement in technology of ECS compared with carrier screening for single conditions provides a rationale for considering the implementation of a systematic population screening program:

> In the older days, I might have said, "No, it's not worth the investment and the technology and the time to test for individual rare conditions." [Now] if you're talking about expanded carrier testing, the whole equation becomes very different from what it used to [be]. (CG)

However, this participant also noted it is unclear whether ECS has reached the stage at which the overall benefits of implementation outweigh the potential disadvantages, and a comprehensive analysis of benefits and harms was recommended "in order to decide whether you would justify offering it to a general population."

In addition, one participant stated that the public health care system in his/her country was

operating on a limited budget. Therefore, the health care system could not prioritize ECS, a screening program likely to benefit only a small part of the population, because of the presence of more pressing health care needs:

> Here, it's not the best we can do with the amount of resources we have.… I do feel that it causes a huge amount of anxiety in families if they have a kid with recessive disorder, although economically it's waste of time.… So you spend huge, *huge* amount of money and you are probably better off [treating] Alzheimer's patients or your cancer patients. (CG; emphasis by interviewee)

Subcategory 3.2: *Providing ECS upon request.* There was a general consensus among participants that ECS should be made available to couples willing to take the test to enhance their reproductive autonomy: "When you think of the autonomy of the prospective parents, the offer should be there" (CG). Notably, willingness to provide carrier screening upon request was also expressed by those participants who believed that actively offering ECS to the general population was premature at present: "[Taking into consideration the disadvantages], I am not sure I would today use carrier screening for many conditions simultaneously, *except if people really want them*" (CG; emphasis by interviewee).

However, some respondents believed that unless the overall benefits of ECS are shown to outweigh the potential harms, prospective parents should be responsible for the cost of the test:

> I do think that something like that at the moment must be paid by the patient. If I decide, because I'm very anxious, to get this kind of tests and see if I'm a carrier of one of those disorders, I have to pay. Not the insurance, not the government.… It's right to have a possibility to do that but also the people should pay for that. (MG)

Subcategory 3.3: *ECS in the context of artificial reproductive technologies.* Despite acknowledging the considerable challenges associated with population-wide ECS, participants agreed that it was justifiable to systematically provide ECS to high-risk groups of prospective parents, such as consanguineous couples or individuals with family histories of a recessive disorder. In addition, several participants believed ECS could be successfully integrated into preimplantation genetic diagnosis (PGD) services, with substantial benefits.

Most participants believed it was premature to implement expanded carrier screening in the context of public health.

> I want to stress especially from the point of couples asking for PGD, I'm in favor of preconception carrier screening. Because they [patients] already have one genetic problem and you don't want them to be confronted with another genetic problem and [have to tell them] in retrospect, "We did have a possibility to identify this problem, but we didn't offer it to you." I think that's not good. (CG)

> Let's say I see a couple and they have a child with a metabolic condition, recessive, and I offer them [ECS]. So it's easy to say, "[these are] disease[s] like your child's, you both have to be carriers, and so on." It takes less time to explain. (CG)

In addition, one participant argued that ECS could be routinely provided to all people undergoing in vitro fertilization treatments in general. This participant emphasized the duty of medical professionals to protect children conceived through medical procedures from preventable harm:

> Both of the procedures [in vitro fertilization and PGD] are basically medical procedures, firstly for the couple to have a baby at all or a couple with a genetic problem not to have this genetic problem. So in this situation, any additional genetic disorder [resulting from] this medical treatment would be somehow iatrogenic failure of the medical procedure. (CG)

Discussion

We investigated the attitudes of European clinical and molecular geneticists toward the implementation of population-wide ECS. All participants recognized the potential benefits of ECS, including the identification of at-risk couples without a preexisting risk for a genetic disorder and subsequently increasing their reproductive autonomy. Furthermore, the ability to incorporate additional disorders for little extra cost into ECS panels was viewed as a significant improvement

over carrier screening for single disorders. However, participants also identified several major challenges to large-scale implementation of ECS.

Our participants noted that, in their current form, ECS tests fail to identify many carriers in the general population because the panels do not include extremely rare or novel pathogenic mutations. This inability to completely exclude the possibility that an individual with a negative screening result could be a carrier was also highlighted as a major limitation of ECS by genetics professionals in a U.S.-based focus group study (Cho et al., 2013). Our participants accepted non-negligible risk of missing carriers to maximize positive predictive value of the test. They recommended limiting ECS to highly penetrant pathogenic mutations with clearly established genotype–phenotype correlations, even if this would result in a decreased sensitivity (unpublished data).

However, our participants raised concerns that the residual risk of having an affected child after a negative test result would lead to undue anxiety in couples where only one partner is found to carry a disease-associated variant in the gene (also referred to as +/− couples; Henneman & ten Kate, 2002). Because individuals in the general population are estimated to carry several pathogenic mutations associated with severe monogenic disorders (Bell et al., 2011), it is reasonable to expect that any ECS test would identify a large proportion of couples as +/− for at least one disorder. Imperfect carrier detection rates for disorders using ECS panels have been reported previously, with authors warning that inconclusive test results could prompt some +/− couples to undergo extensive and costly follow-up genetic evaluation, often with little benefit (Skirton, 2015; Stoll & Resta, 2013). Because the proportion of carrier couples in the general population is low and population-based ECS tests using mutation panels would identify couples even less at risk, only a small proportion of screened couples would receive actionable findings (Bajaj & Gross, 2014; Stoll & Resta, 2013).

For most couples, as emphasized by our participants, ECS would be of no medical benefit, would constitute an unnecessary, potentially burdensome medical intervention, and may lead to emotional distress because of inconclusive test results. These potential negative outcomes of ECS need to be factored in when assessing the desirability of ECS.

Given the many complex issues related to ECS, our participants viewed it as essential to ensure that all prospective parents who undergo screening possess adequate knowledge of the implications and limitations of the test. This is in line with recent recommendations from professional organizations that have encouraged providers of ECS to focus pretest education and consent processes on explaining these issues, including the meaning of being a carrier, the pattern of inheritance, and the technical limitations of the tests (Edwards et al., 2015; Henneman et al., 2016). These recommendations are aimed at facilitating informed decision making for potential parents, yet the effectiveness of this approach will greatly depend on the couple's genetic literacy. Participants in our study questioned the capacity of the general population to comprehend the complex issues surrounding ECS and viewed this as an important barrier to the successful provision of population ECS.

To ensure the understandability of the information related to carrier screening, it may be necessary to improve the general public's knowledge of genetics (Health Council of The Netherlands, 1994). Furthermore, our participants were concerned that many health care professionals lack the necessary expertise to inform and counsel their patients on various aspects of ECS, as advanced by genetics professionals in another study (Cho et al., 2013). Lack of expertise about carrier screening among nongeneticist health care providers poses an important challenge, because their competence and cooperation will be crucial for successful implementation of screening programs (Bailey, Lewis, Roche, & Powell, 2014; Metcalfe, 2012). Moreover, as the information on ECS becomes more widely accessible, nongeneticist health care providers, such as general practitioners, are likely to be confronted with enquiries related to carrier screening from their patients (Poppelaars et al., 2003). It is therefore critical to ensure that health care providers possess sufficient knowledge to discuss carrier screening with their patients.

Some participants anticipated that ECS would result in a lower prevalence of recessive disorders in the population. Their expectation is supported by historical data on population-wide cystic fibrosis carrier screening, which suggests that an offer of carrier screening does lead to reductions in the number of affected births over time (Castellani et al., 2015). In line with the

concerns raised by our participants, considerable attention in the literature has been devoted to ethical issues such as perceived eugenic undertones of carrier screening and negative implications for people with the screened disorders (Bruni, Mameli, Pravettoni, & Boniolo, 2012; De Wert, Dondorp, & Knoppers, 2012). It is important to acknowledge the significance of these concerns and take preemptive measures to mitigate the potential harm of widespread ECS. First, population carrier screening offers must be voluntary, where informed couples can exercise their reproductive autonomy and feel free to decline participation (G. M. De Wert et al., 2012). Second, people with disabling monogenic conditions must continue to receive adequate medical care and suffer no foreseeable discrimination as a result of the program (Henneman et al., 2016; Raz, 2005). Contrary to the beliefs expressed by some of our participants, authors of studies with people with recessive disorders and their family members have reported positive attitudes toward population carrier screening (Henneman et al., 2001; Hietala et al., 1995; Janssens et al., 2015). However, views on carrier screening can vary substantially across cultures, and societal issues surrounding ECS should be discussed with different stakeholders from the general public, including people with recessive disorders (Mosconi, Castellani, Villani, & Satolli, 2014).

Because of significant challenges and concerns associated with population ECS, some participants suggested that any plans for routine integration of ECS into medical services should be preceded by a careful analysis of anticipated benefits and risks. These participants favored an evidence-based approach to ECS and were reluctant to accept its implementation in the absence of demonstrated overall benefit. However, such an evaluation is challenging and may require carrying out pilot studies (Wilfond & Goddard, 2015). Furthermore, because carrier screening programs should emphasize voluntary participation and avoid a focus on increasing uptake (Poppelaars et al., 2003), a population-wide carrier screening program cannot aim to achieve a targeted participation rate. Consequently, it may be unclear to policymakers whether spending public resources on ECS is justified, particularly in light of other public health interventions competing for the same pool of resources. Therefore, as several participants in our study noted, some countries may not be in a position to prioritize ECS because of the presence of more pressing public health issues and limited available resources.

Although most participants believed that systematically offering ECS to all couples in the general population was associated with significant challenges, there was a general consensus that ECS should be made available to prospective parents who request it. This observation is in line with findings of other attitudinal studies, where health care professionals were more supportive of carrier screening if their patients requested the test (Baars, Henneman, & ten Kate, 2004; Benn et al., 2014). In addition, some participants believed ECS could be routinely offered to select groups of prospective parents, such as those who pursue pregnancy through artificial reproductive technologies, which mirrors the findings of others (Cho et al., 2013). Routine provision of ECS in the context of artificial reproduction has been gaining support because of professional obligations to avoid harm to future children (G. De Wert et al., 2011) and the relative ease and low incremental cost of integrating ECS into extant fertility services (Bell et al., 2011; Cho et al., 2013; Kingsmore, 2012).

An important disadvantage of a limited offer of ECS is that initially not all members of the general public would be aware of its existence (Baars et al., 2004). Furthermore, assuming a fee-for-service model of provision, it is likely that some prospective parents interested in ECS will not be able to afford the service, which raises concerns over equity in access to screening. Additionally, geneticists and reproductive health care providers in other studies have raised concerns that failure to offer carrier screening may result in lawsuits in some jurisdictions, should a child with a detectable disorder be born (McGowan et al., 2013; Stark et al., 2013). These concerns indicate that there would be advantages to systematically offering carrier screening to all couples of reproductive age. To this end, it is important that in the near future a comprehensive risk–benefit analysis of ECS is carried out, assessing the expected medical, psychosocial, and economic impact of ECS. Should such analyses show an overall benefit of ECS, the practice could be introduced as a standard of care, resulting in an equitable offer of population carrier screening (Ferreira et al., 2014).

Strengths and Limitations

Because the literature on ECS is still sparse, our study provides a valuable contribution by

A comprehensive risk–benefit analysis of expanded carrier screening that incorporates economic and psychosocial implications is required.

exploring potential challenges associated with the implementation of this emerging technology. To this end, the principal strength of our study is that we interviewed genetic professionals with expertise in carrier screening for recessive disorders who, arguably, are the most qualified stakeholders to discuss these issues. However, it should be noted that the vast majority of our participants were affiliated with established health care institutions, such as hospitals, academic medical centers, and other publicly funded bodies. Consequently, our participants largely discussed ECS in the context of public health, which may explain their adoption of a cautious, evidence-based approach to the implementation of ECS. Studies with other stakeholders are required to gain a deeper and more comprehensive insight into the benefits and disadvantages of the implementation of ECS.

Conclusion

Although our participants had positive attitudes toward ECS, they also identified several major challenges to a population-wide offer of carrier screening and were reluctant to accept systematic ECS in the absence of demonstrated overall benefit. This observation indicates a strong need for a comprehensive risk–benefit analysis of ECS, factoring in expected medical, psychosocial, and economic impacts.

Regardless of the desirability of a systematic ECS offer to all couples considering pregnancy, our participants believed that ECS should be made available to those couples who request the test. In addition, there was a consensus that ECS could be routinely offered to all people who receive assisted reproduction services, such as PGD and, more generally, in vitro fertilization. Although limited availability of ECS offers benefits to some prospective parents, it also raises concerns over equity in access. Therefore, assuming feasibility and desirability of ECS, efforts will need to focus on making screening accessible to all couples of reproductive age in the general population.

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