Expanded carrier screening in reproductive healthcare: perspectives from genetics professionals

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STUDY QUESTION: How do genetics professionals assess the potential benefits and challenges of expanded carrier screening (ECS) in reproductive healthcare?

SUMMARY ANSWER: Genetics professionals believe that current ECS products have major limitations and are not ready for routine use in reproductive healthcare.

WHAT IS KNOWN ALREADY: Non-targeted approaches to carrier screening have been met with uneven enthusiasm from relevant professional organizations. With declining genotyping costs, it is reasonable to expect that the number of genetic conditions evaluated by carrier-screening products will continue to increase. Reproductive healthcare providers will play a critical role in the adoption of ECS and need to be prepared for the potential challenges that lie ahead.

STUDY DESIGN, SIZE, DURATION: Focus groups were convened at six academic medical centers in the USA in March 2011 to examine genetics professionals’ views on ECS.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Forty genetic professionals participated in six focus groups for this study. A clinical case report was presented to each focus group to examine participants’ opinions about the use of highly multiplexed forms of carrier screening in reproductive healthcare. Focus group transcripts were analyzed for major themes and thematic density across sites using qualitative data analysis software (ATLAS.ti v5.8).

MAIN RESULTS AND THE ROLE OF CHANCE: Participants believed that current ECS products have major limitations pertaining to the analysis of select alleles and genetic mutations. Participants highlighted multiple interpretive and counseling challenges that reproductive healthcare providers may face in communicating ECS results to patients. Participants stressed the importance of communicating these and other limitations to patients before recommending ECS. Participants recommended collaboration with genetic counselors and medical geneticists in providing ECS.

LIMITATIONS, REASONS FOR CAUTION: To the extent that ECS products have not been widely used to date, participants may have had limited familiarity and direct clinical experience with these products. Given that this study was conducted with genetic professionals from academic medical centers in the USA, participant perspectives may not be representative of professional practices and norms in other healthcare settings.

WIDER IMPLICATIONS OF THE FINDINGS: In considering the use of ECS products in their practices, reproductive healthcare providers may find it helpful to consider the perspectives of genetics professionals. These specialists have considerable experience with diverse forms of genetic testing and can provide valuable insights regarding new genomic risk assessment tools such as ECS.

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Key words: carrier screening / reproductive healthcare providers / genetics / focus groups

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Carrier screening has been a routine aspect of reproductive healthcare for over a decade (Doksum et al., 2001), and is often recommended for individuals with a family history of genetic disease and for ethnic populations with higher rates of severe recessive conditions (Kronn et al., 1998; Dolan and Moore, 2007; Gross et al., 2008). Non-targeted approaches to carrier screening that do not consider family history or ancestry have been a more recent development (Kaufman et al., 2001), and have been met with uneven enthusiasm from relevant professional organizations. For instance, in 2001 the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) released a joint statement encouraging cystic fibrosis (CF) carrier screening for all couples (Grody et al., 2001). The ACMG has also recommended non-targeted carrier screening for spinal muscular atrophy (SMA), while ACOG has taken a position opposing SMA screening in the general population (Prior, 2008; Committee on Genetics, 2009). Guidelines issued by European professional societies stress that carrier screening should be limited to severe health problems and involve validated tests with known predictive power, criteria which are challenged by the introduction of new conditions and non-targeted carrier screening (Borry et al., 2011).

The scope of non-targeted carrier screening will be influenced by new genetic sequencing technologies that enable inexpensive evaluation of large numbers of recessive diseases (Jackson and Pyeritz, 2011). Several commercial laboratories in the USA have developed products that evaluate more than 100 recessive conditions (Srinivasan et al., 2011; Jordan, 2012). With declining genotyping costs, it is reasonable to expect that the number of genetic conditions evaluated by expanded carrier-screening (ECS) products will continue to increase (Bell et al., 2011). For example, Bell et al. (2011) have shown that a carrier screening assessing 448 severe recessive diseases could be administered at a cost that would support its use in reproductive healthcare. While not yet in widespread use in the USA, ECS products appear to be gaining greater acceptance among reproductive healthcare providers so long as the cost would be comparable with conventional carrier screening (Ready et al., 2012).

Reproductive healthcare providers will play a critical role in the adoption of ECS products and need to be prepared for the potential challenges that lie ahead. Toward this end, reproductive healthcare providers may find it helpful to consider the perspectives of genetics professionals. These specialists have considerable experience with diverse forms of genetic testing and can provide valuable insights regarding the expansion of carrier screening.

We report results from a research study in which genetics professionals were asked how they would introduce expanded forms of carrier screening into patient care and discuss ECS with couples planning a pregnancy. A primary aim of the study was to clarify how genetics professionals view the potential benefits and challenges of ECS. A secondary aim was to solicit advice from genetics professionals regarding how best to integrate ECS into preconception reproductive healthcare. The results we present highlight several potential challenges that reproductive healthcare specialists will likely encounter as they seek to integrate ECS into their practices.

Focus groups were used to examine genetics professionals’ perspectives on the expansion of carrier screening (Macnaghten and Myers, 2004; Merriam, 2009). The focus-group data reported here comprise part of a larger study to assess genetics professionals’ perspectives on the return of diagnostic results from a variety of genomic tests.

A purposive sampling strategy was used to identify genetics professionals at academic medical centers with well-established genetics programs. The research team organized focus groups in Ann Arbor; Baltimore; Cleveland; Denver; Philadelphia; and Seattle (Uhlmann and Sharp, 2012). Sites were selected based on their geographical location, training programs in medical genetics and genetic counseling, translational research programs and clinical practice settings (e.g. pediatric versus adult clinics, public versus private institutions, etc.). With the approval of the Institutional Review Board at each study site, collaborators at Cleveland Clinic, Johns Hopkins University, University of Colorado, University of Michigan, University of Pennsylvania and University of Washington assisted in identifying participants with appropriate expertise in genetics. These individuals were approached by the Principal Investigator (R.R.S.) and recruited to participate in focus-group sessions. Participants provided written consent to participate and received $100 for their participation.

Six focus-group sessions were conducted in March 2011. A clinical case report was presented to each focus group to examine participants’ opinions about the use of highly multiplexed forms of carrier screening in reproductive healthcare. This case report consisted of a hypothetical patient’s medical history, reasons for seeking preconception reproductive counseling and an anonymous laboratory report presenting ECS results from a commercial laboratory. This laboratory was not involved in any aspect of this study. The ECS product discussed at the focus-group sessions must be ordered by a licensed physician and evaluates approximately 350 recessive mutations associated with 78 severe or common genetic diseases affecting children. Although carrier status for several of these conditions are often assessed in preconception and prenatal care in the USA (e.g. CF), this ECS product also includes many conditions that are not routinely evaluated by reproductive healthcare specialists, including Fanconi Anemia, Bloom Syndrome, Krabbe Disease, Pompe Disease and Maple Syrup Urine Disease.

Focus groups were moderated by R.R.S., who used a moderator guide to promote consistency across sites. Discussions of ECS lasted 30–60 min. Participants were asked to consider how they would prepare for a clinical appointment in which they would report test results to this hypothetical patient and counsel her about the potential implications of the results for pregnancy planning. Additional questions examined participants’ attitudes about the clinical implementation of ECS, including participants’ opinions about whether ECS might be preferable to more targeted approaches to carrier screening based on a patient’s family history or ethnicity. Participants were asked to identify potential challenges in the interpretation and communication of ECS results and to describe their overall levels of enthusiasm for ECS.

Focus-group discussions were audio-taped and transcribed to enable thematic analysis (Kondracki and Wellman, 2002). In an iterative process of independent review and consensus-building conferences, R.R.S., M.M. and J.M. created a coding scheme and codebook with definitions to categorize the text into primary thematic domains, subdomains and more specific categories. To promote construct validity and reliability of the conceptual domains identified through coding, a common set of initial focus-group transcripts was coded by two data analysts (D.C. and J.M.) to establish consistent application of code definitions. Using the coding scheme, the remaining transcripts were coded independently by...
Results

Forty genetic professionals participated in six focus groups for this study. Focus groups included professionals specializing in medical genetics, pediatric genetics, genetic counseling, public health genetics, primary care medicine, laboratory medicine, health communication, law and bioethics. Many participants’ professional responsibilities involve direct contact with patients, though some participants’ professional expertise in genetics is in the realm of research and scholarship. Four themes related to clinical applications of ECS emerged from focus-group discussions: potential benefits of ECS for specific patient populations; limitations of the test; complexities of pre- and post-test counseling; and the role of medical geneticists and genetic counselors in interpreting results. We present these major findings in greater detail below.

Potential benefits of ECS in reproductive healthcare

Participants felt there were many potential benefits supporting the use of ECS in reproductive healthcare, and that many patients would be interested in ECS. Drawing comparisons to conventional forms of carrier screening, a participant described how ECS could be helpful to patients seeking carrier status information for reproductive decision-making:

There are going to be some people very grateful to have this information, that see an opportunity to do some informed decision making and have some control over their reproductive lives and then there are other people who say ‘What God gives me, I will take and I don’t want anyone to tell me what to do’...It’s a continuum (FG5).

Discussions about the potential benefits of ECS focused largely on preventing the generational transmission of genetic disease. Participants agreed that there were no effective treatments for many of the diseases evaluated by ECS products and discussed reproductive options that couples could pursue. The reproductive options described by participants included in vitro fertilization and preimplantation genetic diagnosis (IVF–PGD), foregoing pregnancy, sperm donation and, in prenatal applications of ECS, testing the fetus or termination of the pregnancy. Of those options, participants agreed that IVF–PGD would be the most expedient pathway to manage couples’ reproductive risks, transferring only those embryos lacking the relevant genetic mutation. Recognizing that there is little insurance coverage for IVF in the USA, one participant described:

It is worth noting that currently if you know ahead of time that you and your partner are carriers for a very severe disease, and you are not interested in a pathway that may lead to prenatal diagnosis and termination, then you have very few options. You can not have kids...you can do PGD if you have lots of money and...you could do donor insemination, which most people don’t want to do (FG6).

Participants also felt that IVF patients may be particularly interested in ECS. Having already undertaken the financial and physical burdens of IVF, participants felt that the additional demands associated with ECS and PGD (following the identification of a shared genetic risk) would be lower for IVF patients than for other couples. As one participant commented, with the use of ECS these couples could increase their chances of having a healthy child for ‘pocket change’ in comparison to the costs of IVF procedures (FG1). As another participant clarified:

If you’re gonna go spend $20,000 to try to make an embryo then you – presumably you would like, you know, you’re not going to do this a whole lot of times so you want to make sure that this is the best possible – you know, you know what you’re at risk for and if it’s possible to test you would want to do that as well (FG2).

Overall, participants agreed that ECS had great financial value when compared with conventional carrier screening. Many viewed ECS as an expansion of carrier screening for single gene mutations with far greater disease coverage at a lower cost. For some participants, this economic value would be a primary basis for preferring ECS to conventional carrier-detection strategies, especially, if genetic screening was indicated for a specific condition based on the patient’s family history or ethnicity. As one participant asked, ‘There are people of Caucasian ancestry who are concerned about CF and...if they can get this for just a couple hundred bucks more...why not?’ (FG1).

Concerns about limitations of ECS

Despite these potential advantages of ECS, participants expressed concerns about the marketing of carrier-screening panels as ‘universal’ applications for all patients. They cautioned that current ECS products do not evaluate rare mutations that could be identified by alternative methods such as DNA sequencing. Participants also noted that many of the mutations evaluated by ECS products would not be pertinent to all ethnic populations or couples, and felt that a screening panel tailored to a particular racial or ethnic population might be more appropriate for some patients. As a participant explained, ‘this might not be the best panel for every [couple], for both partners of every couple. It might be good to pick up in one and then for the other you’d have to do sequencing to have a meaningful impact’ (FG2). Some participants also expressed concerns that reproductive healthcare providers might fail to recommend more conventional forms of targeted genetic evaluation, such as screening tests indicated by a couple’s ethnicity, based on perceptions about the coverage of ECS products that are marketed as universal in scope.

Lack of professional guidelines on the use ECS added to participants’ difficulty in determining when it would be appropriate to recommend these products. Participants discussed this issue by highlighting existing US-based professional societies’ guidelines on carrier screening for CF, SMA and diseases that are more common in the Ashkenazi Jewish population:

It would be really important to convey to the colleague [a specialist in reproductive healthcare] that these tests for far more conditions than are currently recommended for routine carrier screening, that there are practice guidelines that identify a set of conditions where it’s recommended to offer routine carrier screening. This test both misses some of those and tests for way more. Therefore...they should test for everything that is recommended and...you need to make a judgment based on your
Participants expressed major concerns about the technical limitations of ECS and felt the most significant limitation of ECS was the inability to fully rule out the possibility of severe recessive diseases due to rare mutations. Participants noted gaps in coverage of both specific genes and individual mutations included in ECS products. For example, participants noted that one of the more comprehensive ECS products available examines just 343 mutations and expressed concerns that rare mutations and variants of unknown significance would not be detected. Furthermore, in reviewing the sample clinical report, participants noted that because less-common mutations in specific ethnic populations are not included, patients and clinicians might be falsely reassured by ‘negative’ results.

**Pre- and post-test counseling**

Participants felt it was critical for reproductive healthcare providers to counsel patients about the limitations of ECS products before pursuing testing. Participants also stressed the need to explain to patients that aneuploidies and other major chromosomal abnormalities are not evaluated by ECS. Participants raised concerns that some patients could mistakenly believe that a negative screening result guarantees that their child(ren) will not have a genetic condition. They emphasized that reproductive healthcare providers would need to address potential misperceptions that ECS provides patients an ‘all clear’ or risk-free pregnancy (FG6). One participant commented that it would be important to stress to patients that, ‘This is only 78 diseases, so beyond 78 we don’t know’ (FG3). Another participant summarized the limitations to review with patients in the following way:

> This obviously really doesn’t cover everything, not even everything in the world that you might be able to test for carrier status; ... it doesn’t cover everything. What it does cover it may not be perfect for giving us an answer for—and then some things are just things we cannot test you for, as carrier status, because it’s not a carrier status question. And so we’re not guaranteeing you a healthy baby (FG3).

There was strong agreement among participants that the choice to recommend ECS should be a highly individualized decision that considers the specific information a patient or couple is seeking.

> It makes a big difference ... the patient request comes through because if the patient were to come in and say, ‘You know, I understand that there is [sic] some genetic tests, what would you recommend?’ My advice would be, recommend those screening tests that have the support of your practice guidelines as opposed to this kind of test [ECS] (FG6).

Participants also felt that in counseling patients about ECS, reproductive healthcare providers should be sensitive to the possibility that some findings may suggest medical interventions that exceed many patients’ financial capacity to pay, such as the use of IVF–PGD to manage reproductive risks. Given the novelty of this form of genetic testing, participants speculated that couples in the USA might face high out-of-pocket costs due to insurance coverage gaps related to additional genetic evaluation or gene sequencing. As one participant cautioned, ‘the cost of that next step may be $4,000 and it’s not going to be covered by insurance so you, you’ve put them on a path they can’t really do’ (FG6).

**Involving specialists in genetics**

Although there are no existing professional guidelines on ECS, participants felt that if and when reproductive healthcare providers offer ECS, it should be accompanied by genetic counseling. There was consensus that patients should receive genetic counseling before and after ECS, and that counseling should be provided by a clinician with expertise in communicating genetic information. Participants discussed the fact that many reproductive healthcare providers are comfortable with carrier-screening tests and have experience with related types of genetic counseling. As one participant commented, ‘this isn’t in uncharted waters in the OB [obstetrics] world either. I mean they’ve been doing this for years and years and years with the Ashkenazi Jewish disorders and with CF testing’ (FG2).

However, participants emphasized how reproductive healthcare providers’ familiarity with conventional carrier-screening tests, such as tests for CF and SMA, may result in receptiveness to ECS products that include a far greater numbers of diseases, including many very rare diseases. Participants argued that it would be a mistake to view conventional forms of carrier screening and ECS as raising similar clinical challenges because of the rarity of the conditions included on the panels.

Although participants did not suggest that reproductive healthcare providers were ill-prepared to use ECS products, they stressed the range of potential findings that could be associated with these tests, and highlighted how results about very rare diseases could suggest a need to involve a medical geneticist or genetic counselor. In reference to the interpretation of the ECS report used to facilitate discussion, one participant commented that ‘this is all Greek to an OB’ (FG2). Another participant’s comments reinforced the counseling challenges posed by the rarity of the mutations included in ECS panels, noting that:

> [When screening for Ashkenazi diseases... when there’s 12 diseases, I can still explain to a patient, ‘Well these are all diseases that are lethal in the first two years of life but when you look at this one over here, this is something that there’s a treatment for—do you want to opt out of this one? You can still opt out.’ So... [with ECS] ... even I would have to go look up all of these diseases. I don’t even know what they are (FG6).

Participants encouraged reproductive healthcare providers to consult a clinician with expertise in communicating genetic information and stressed that there would likely be situations in which ECS results would necessitate additional evaluation by a medical geneticist or genetic counselor.

**Discussion**

To our knowledge, this is the first study to examine genetics professionals’ views regarding the value of ECS in reproductive healthcare. Our findings suggest that genetics professionals believe current ECS products have major limitations. To the extent that current ECS products examine only a fraction of the many genes associated with genetic disorders, limit their evaluation to common genetic mutations within those genes, genetics professionals felt that reproductive healthcare providers will encounter a number of challenges in interpreting ECS results and counseling patients about their significance for pregnancy planning. Of special concern was the possibility that...
patients who receive 'negative' ECS results may garner a false sense of reassurance about reproductive risks in the context of pregnancy planning.

Genetics professionals also stressed how ECS presents a more complex array of clinical challenges in comparison to traditional methods of carrier detection, given the rarity of conditions included in the panel and the prospect that variants of unknown significance might not be detected depending on the panel composition. This finding reflects concerns raised by Kohane et al. (2006) that as the number of individual assays on a multiplexed genetic test increases, the likelihood of erroneous results (e.g., false positives) or clinically ambiguous findings (e.g., variants of unknown significance) increases significantly. In addition to these challenges, as carrier-screening panels expand to include less-common genetic diseases, the interpretation of mutational results is hindered by the lack of data on clinical phenotypes associated with rare variants. Previous research has shown that reproductive healthcare providers often receive limited training in genetics (Firth and Lindenbaum, 1992; Kershner et al., 1993; Macri et al., 2005). If ECS is to be integrated effectively into reproductive healthcare, potential gaps in genetic knowledge will need to be addressed.

Given the extent to which ECS departs from more conventional approaches to carrier screening, it will be important for reproductive healthcare providers who are considering ECS products to develop strong collaborative relationships with medical geneticists and genetic counselors. Previous research has reported that women’s healthcare providers would find post-test genetic counseling for ECS useful (Ready et al., 2012). Our findings suggest that genetics professionals also believe that a significant proportion of patients evaluated by ECS products may need to be referred to a medical geneticist or genetic counselor for post-test counseling or additional evaluation. In addition, medical geneticists and genetic counselors may be able to assist reproductive healthcare providers in developing counseling strategies to ensure that patients considering ECS products are positioned to make informed decisions about their value in pregnancy planning. Notably, participants’ discussions focused on assessing the implications of ECS results for preconception reproductive counseling, and did not extend to familial or personal health impact of the expansion of carrier detection. Future research should assess implications of ECS beyond preconception counseling for individual patients.

The genetics professionals we consulted agreed that while offering ECS to patients may be appropriate in select circumstances (e.g., for patients who are already pursuing IVF whose family history, race and/or ethnicity indicates the suitability of ECS), they articulated that widespread use of ECS products would represent a significant departure from clinical practice guidelines in genetics and reproductive healthcare in the USA. Carrier-screening guidelines currently exist for very few of the genetic disorders evaluated by ECS products (Grody et al., 2001; Prior, 2008; Committee on Genetics, 2009). While the merit of these guidelines was not explicitly debated in the context of the focus groups, literature documenting the controversy over these guidelines may be instructive as reproductive healthcare providers consider whether to offer ECS to their patients (Watson et al., 2004; Leib et al., 2005; Pletcher et al., 2008). For example, while the ACMG has recommended population-wide carrier screening for SMA, ACOG has not recommended SMA screening for the general population. In support of this position, the ACOG Committee Opinion stated that ‘the threshold for carrier frequency any disease must meet to be considered for widespread screening has never been formally addressed by genetics and public policy professionals’ (Committee on Genetics, 2009). For this reason, ACOG suggested that additional research be done ‘assessing pilot screening programs, cost effectiveness analysis, development of appropriate educational materials and the development of laboratory assay standards and result reporting’ before recommending population-wide carrier screening for SMA (Committee on Genetics, 2009).

ACOG’s position on SMA screening is noteworthy when one considers the future of ECS. The large number of genetic diseases evaluated by ECS products will pose significant challenges to gathering the types of data that ACOG suggests is necessary in order to make informed recommendations about population-wide carrier screening. Lacking such data, it may be difficult to achieve consensus on whether to recommend ECS, leaving individual clinicians with little guidance about whether and when to introduce ECS products to their patients. In the absence of professional consensus regarding the composition of conditions in ECS panels, professional societies may find it helpful to produce recommendations that address patient counseling about the general use of ECS for preconception and prenatal carrier screening. It is noteworthy that while study participants raised concerns about the marketing of ECS as a ‘universal’ carrier screen and noted gaps in the coverage of genetic conditions and mutations, they did not raise concerns about the provision of ECS via commercial laboratories. Given the growing commercial market for these types of testing, future research is indicated to explore clinicians’ attitudes toward various commercial providers and the composition of their ECS test platforms.

There were several limitations associated with this study. As focus groups consisted of participants from large academic medical centers in the USA, some of the outcomes may be context-specific and may not be representative of professional practices and norms in other healthcare settings. To the extent that ECS products have not been widely used to date, participants may have had limited familiarity and direct clinical experience with these products. In addition, since the focus of this study was on genetics professionals’ views of ECS, reproductive healthcare providers were not included in focus-group discussions and the frequency of participants’ interactions with reproductive healthcare providers was not assessed. Future research should examine reproductive healthcare providers’ use and opinions of ECS.

**Conclusion**

Our results suggest that genetics professionals believe current ECS products have major limitations and are not ready for routine use in reproductive healthcare. Although ECS products have been marketed as improved versions of traditional carrier screening, genetics professionals in this study felt that ECS differed from conventional risk assessment strategies in several important ways that would present significant interpretive challenges. These genetics professionals also stressed the extent to which ECS products depart from standards of care in medical genetics and reproductive healthcare and would introduce a host of difficult patient counseling challenges.

As new genetic technologies enable a wider array of genetic testing options in reproductive medicine, it is important for healthcare providers to consider the potential opportunities and challenges associated
with these new modes of risk assessment. In considering the use of ECS products in their practices, reproductive healthcare providers may find it helpful to consider the perspectives of medical geneticists and genetic counselors. These genetics professionals have considerable experience with diverse forms of genetic testing and can provide valuable insights regarding new genomic risk assessment tools such as ECS.

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**Authors’ roles**

R.R.S. was involved in study design, data collection, drafting the manuscript and critical discussion of its contents. D.C. and M.L.M. contributed equally to the work reported in this manuscript and prepared an initial draft of the manuscript. D.C., M.L.M. and J.M. were involved in data analysis, manuscript preparation and critical discussion of its contents.

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**Conflict of interest**

None declared.

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