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Expanded carrier screening: counseling and considerations

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Abstract

The primary goal of carrier screening is to identify asymptomatic individuals who carry variants associated with genetic diseases, to inform about the risk of having a child with a genetic disease. Carrier screening can be accomplished through different approaches including ethnicity-based screening, pan-ethnic screening, and expanded carrier screening (ECS), and the decision to pursue carrier screening is voluntary. ECS takes a broad approach by screening for a large number of genetic diseases irrespective of ethnic background, and ideally is performed prior to conception. ECS has many benefits, including that it does not depend on accuracy of reported ancestry, as well as its greater yield of information that can be used for reproductive decision-making. However, there are also many important limitations of ECS to consider, ranging from the yield of unexpected information, uncertainty about the phenotype of a particular disease for which an individual is a carrier, and greater downstream costs associated with further testing and genetic counseling. Detailed genetic counseling both prior to and after ECS is essential in order for patients to understand the breadth of this approach, potential and actual results, and limitations.

Introduction

The primary goal of carrier screening is to identify asymptomatic individuals who carry variants associated with genetic diseases, in order to inform about the risk of having an affected child. The chance of an individual being a carrier for a genetic disease is dependent in part on ethnic background and family history, with some populations having a greater baseline prevalence of certain diseases. However, genetic variants can also occur de novo, and it is well known that genetic diseases are not isolated within certain populations (ACOG Committee 2017a, b; Grody et al. 2013; Edwards et al. 2015).

Genetic carrier screening during pregnancy was introduced in the 1970s, beginning with the hemoglobinopathies. Since that time, the approach to carrier screening has expanded to include additional genetic diseases such as Fragile X syndrome, cystic fibrosis, Canavan disease, familial dysautonomia, Tay Sachs disease, spinal muscular atrophy, and many others (ACOG Committee 2017a). Prenatal carrier screening has traditionally been focused on the detection of a select number of genetic diseases, based on patient-reported ethnicity and family history. However, limitations of this approach include that genetic diseases are not

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isolated within certain populations, and in the setting of increasingly multiethnic populations, it is challenging to accurately estimate genetic risk based on ancestry. A much broader approach to prenatal carrier screening called expanded carrier screening (ECS) has emerged in recent years, as a method that takes a pan-ethnic approach to screening for a larger number of genetic diseases.

ECS has many benefits, including its pan-ethnic approach that does not depend on accuracy of reported ancestry, as well as a greater yield of information that can be used for reproductive decision-making. However, there are also many important limitations of ECS, ranging from the yield of unexpected information, uncertainty about the phenotype of a particular disease, and greater downstream costs associated with further testing and genetic counseling (ACOG Committee 2017b; Grody et al. 2013; Edwards et al. 2015). Detailed genetic counseling both prior to and after ECS is essential in order for patients to understand the voluntary nature and breadth of this approach, potential and actual results, and limitations.

Purpose of genetic carrier screening

Genetic carrier screening is optional for patients who are considering pregnancy or currently pregnant. It offers the advantages of more informed reproductive decision-making with earlier preconception diagnosis if preimplantation genetic diagnosis is pursued, earlier prenatal diagnosis if invasive diagnostic testing is done, and more targeted perinatal care with anticipation of neonatal needs when a diagnosis is made during pregnancy. Multiple approaches to carrier screening exist, though, and it is essential for patients and providers to understand the benefits and limitations of each type. The American College of Obstetricians and Gynecologists (ACOG) has stated that ethnicity-based, pan-ethnic, and ECS are all acceptable strategies to screen individuals for carrier status prior to and during pregnancy (ACOG Committee 2017b). However, it is advised that providers develop a routine approach that is consistently and equitably offered to all patients in the setting of these available screening strategies. These approaches are discussed in further detail below.

When individuals are screened for genetic disease carrier status prior to conception, there is more ample time to provide detailed pre- and post-test genetic counseling, thoroughly address questions, and complete follow up testing that may become indicated. With ECS in particular, additional testing and counseling become indicated more commonly than with traditional ethnicity-based screening, owing to the large number of diseases screened and the substantial proportion of individuals identified as carriers (ACOG Committee 2017b).

If individuals learn that they are carriers of a particular genetic disease prior to conception, this allows them time to meet with reproductive specialists to discuss the possibility of preimplantation genetic diagnosis, donor gametes, and other options. Genetic carrier screening can also be done during pregnancy, although this may result in less time for follow up testing, counseling, and decision-making. When diagnostic testing is done during pregnancy and a fetus is found to be affected with a particular genetic disease though, families can process this information, gather data about the disease, consider decisions such as continuing or terminating the pregnancy, and anticipate outcomes after birth.

Beyond these considerations, when a fetus is found to be affected with a genetic disease in utero, knowledge of this status may lead to critical changes in perinatal management to optimize the outcomes for that fetus. For example, if a fetus is found in utero to be affected by a urea cycle defect that is associated with life-threatening risks in the neonatal period without appropriate management, providers may recommend delivery at a tertiary care hospital, and neonatologists as well as other specialists may anticipate treatments and arrange for them ahead of time. Further, parents may form expectations for the neonatal period, and anticipate certain decisions or outcomes that they may encounter. Because of the large number of genetic diseases included on most ECS panels, the ability to anticipate neonatal outcomes for rare diseases may be significantly increased from years prior. The benefits of this approach must be carefully weighed with the risks though, as discussed below.

Ethnicity-based carrier screening

Traditionally, recommendations for genetic carrier screening in the preconception and prenatal populations have been based on patient-reported ethnicity and family history. For example, screening for Tay Sachs carrier status is recommended in patients of Ashkenazi Jewish, French Canadian, or Cajun heritage, due to the increased prevalence of the disease in these populations (ACOG Committee 2017a, b). When ethnicity-based carrier screening is applied, the ACOG also recommends screening individuals of Ashkenazi Jewish, French Canadian, or Cajun descent for Canavan disease, cystic fibrosis, and familial dysautonomia (ACOG Committee 2017a, b). The American College of Medical Genetics and Genomics (ACMG) further recommends screening these populations for five additional diseases (Fanconi anemia group C, Niemann Pick type A, Bloom syndrome, mucolipidosis IV, and Gaucher disease), and the ACOG supports consideration of screening for these diseases (ACOG Committee 2017b; Grody et al. 2013). Further recommendations have been published by both the ACOG and ACMG for ethnicity-based carrier screening for several other genetic diseases.

Benefits and risks of ethnicity-based screening

While ethnicity-based screening may work well to identify genetic carriers among higher risk populations, it is dependent on accurate patient-reported ancestry. In the setting of increasingly multiethnic populations with individuals of mixed descent, the application of ethnicity-based carrier screening becomes more challenging. Opportunities to screen individuals who may actually be at higher risk are missed when ethnic background is mixed or incompletely known. This may significantly alter the residual risk and decrease the accuracy of counseling about risk of disease. Additionally, while genetic diseases may be more prevalent in certain ethnic populations, they are not isolated to those populations, and individuals of non-traditional ethnic backgrounds who are actually genetic carriers do not receive screening. Further, screening for a select few genetic diseases limits the information provided to individuals in order to make reproductive decisions (ACOG Committee 2017b; Grody et al. 2013; Edwards et al. 2015).

Because of these considerations, a pan-ethnic approach to carrier screening may be pursued, meaning that individuals are screened for select diseases irrespective of reported ethnicity or family history. Alternatively, ECS takes an even broader approach to pan-ethnic screening, by screening each individual for up to hundreds or thousands of diseases at one time irrespective of reported ethnic background (Chokoshvili et al. 2017).

Expanded carrier screening

ECS takes a pan-ethnic approach to genetic carrier screening, and may include as few as less than ten genetic diseases to as many as thousands (ACOG Committee 2017b). With advances in next-generation sequencing, along with decreasing costs of this technology, it has become possible to screen for carrier status for a large number of genetic diseases at one time. Laboratory techniques used for ECS include targeted high-throughput analysis for specific variants within genes known to be associated with disease, or a broader approach with next-generation sequence analysis covering the entire coding regions of each gene (Nazareth et al. 2015).

ECS provides the most accurate estimate of risk to a pregnancy when both reproductive partners are screened. ECS is ideally performed prior to a pregnancy when there are fewer time limitations. This allows partners to be screened in sequence rather than in parallel, meaning that one reproductive partner can undergo screening if the other reproductive partner is found to be at risk for transmitting a genetic variant capable of causing disease. When ECS is not performed until during a pregnancy, screening is often done in parallel for both partners to allow adequate time for decision-making about diagnostic testing after screening results return. ECS still can and should be offered in situations where one reproductive partner is not available though, such as when a woman undergoes preconception screening during her reproductive years before she is partnered or ready to conceive. With this should come appropriate counseling to explain that the estimate of genetic risk to a pregnancy is less precise when only one partner is screened and that risks to a pregnancy may change with different partners.

Benefits of expanded carrier screening

There are several important benefits associated with ECS, many of which were outlined above. ECS takes a pan-ethnic approach to carrier screening rather than focusing on ethnicity-based risks, given the inaccuracies that have been demonstrated in individual reports of ethnic background (Nazareth et al. 2015). Additionally, ECS has been shown to reduce disparities in detecting carriers within couples of different ethnic backgrounds (Haque et al. 2016).

Because of the large number of diseases screened with ECS panels, greater opportunity exists for identifying carrier status, and thus disease status in an embryo or fetus prior to or during pregnancy. A greater yield of information can be quite informative for some couples who wish to have more data upon which to base their decisions. Further, the greater yield of information can be informative for providers, enabling a more targeted approach to care when a specific disease is diagnosed in the fetus. This may include management decisions such as monitoring during the pregnancy, timing of delivery, site of delivery, anticipation of

neonatal care and treatments, and many others. While there are many benefits of ECS, there are also risks that are essential to consider though, ranging from the high likelihood of being a carrier for at least one disease to the time and cost associated with downstream genetic testing.

Risks of expanded carrier screening

While guidelines have been published by professional societies with regard to diseases for inclusion on ECS panels (ACOG Committee 2017a, b; Grody et al. 2013), there are not currently uniform or standardized best practices for the utilization of ECS, nor is there regulatory oversight of ECS companies (Chokoshvili et al. 2017). The criteria for inclusion of diseases on ECS panels are not consistent across laboratories, and at present, most panels include many diseases that are not recommended for routine screening (Stevens et al. 2017; Norton 2017). Additionally, the number and types of diseases included on ECS panels vary from one laboratory to another. Although the technology exists to screen for hundreds of genetic diseases at once with relatively low upfront associated cost, caution should be exercised in doing so due to a variety of associated risks (Grody et al. 2013; Edwards et al. 2015). Further, while this document focuses on ECS panels that are offered to patients through providers in health-care settings, there are some companies that offer ECS on a direct to consumer basis (Chokoshvili et al. 2017). The risks of ECS as discussed below should be considered even more carefully in the context of direct to consumer ECS, given the lack of genetic counseling prior to and after the test in this setting.

Low prevalence of disease—The prevalence of each genetic disease included on ECS panels varies, with some being relatively common but others being exceedingly rare. For example, cystic fibrosis has a prevalence of 1 in 3200 to 1 in 31,000 depending on the population (Ong et al. 2017), while the prevalence of alpha mannosidosis is less than 1 in 300,000 (Malm and Nils-sen 2012). For the very rare diseases, less is often known about causative alleles and variants, spectrum of phenotypes, and long-term outcomes. This impacts not only the accuracy of counseling when individuals are identified as a carrier of one of these diseases, but also limits estimations of residual risk when individuals receive a normal result.

High prevalence of carrier status—Because of the large number of genetic diseases included on ECS panels, there is a substantial chance that individuals will be identified as a carrier of at least one disease, even though the prevalence of many of the diseases is quite low. In fact, approximately 24% to well over 50% of all individuals screened with ECS panels may be identified as carriers (ACOG Committee 2017b; Peyser et al. 2019; Lazarin et al. 2013). In a cohort of over 23,000 individuals undergoing preconception or prenatal carrier screening for 108 genetic diseases, 24% were found to be carriers of at least one disease and 5% were carriers of more than one disease (Lazarin et al. 2013). In another large retrospective study, 29% of individuals were found to be carriers of a genetic disease using ECS panels, as compared to only 8% with an ethnicity-based approach to screening (Peyser et al. 2019). Significant time and cost may be associated with downstream genetic testing when individuals are identified to be carriers, including those associated with screening for the partner, preimplantation genetic diagnosis prior to pregnancy, diagnostic testing during a

pregnancy, ultrasound surveillance during a pregnancy, and many other considerations. Decisions about whether or not to proceed down this further diagnostic pathway are best rooted in the preferences of the individual patient or couple after careful genetic counseling, with higher priority given to further testing for severe childhood-onset diseases, more prevalent diseases, and other such considerations as discussed later in this article.

Additional variants may also be detected when full exon sequencing is performed for ECS as opposed to targeted sequencing, and the sensitivity of the test increases when the methodology allows for detection of higher prevalence diseases as well as those with more complex molecular genetics (Beauchamp et al. 2018). In a retrospective modeling analysis designed to quantify the risk of recessive conditions identified through ECS in a diverse population, approximately 29% of the modeled population were found to be carriers when full exon next-generation sequencing was performed, compared to 14–19% when targeted sequencing was done (Haque et al. 2016). For many of the modeled couples, the ECS approach reduced disparities though, in terms of detecting carriers within couples of different ethnic backgrounds.

Mild phenotype—ECS panels may include genetic diseases with very mild phenotypes. An example of this is achromatopsia, a condition that may be associated with reduced visual acuity, nystagmus, photophobia, scotoma, and/or color blindness. Variants in *CNGB3, CNGA3, GNAT2,* and several other genes can lead to achromatopsia. However, this condition is not progressive and it affects no other organ systems (Kohl et al. 2018). In comparison to other diseases with life-threatening complications or the need for immediate intervention, the prenatal diagnosis of achromatopsia offers no opportunities to optimize perinatal management and is controversial for inclusion on ECS panels.

Late-onset disease—In addition to diseases with mild phenotypes, ECS panels often include diseases with onset that is typically later in life. For example, Wilson disease is a disorder of copper metabolism that presents with hepatic, neurologic, or psychiatric manifestations, and is caused by variants in the *ATP7B* gene. Treatment for Wilson disease is lifelong, with copper chelating agents or zinc to ameliorate disease manifestations for some and liver transplant becoming indicated for others. However, this disease usually does not have symptom onset until adolescence through the sixth decade of life (Weiss 2016). Diseases such as this with onset later in life have raised questions about appropriateness for inclusion on ECS panels, primarily as no opportunities exist for optimizing management surrounding pregnancy even if this diagnosis is made in utero.

Variable expressivity and incomplete penetrance—The concepts of penetrance and expressivity are essential for counseling about ECS. Penetrance describes the proportion of individuals that manifest a particular disease among the total number of individuals with the same genotype. It is often that not all individuals with a particular genotype will show evidence of the associated disease. On the other hand, expressivity describes variability in degree of disease manifestations across individuals with the same genotype. In other words, this refers to severity or spectrum of disease.

Many genetic diseases included on ECS panels are associated with variable expressivity and incomplete penetrance. For example, short-chain acyl-CoA dehydrogenase (SCAD) deficiency is a disorder of fatty acid oxidation that is caused by variants in the *ACADS* gene. The majority of individuals identified on newborn screening over the years have not shown evidence of disease manifestations, so SCAD is now referred to as a biochemical phenotype rather than a disease (Wolfe et al. 2018). However, a screen positive result for SCAD on ECS might lead to uncertainty, as a small proportion of affected individuals can have developmental delay or other features, and many individuals might find this uncertainty as well as any further diagnostic testing to be anxiety provoking. A large number of other genetic diseases included on ECS panels are similar in terms of their variable expressivity and incomplete penetrance, and genetic counseling surrounding these diseases becomes much more complex.

Optimal method of carrier status detection—For some diseases on ECS panels, sequencing is not the best method by which to detect carrier status. An example of this is Tay Sachs disease, for which assays of hexosaminidase A enzymatic activity in serum or leukocytes is a very accurate and cost-effective means by which to identify carriers. Further, pseudodeficiency alleles that do not actually reduce enzyme activity may be identified on sequencing, and in some populations a characteristic deletion in the *HEXA* promoter and exon 1 leads to disease (Kaback and Desnick 2011). When such diseases are of particular interest, testing with the most sensitive modality should be explored, rather than relying on sequencing through an ECS panel.

Interpretation of genetic variants—When full exon next-generation sequencing is performed for ECS rather than targeted sequencing, it is possible to identify variants of uncertain clinical significance (VUS). Standard criteria have been published by the ACMG for interpretation of genetic variants (Richards et al. 2015). However, clinical interpretation of variants can be challenging, especially in situations where they are rarely seen, the genetic disease itself is very rare, or associated outcomes are not clear (Grody 2016). Assumptions may be made in these situations based on information available at the time in variant databases and published literature, but these interpretations are less certain and are subject to change. As such, individuals undergoing ECS should be aware that the interpretation of a variant reported as potentially pathogenic could change over time as additional data emerge. Further, variants not reported if deemed unlikely to lead to disease could later be found to be pathogenic.

Further testing—Following a positive result on ECS for an individual, carrier testing for that individual's partner becomes indicated to determine their risk of conceiving a child with the implicated genetic disease. If ECS identifies both members of a couple to be carriers for the same genetic disease, further testing may become indicated, and with this further testing comes greater time and cost for both the individuals being tested and the providers caring for them.

When carrier status is discovered prior to pregnancy, families may decide whether to pursue preimplantation genetic diagnosis to determine if embryos carry the genetic variants leading to disease. If this is deferred or carrier status is learned during pregnancy, chorionic villus

sampling or amniocentesis can be done to determine whether a fetus is affected with the disease in question. Additionally, situations may arise in which additional testing becomes indicated to determine whether fetuses carry variants in *cis* or in *trans,* or whether additional disease-modifying variants or alleles are present. While it is possible that follow-up testing leads to a clear diagnosis, uncertainty may still remain in terms of phenotype, outcomes, and long-term prognosis.

Residual risk—When the results of ECS panels return normal, it is essential to counsel families about residual risk. Residual risk depends in part on the underlying carrier frequency of each disease within a population based on ethnic background (ACOG Committee 2017b). Along these lines, residual risk also depends on accurate knowledge of individual ethnic background. Other important considerations for estimation of residual risk are baseline knowledge of the alleles and variants leading to the disease, as well as the ability of the testing platform used to detect disease-causing variants. Platforms that perform full exon sequencing will detect more variants than those employing targeted sequencing for known disease-causing variants (Beauchamp et al. 2018). For many diseases that are rare, disease-causing variants may not be well understood, and knowledge of disease-causing variants may be especially lacking for some ethnic groups (Nazareth et al. 2015). Further, our understanding of disease-causing variants may change over time, so residual risk may also change over time. Particularly in the setting of rare and less well understood diseases, caution should be exercised in the interpretation of normal ECS results.

Anxiety—Significant anxiety on the part of individuals and families undergoing genetic screening may occur. This may stem from emotional reactions to receiving a positive screen result, personal connection to a disease, mode of inheritance, stage of life, and many other factors (Nazareth et al. 2015). There is some evidence to suggest though that initial emotional reactions to a positive screen result when done prior to conception largely dissipate over the course of a few months. More research is necessary to explore the impact of ECS testing and results on individual well-being.

Professional society recommendations for expanded carrier screening

Resulting from these considerations, the ACOG has recommended that ECS include only genetic diseases with a carrier frequency of at least 1 in 100 (or a disease prevalence threshold of 1 in 40,000), a well-defined phenotype, early onset in life, significant impact on quality of life, association with physical or cognitive impairment, or need for medical or surgical intervention (ACOG Committee 2017b). The ACOG additionally specifies that diseases included on ECS panels should be able to be diagnosed in utero, and there should be opportunities to optimize perinatal management when a disease is diagnosed.

Similarly, the ACMG has published recommendations for inclusion of genetic diseases on ECS panels (Grody et al. 2013), which include the following major points: (1) genetic diseases should be of a nature that most at-risk individuals would consider prenatal diagnostic testing to allow for reproductive decision-making; (2) genetic diseases with a mild phenotype, variable expressivity, or incomplete penetrance should be made clear and individuals should have the ability to opt out of testing for these; (3) when adult-onset

diseases are included on ECS panels, individuals should consent to screening for these and understand that there could health implications for themselves as well; (4) the causative genes, variants, and variant frequencies for each disease should be known, to counsel individuals about residual risk if results are normal; (5) the association between genetic variants detected and severity of the disease phenotype should be well known; and (6) laboratories performing ECS should adhere to quality control and proficiency testing standards, and these processes should be transparent.

Additional society recommendations include those from the European Society of Human Genetics (ESHG) (Henneman et al. 2016). These recommendations include that ECS panels should focus on a comprehensive set of severe childhood-onset disorders, tests should have established clinical utility, tests should be designed to achieve high clinical validity, and sequence variants that are reported should be those that are pathogenic and clearly affect function.

At present, a substantial proportion of diseases on ECS panels do not meet the criteria as outlined by the ACOG, ACMG, or ESHG for routine screening. Six US-based commercial laboratories offering ECS were recently reviewed in a study to determine the proportion of genetic diseases on these panels meeting criteria for inclusion (Stevens et al. 2017). The proposed criteria by these authors for inclusion of genetic diseases on ECS panels were similar to those put forth by the ACOG and ACMG, but were focused on early-onset autosomal recessive diseases with a carrier frequency of at least 1 in 100, moderate to severe phenotype with complete penetrance, and a minimum detection rate of 70% for carrier status. Applying their proposed criteria, the authors found that an average of only 27% (96 genetic diseases) met criteria for inclusion, with a range of 22–68% per panel. The two most common reasons that genetic diseases failed to meet criteria for inclusion were a carrier frequency of less than 1 in 100 and a disease detection rate of less than 70%.

Further considerations for expanded carrier screening

Genetic counseling

Genetic counseling is essential prior to sending ECS panels, as well as after results return. Whenever possible, counseling by a provider trained in genetics is ideal to adequately address the risks and benefits outlined above. Given the large number of genetic diseases included on most ECS panels though, it is not feasible to explain the risks and benefits of screening for each individual disease. As such, the ACOG and ACMG have recommended more general counseling to increase patient awareness of the types and breadth of conditions on each panel (ACOG Committee 2017b; Grody et al. 2013).

Pre-test counseling should include that carrier screening can be done through different approaches including ethnicity-based screening, pan-ethnic screening, and ECS, and the decision to pursue carrier screening is voluntary. It is possible that non-paternity could be uncovered in the process of ECS or follow up testing. While most diseases on ECS panels are autosomal recessive in inheritance, some are, for example, autosomal dominant. This means that findings from ECS could have implications for the current or future health of the

individuals themselves being screened, and could result in diagnosis of a genetic disease in the individual being screened.

There should be opportunity to opt out of screening for certain diseases, particularly those with later onset, incomplete penetrance, or variable expressivity (Grody et al. 2013). The ACOG has also noted that providers should evaluate the appropriateness of a panel for their practice, and providers may choose to work directly with companies offering ECS to customize a panel for their practice (ACOG Committee 2017b). Categories to consider when deciding if a genetic disease should be included on ECS panels include the scope (disease prevalence, frequency of the gene, and penetrance of the phenotype), impact (effect on quality of life, degree of impairment, and need for intervention), age of onset (childhood versus adult), and actionability (availability of preconception or prenatal diagnosis, relevance to reproductive decision-making, and ability to optimize perinatal management when diagnosis of the disease is made) (Kraft et al. 2018a).

After results of ECS return, counseling should cover any follow-up testing that becomes indicated, or residual risk when results are normal. All available reproductive options should be reviewed. Results of ECS for a given couple apply only to pregnancies for that couple, and if a different partner becomes involved in the future, screening would need to be done for the new partner. At present, recommendations from professional societies are that ECS should only be done once in an individual's lifetime. Individuals should be encouraged to maintain records of their ECS results, and repeat screening surrounding subsequent pregnancies is not recommended (ACOG Committee 2017b; Grody et al. 2013). Focused genetic counseling and testing should be offered in situations where a particular disease was not tested. Finally, ECS does not replace the need for newborn screening.

Timing of ECS

As discussed above, ECS is best suited for the preconception period. Professional societies have recommended preconception genetic carrier screening to allow more ample time to provide detailed pre- and post-test genetic counseling, as well as for follow-up testing that may become indicated. When one reproductive partner is found to be a carrier for a genetic disease, testing should be offered to the other partner for that genetic disease. When ECS is done prior to pregnancy, there are usually fewer time limitations, allowing testing of partners to be done in sequence rather than in parallel. Because several weeks may be needed to obtain screening results, and follow up prenatal diagnostic testing also takes time to return, there is often more time pressure during pregnancy to reach a diagnosis. Eighty-four percent of reproductive-aged women between 18 and 39 years of age see a health-care provider at least once per year, which is an ideal opportunity for discussing and offering genetic screening (Petterson et al. 2014).

Genetic disease within a family

When a particular genetic disease is present in a family, and members of that family wish to pursue carrier testing for that disease, it is ideal to identify the specific familial genetic variant. Other family members should then be tested for that specific genetic variant, rather

than undergoing ECS for the purpose of screening for the familial disease. This leads to improved efficiency as well as a more rapid diagnosis.

Patient perceptions of expanded carrier screening

Limited data have been published on patient perceptions of ECS. One recently published trial randomized patients to receive genome sequencing or single disease carrier screening (Kraft et al. 2018b). The authors interviewed patients in each group to better understand views about carrier screening. Patients in both groups found it useful to group diseases into categories (such as serious conditions and conditions that begin as adults), to understand the scope of diseases and decide which to include. In this cohort, the vast majority of patients in the genome sequencing group chose to have testing for all categories of diseases, with the most common perception being that more information was better. In a different study based on focus groups, the authors identified barriers to screening, which included fear or anxiety about potential results, concerns about necessity of screening, and concerns about partner participation (Schneider et al. 2016). Other studies have suggested that limited time, lack of interest, and not wanting to know the results are other major reasons that patients decline ECS (Gilmore et al. 2017). Additional research is necessary based on diverse patient populations to further explore preferences for which diseases to test, as well as to assess patients' understanding of associated benefits, risks, and results.

Provider perceptions of expanded carrier screening

In a 2012 survey of ACOG members, 15% reported routinely offering ECS to their patients, and over half provided ECS when directly requested by a patient (Benn et al. 2014). Sixty-seven percent of those surveyed preferred testing for only genetic variants of known significance. Importantly, one-third of providers felt comfortable counseling patients about ECS prior to sending this test, and only one-quarter felt comfortable explaining the results when they returned. In another survey-based study of ACOG members, 39% of providers rated genetic issues as lowest on the priority list for office visits and 65% were not confident in their understanding of genetics (Wilkins-Haug et al. 2000). Additional barriers that have been identified from the provider perspective include lack of time in clinical settings to offer ECS and provide counseling, lack of supporting services, and lack of understanding of current professional society recommendations (Henneman et al. 2016). This highlights the necessity of ongoing education about genetics and carrier screening for providers of obstetric, gynecologic, and primary care, to keep pace with the rapidly changing landscape of available tests and improve providers' comfort level with and knowledge of these tests.

Psychosocial implications

Important to consider with ECS are the potential psychosocial implications, specifically perception of health, psychological well-being, and potential stigmatization or discrimination. Limited research has assessed individual psychological well-being and perceptions of health following any genetic screening, and ECS specifically has not been well investigated. Findings from these studies ranged from no impact to negative impacts on personal views of health, with theories for negative impacts being decreased optimism about health or poor understanding of test results (Henneman et al. 2016). There is potential for stigmatization if individuals feel targeted or singled out by learning of their own genetic

profile and risk. There is also the potential for discrimination, either by others who learn of an individual's genetic profile or even by the person undergoing testing if his or her views of a particular genetic disease impose discrimination on an individual or societal level. These possible implications are essential for patients to understand through the consent process prior to undergoing ECS, and are important for professional societies to factor into their recommendations.

Opportunities for further research

Many areas for further research on ECS exist. Ongoing evaluations of genetic variants detected and the proportion of individuals who screen positive with different panels and platforms are warranted, particularly as we learn more about disease-causing variants over time. Much more remains to be learned about the ideal group of genetic diseases to include on ECS panels, and how this group of diseases can be modified according to individual preferences and values. An optimal approach to counseling patients about ECS is not clear, specifically with regard to the range of genetic diseases, spectrum of potential results, associated risks, and choices about opting out of testing for certain types of diseases. Development of an approach for both patient and provider education, as well as shared decision-making, will be essential for optimizing patient care and satisfaction with ECS. Future research should also focus on barriers to genetic screening, particularly in the preconception period, across patient subgroups to address inequities, and across providers to identify opportunities for further education. Finally, cost-effectiveness analyses will be essential to clarify the downstream costs associated with detection of carrier status, including costs to the individual and the health-care system, as well as impacts on quality of life.

Conclusions

ECS offers many important benefits including a pan-ethnic approach to genetic carrier screening that can identify significantly more carriers than ethnicity-based screening, leading in turn to greater information available with which to make reproductive decisions. However, there are many significant limitations of ECS that must be discussed with patients prior to performing this test. Importantly, along with greater information yield from ECS may also come unexpected information, uncertainty about anticipated phenotype, and greater downstream costs associated with further testing and genetic counseling. Choosing whether to pursue genetic carrier screening, as well as which method of carrier screening, should be based on individual values and choices of the individual or couple. Genetic counseling is central to this decision-making, both prior to test as well as after results return. As with all medical care, the principle of *primum non nocere* (first do no harm) applies. Providers as well as patients should consider whether ECS is being sent simply because we can, or whether this choice is based on an informed decision to do so.

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