UPDATE Prenatal carrier screening

Mary E. Norton, MD
Dr. Norton is Professor of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Francisco.

The author reports receiving grant or research support from Natera and being a consultant to Invitae.

The benefit of expanded carrier screening over standard testing is not clear. Recent data shed light on advantages and drawbacks of expanded panel testing.

Prenatal care has long included carrier screening for genetic diseases, such as cystic fibrosis and Tay-Sachs disease. Recently, advances in genetics technologies led to the development of multiplex panels that can be used to test for hundreds of genetic disorders simultaneously, and can be used to assess carrier status for expectant couples or those planning a pregnancy. Although such screening covers many more conditions than those recommended in traditional guidelines, the benefit of expanded carrier screening (ECS) over standard gene-by-gene testing is not clear.

In this Update, I review recent ECS research that can be helpful to those who practice reproductive endocrinology and infertility medicine, maternal–fetal medicine, and general ObGyn. This research considered some of the many complexities of ECS:

- number and type of severe autosomal recessive conditions identified by an ECS panel, or by panethnic screening for 3 common conditions (cystic fibrosis, fragile X syndrome, spinal muscular atrophy)
- whether the disorders covered by ECS panels meet recommended criteria regarding severity, prevalence, and test accuracy
- women's thoughts and perspectives on ECS
- whether the marketing materials disseminated by commercial providers of ECS are accurate and balanced.

IN THIS ARTICLE

Ideal expanded carrier screening panel
page 15

Women's perspectives on expanded carrier screening
page 16

Marketing of expanded carrier screening
page 18

Genetic diseases identified by expanded carrier screening

Haque IS, Lazarin GA, Kang HP, Evans EA, Goldberg JD, Wapner RJ. Modeled fetal risk of genetic diseases identified by expanded carrier screening. JAMA. 2016;316(7):734–742.

Screening during pregnancy to determine if one or both parents are carriers of genetic disorders historically has involved testing for a limited number of conditions, such as cystic fibrosis, hemoglobinopathies, and Tay-Sachs disease. Patients usually are offered testing for 1 or 2 disorders, with test choices primarily based on patient race and ethnicity. Unfortunately, ancestry-based screening may result in inequitable distribution of genetic testing and resources, as it has significant limitations in our increasingly multicultural society, which includes many people of uncertain or mixed race and ethnicity.

CONTINUED ON PAGE 15

CONTINUED FROM PAGE 12

Advantages of expanded carrier screening

Several commercial laboratories now offer ECS. Haque and colleagues used data from one of these laboratories and modeled the predicted number of potentially affected fetuses that would be identified with traditional, ethnicity-based screening as compared with ECS. In one of their hypothetical cohorts, of Northern European couples, traditional screening would identify 55 affected fetuses per 100,000 (1 in 1,800), and ECS would identify 159 per 100,000 (almost 3 times more). The numbers identified with ECS varied with race or ethnicity and ranged from 94 per 100,000 (about 1 in 1,000) for Hispanic couples to 392 per 100,000 (about 1 in 250) for Ashkenazi Jewish couples.

In Australia, Archibald and colleagues conducted a similar study, of panethnic screening of 12,000 women for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy.[1] The number of affected fetuses identified was about 1 per 1,000 screened couples—not much different from the ECS number, though comparison is difficult given the likely very different racial and ethnic backgrounds of the 2 cohorts.

Although these data suggest ECS increases detection of genetic disorders, and it seems almost self-evident that more screening is better, there are concerns about ECS.[2] Traditional carrier screening methods focus on conditions that significantly affect quality of life—owing to cognitive or physical disabilities or required lifelong medical therapies—and that have a fetal, neonatal, or early-childhood onset and well-defined phenotype. In ECS panels, additional conditions may vary significantly in severity or age of onset. Although some genetic variants on ECS panels have a consistent phenotype, the natural history of others is less well understood. Panels often include conditions for which carrier screening of the general population is not recommended by current guidelines—for example, hemochromatosis and factor V Leiden. Moreover, almost by definition, ECS panels include rare conditions for which the natural history may not be well understood, and the carrier frequency as well as the proportion of condition-causing variants that can be detected may be unclear, leaving the residual risk unknown.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

This study provides additional information on the number and type of conditions that can be detected with ECS in different populations. Although ever larger panels can detect more conditions, the veracity of the results and the types of conditions detected are important considerations as providers and patients weigh the risks and benefits of this screening.

FAST TRACK

Although expanded carrier screening was found to detect almost 3 times more affected fetuses, additional conditions screened for may vary in natural history and current understanding

The ideal expanded carrier screening panel

Stevens B, Krstic N, Jones M, Murphy L, Hoskovec J. Finding middle ground in constructing a clinically useful expanded carrier screening panel. Obstet Gynecol. 2017;130(2):279–284.

Both the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) have proposed criteria for including specific disorders on ECS panels.[3,4] These criteria consider disorder characteristics, such as carrier prevalence, which should be at least 1 in 100; severity; early-childhood onset; and complete penetrance. In addition, they consider test characteristics, such as sensitivity, which should be at least 70%.

Details of the study

Stevens and colleagues evaluated the ECS panels offered by 6 commercial laboratories

CONTINUED ON PAGE 16

CONTINUED FROM PAGE 15

WHAT THIS EVIDENCE MEANS FOR PRACTICE

For practices that want to offer ECS, it is important to consider the type of conditions on a given laboratory's panel. Panels that include more conditions will detect at least one condition in more patients. As each positive test requires follow-up (typically partner testing), careful consideration should be given up-front to which test is used.

in the United States. They found that only 27% of included conditions met the recommended criteria, and concluded that these panels are putting patients at risk for undue anxiety, and that time and money are being spent on follow-up testing for rare and mild conditions for which the benefits of testing are unclear or unlikely. The potential benefits of the extra screening should be weighed against the significant resulting harms.

Across the 6 ECS panels, 96 conditions met the criteria. As some laboratories allow providers to customize their panels, members of my practice, after reviewing this thought-provoking article, agreed we should create a custom panel that includes only these 96 conditions. Unfortunately, no commercial laboratory includes all 96 conditions, so it is not feasible to create an "ideal" panel at this time.

Arguments favoring ECS include its low cost and the efficiency of screening with multigene panels. In a 2013 study, however, 24% of patients were identified as carriers, and in most cases this finding led to screening for the reproductive partner as well.[5] If the rate of detection of the disorder is low, the utility of screening with the same panel may be limited, and couples may require more extensive testing, such as gene sequencing, which is far more expensive. These findings and the additional testing also will increase the need for genetic counseling, and may lead to invasive prenatal diagnostic testing with further increases in costs. If counseling and prenatal testing yield improved outcomes—increased detection of important findings—the benefit will justify the higher costs. However, if the increased costs are largely generated chasing down and explaining findings that are not important to patients or providers, the costs may be incurred without benefit.

FAST TRACK

Only 27% of included conditions on 6 commercially offered ECS panels met the criteria outset by ACOG and the American College of Genetics and Genomics as appropriate for inclusion on ECS panels

Pregnant women's perspectives on expanded carrier screening

Propst L, Connor G, Hinton M, Poorvu T, Dungan J. Pregnant women's perspectives on expanded carrier screening [published online February 23, 2018]. J Genet Couns. doi:10.1007/s10897-018-0232-x.

Although several authors have discussed ECS detection rates, less has been reported on how women perceive ECS or how they elect or decline screening. Studies have found that the decision to undergo screening for cystic fibrosis is influenced by factors that include age, sex, ethnicity, socioeconomic status, lack of family history, cost, fear of a blood test, lack of knowledge about the condition, already having children, wanting to avoid having a disabled child, abortion preferences, and feeling pressured by health care providers.[6,7]

Propst and colleagues asked women for their perspectives on ECS, on electing or declining screening, and on any anxiety associated with their decision.

Details of the study

Women who declined ECS said they did so because they:

- had no family history
- knew there was a very small chance their partner carried the same condition
- would not change the course of their pregnancy on the basis of the test results.

Women who elected ECS said they did so because they wanted to:

- know their risk of having a child with a genetic condition

CONTINUED ON PAGE 18

CONTINUED FROM PAGE 16

- have all available information about their genetic risks
- be able to make decisions about continuing or terminating their pregnancy.

Women also were asked what they would do if they discovered their fetus had a genetic disorder. About 42% said they were unsure what they would do, 34% said they would continue their pregnancy and prepare for the birth of an affected child, and 24% said they likely would terminate their pregnancy.

The most common reason women gave for declining ECS was that they had no family history. However, ECS is not a good option for women with a positive family history, as they need genetic counseling and specific consideration of their own risks and what testing should be done. The majority of couples who have a child with a genetic disease have no other family history of the disorder. In a study of reproductive carrier screening in Australia, 88% of carriers had no family history.[1] Careful pretest counseling is needed to explain the distinction between, on one hand, genetic counseling and testing for those with a family history of genetic disease and, on the other hand, population screening performed to identify unsuspecting individuals who are healthy carriers of genetic disorders.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Different pregnant women may have very different preferences regarding genetic testing. Although many are unsure how they would proceed following the diagnosis of a fetal genetic disorder, it is important to carefully explain their options before any testing is done.

Another crucial point about carrier screening is the need to consider how its results will be used, and what options the carrier couple will have. For women who are pregnant when a risk is identified, options include expectant management, with diagnosis after birth, or prenatal diagnosis with termination of an affected fetus, out-adoption of an affected fetus, or expectant management with preparation for caring for an affected child. For women who are not pregnant when they have ECS, additional options include use of a gamete (ovum or sperm) donor to achieve pregnancy, or preimplantation genetic diagnosis with implantation of only unaffected embryos.

FAST TRACK

Women most commonly declined ECS because they had no family history; however, up to 88% of carriers have no family history. Therefore, careful pretest counseling is needed.

Marketing of expanded carrier screening

Chokoshvili D, Borry P, Vears DF. A systematic analysis of online marketing materials used by providers of expanded carrier screening [published online December 14, 2017]. Genet Med. doi:10.1038/gim.2017.222.

Prenatal carrier screening can be helpful to women and their families, but it is also a high-volume, lucrative business, with many commercial laboratories competing for the growing ECS market. Professional medical societies recommend making all screening candidates aware of the purpose, characteristics, and limitations of the tests, and of the potential significance of their results. As becoming familiar and comfortable with the tests and explaining them to each patient can be time-consuming, and daunting, many busy clinicians have started relying on marketing materials and other information from the commercial laboratories. Therefore analysis of the accuracy of such materials is in order.

Details of the study

Chokoshvili and colleagues performed a systematic analysis of the quality and accuracy of online marketing materials for ECS. They identified 18 providers: 16 commercial laboratories and 2 medical services providers. All described

CONTINUED ON PAGE 20

CONTINUED FROM PAGE 18

Ideally, carrier screening should be done prior to pregnancy

Determining that a woman carries a genetic disorder in the preconception period allows more time to evaluate her reproductive partner. If both partners in the couple carry the same genetic disorder, there are more options available to avoid an affected pregnancy. These options include the use of an ovum or sperm donor, or use of preimplantation genetic diagnosis on embryos conceived through in vitro fertilization. While obstetric providers commonly offer carrier screening, and most women are only screened during pregnancy, such genetic testing should be part of pregnancy planning. When gyn providers see patients who are considering a pregnancy, he or she should discuss the options of expanded carrier screening, or ethnicity-based screening.

ECS as a useful tool for family planning, and some were very directive in stating that this testing is "one of the most important steps in preparing for parenthood." In their materials, most of the companies cover some limitations, such as residual risk, but none of the commercial laboratories indicate that ECS can overestimate risk (many variants have incomplete penetrance, meaning that some individuals with a positive test result may in fact be asymptomatic throughout their lifetime).

In addition, whereas a large amount of the marketing materials implies the test was developed in line with professional recommendations, none in fact complies with ACOG and ACMG guidance. Finally, though some of the online information provided by laboratories can be helpful, it is important for clinicians to remember that reproductive genetic counseling should be nondirective and balanced. Carrier testing should be based on patient (not provider) values regarding reproductive autonomy.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Laboratories' educational materials can be useful, but clinicians must carefully assess them before recommending them to patients. Some commercial laboratory information is helpful and balanced; other information is directive or even coercive. Nonbiased information on prenatal genetic testing, for both patients and clinicians, is available in the Genetic Education Modules offered by the Perinatal Quality Foundation (https://www.perinatalquality.org).

Summary

ECS increasingly is being adopted into clinical practice. According to ACOG, traditional ethnicity-based screening, panethnic screening (the same limited panel of tests for all patients), and ECS are all acceptable alternatives for prenatal carrier screening.[3] For providers who offer ECS, it is important to have a good understanding of each selected test and its limitations. Providers should have a plan for following up patients who have positive test results; this plan may include having genetic counseling and prenatal genetic diagnostic testing in place. Although treatment is available for a few genetic conditions, for the large majority, prenatal screening has not been proved to lead to improved therapeutic options. Providers should try to make sure that patients do not have unrealistic expectations of the outcomes of carrier screening.

References

1. Archibald AD, Smith MJ, Burgess T, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests [published online October 26, 2017; published correction appears in Genet Med. 2018. doi:10.1038/gim.2017.266]. Genet Med. doi:10.1038/gim.2017.134.
2. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015;125(3):653–662.
3. Committee on Genetics. Committee opinion no. 690: carrier screening in the age of genomic medicine. Obstet Gynecol. 2017;129(3):e35–e40.
4. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med. 2013;15(6):482–483.
5. Lazarin GA, Haque IS, Nazareth S, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med. 2013;15(3):178–186.
6. Chen LS, Goodson P. Factors affecting decisions to accept or decline cystic fibrosis carrier testing/screening: a theory-guided systematic review. Genet Med. 2007;9(7):442–450.
7. Ioannou L, McClaren BJ, Massie J, et al. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. Genet Med. 2014;16(3):207–216.