Expanded carrier screening: what the reproductive endocrinologist needs to know

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Expanded carrier screening refers to identification of carriers of single-gene disorders outside of traditional screening guidelines. New genetic testing technologies allow for such screening at costs that are comparable to single-gene testing. There is a high degree of variability among genetic testing laboratories as to the inclusion of different disorders, some of which have mild or unpredictable phenotypes. This review discusses the pros and cons of using expanded carrier screening in the preconceptional patient and reviews guidelines currently endorsed by professional organizations. (Fertil Steril® 2018;109:183–9. ©2017 by American Society for Reproductive Medicine.)

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Carrier screening is a long-established aspect of reproductive care. Preconception carrier screening refers to the process of identifying individuals/couples seeking pregnancy who would be at risk for transmitting autosomal recessive (AR) or X-linked genetic disorders to their offspring. The vast majority of such couples have no known family history of these disorders (unless consanguineous). Because most of these disorders are asymptomatic in the heterozygous carrier state, carrier individuals are not aware of their status unless this screening is performed. Prenatal carrier screening involves the same concepts but is performed in women (and the reproductive partner) after a pregnancy is established. The ideal time to assess carrier status of Mendelian disorders is before conception, so that all reproductive options can be considered (1). Reproductive pairs found to be at risk (25% for AR conditions) generally will have the option to pursue preimplantation genetic diagnosis (PGD) for the condition(s) in question, or can choose donor gametes (assuming the donor has been screened for the same condition).

The purpose of this review is not to rehash Mendelian inheritance, for which several reference texts are available. Rather, the focus will be on clinical aspects of expanded carrier screening (ECS), which essentially means offering carrier screening of the same list of genetic conditions to all individuals, regardless of ethnic background (2). The arguments for and against ECS will be put forth.

Historically, carrier screening for select disorders has been offered to women from specific ethnic groups, and this is still an approach used by many, if not most, reproductive clinicians today (3). For example, individuals of Ashkenazi Jewish descent are known to carry certain AR gene mutations at a higher frequency than does the general population, such as in hexosaminidase A, which is associated with Tay-Sachs disease. The carrier frequency in the Ashkenazi Jewish and Cajun populations is approximately 1 in 30, vs. in the general population, whose carrier frequency is approximately 1 in 300. Before recent molecular genetic assay advances, the screening was typically performed as a biochemical test measuring enzyme activity, reserving confirmatory DNA analysis for those individuals with abnormal screening. Detection rates are high with this approach, but ultimately it requires multiple assays and steps for confirmation. The drawback of identifying people with a pseudodeficiency (reduced enzyme activity measured by laboratory assay but not a true in situ deficiency) exists.

More recently, advances in throughput and cost savings have resulted in the introduction of ECS. As defined here, ECS has been available since the beginning of the decade but has been somewhat slow to be embraced by the clinical community.

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Since then, however, many commercial laboratories, including major national clinical laboratories, are offering ECS (4). This encompasses the mutation analysis in a growing number of genes for increasingly rare disorders. Although on the face of it this may sound like a promising development, such technological advancements come with many caveats (5), which will be discussed below.

ETHNICITY-BASED SCREENING VS. UNIVERSAL SCREENING

Screening select individuals on the basis of ethnicity is a long-standing traditional method of undertaking this assessment. Universal screening implies all individuals, regardless of ethnic background, should be screened for the disorder in question (Table 1). Several proponents of ECS have put forth arguments that traditional approaches may be outdated, because there is an increasing prevalence of mixed-ethnicity individuals. Some people may be unaware of their complete ethnic backgrounds. In addition, the ethical principle of justice would mandate that all individuals should have an opportunity to be screened. However, establishing the cost-effectiveness and potential harms of more widespread screening have been obstacles in the adoption of ECS by many.

The feasibility of screening reproductive adults for a large array of single-gene disorders was demonstrated by Bell et al. (6) when they used next-generation sequencing (NGS) technologies to screen for established pathogenic mutations in 437 genes associated with highly penetrant and serious disorders. This group demonstrated the average patient's genome contained 2.8 recessive mutations and that the assay would cost <$1 per test per condition.

Continued improvements in high-throughput NGS technologies now allow for ECS at a laboratory cost similar to that for older forms of molecular testing for only one or two disorders. From a cost–benefit perspective, it would seem it makes little sense to limit the number of disorders screened on the basis of cost concerns.

Electing genetic carrier screening is a decision that should be made after counseling and informed consent (3). Many patients erroneously conclude that absence of genetic disorders in the respective families protects them against the likelihood of being a carrier. Most persons found to be a carrier of an AR disease have a negative family history (given the low statistical likelihood of mating with another, nonrelated carrier). An exception to this generalization is that consanguineous couples will be at higher risk of carrying the same mutation than nonconsanguineous couples.

If an individual *does* relate a positive family history of one or more genetic condition(s), that person is best referred to a genetics specialist to ensure that appropriate molecular testing has been done in the affected individual, as well as in the prospective couple to exclude carrier status of the familial mutation, which may be undetected in limited mutation screening as done by some ECS panels.

PATIENT VS. COUPLE SCREENING

The most traditional approach to performing carrier screening in the prenatal setting has been to screen the pregnant woman first and then follow up with the partner only if she is positive for any of the disorders analyzed. This approach may also work in the preconception setting, with the recognition that waiting for the patient's result before offering carrier screening to the partner will inherently delay risk assessment for the *couple* by 2 to 3 weeks (the average length of time most of these carrier assays require). If time is critical for a couple entering an assisted reproductive technology cycle, for example, then couple screening (both partners screened simultaneously) may be more time-efficient. It would also be more efficient from the standpoint of time spent in posttest counseling of the couple about genetic disorders each was found to carry.

An additional consideration in the counseling of a reproductive partner is whether disease-specific testing should be done only for the disorder(s) found in the patient, or whether the partner should undergo/be offered full panel screening. Many of the laboratories doing ECS will charge the same price whether a single or all of the genes are screened. Knowledge of carrier status in the partner, even if not the same as in the original patient, can be useful for other family members or in future reproductive partnerships.

SELECTION OF GENES TO ANALYZE

The first Mendelian disorder that was advanced for universal carrier screening was for cystic fibrosis (CF) due to mutations in cystic fibrosis transmembrane regulator (*CFTR*) (1). The introduction of CF carrier screening followed years of debate (it was cloned and sequenced in 1989 but not endorsed for carrier screening until 2001). Several arguments were raised both for and against carrier screening for this disorder. Ultimately both the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) provided endorsement and guidance for the implementation of CF screening. That same process has not been followed for the introduction of ECS. (It would have been impossible to debate the specifics of each gene, given the large number of disorders). Instead clinicians now find themselves at the point where they need to decide whether they will incorporate this into their practices or remain with traditional ethnicity-based screening. Even the limited approach is not without some inconsistencies; for example, different laboratories promote their "Ashkenazi Jewish panels," which can vary from 4 to >100 conditions.

TABLE 1

Comparison of screening approaches, with disease examples.

Type of screening	Targeted approach	Expanded approach
Ethnicity-based	β-Thalassemia (Mediterranean populations)	Ashkenazi Jewish panels
Universal	Cystic fibrosis, spinal muscular atrophy	Broad-scope screening for all individuals

Note: Adapted from van der Hout et al. (5).

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