Best Practices for Use of Expanded Genetic Carrier Screening: A Q&A With Erica Ramos, MS

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***AJMC®*: Why is carrier screening offered for genetic disorders?**

RAMOS: Carrier screening can generally be [sorted] into 3 categories:

1. Population-based carrier screening (offered to all women or a large, defined population, [such as] individuals of Ashkenazi Jewish descent)
2. Carrier screening due to a known family history of a recessive genetic disease
3. Screening for a common genetic cause [of] nonspecific personal or family history of disease (eg, screening for fragile X syndrome with a family history of autism, screening for hemoglobinopathies due to a low maternal mean corpuscular volume)

The primary goal of all carrier screening is to identify couples who have an increased chance of having a child with a recessive genetic disorder. For autosomal recessive disorders, both parents have to carry a disease-causing (pathogenic) variant and both have to pass that variant to the child, resulting in a 25% risk for each pregnancy to be affected. For X-linked recessive disorders, typically the mother is a carrier and each [pregnancy of a male child] has a 50% chance of being affected. [Although] carriers of genetic disorders are often asymptomatic, there are some conditions [in which] the carriers can show a mild or attenuated phenotype.

If a couple knows their carrier status prior to pursuing pregnancy, they have several options for avoiding an affected pregnancy before conception, including egg or sperm donation, adoption, or preimplantation genetic diagnosis in the context of in vitro fertilization. Prenatal testing is also an option via noninvasive prenatal diagnosis, chronic villus sampling, and/or amniocentesis.

***AJMC®*: How would you describe the origin and evolution of carrier screening for genetic disorders?**

RAMOS: Carrier screening for genetic disorders became more routine in the 1990s, as the genes for some of the more common recessive genetic disorders and the specific genetic variants causing disease were identified. Routine carrier screening was offered first to people with a family history of the disease and then to individuals who were higher risk based on ethnicity. Two early examples of ethnic-based carrier screening are testing for Tay-Sachs disease in the Ashkenazi Jewish population and cystic fibrosis in individuals of European descent. To keep screening costs low and limit uncertainties in interpretation, most carrier screening tests were constructed to include only disease-causing variants that were commonly seen in a specific ethnic background.

As our understanding of genetic disease evolved, so did the considerations for how to determine an approach to screening for these disorders. Wilson and Jungner's criteria, used to determine which conditions were appropriate for screening in 1968, were updated by the World Health Organization in 2008.[1] When addressing clinical utility, the primary considerations for addressing clinical utility are that the condition should address a recognized medical need, the objectives of screening should be well defined, and target a defined population, and the benefits of screening should outweigh the harm. Also significant, particularly regarding access, is the position that "the program should promote equity and access to screening for the entire target population" while maintaining "informed choice, confidentiality and respect for autonomy."[2]

Next-generation sequencing (NGS) technology has fundamentally changed the context of carrier screening for genetic diseases. Testing for even 1 gene is far less expensive than it was before, and NGS allows for multiple genes to be sequenced completely with a rapid turnaround time and only a small incremental increase in cost per gene. This is, in part, why there is growth in "expanded" carrier screening (ECS) offerings, which screen for hundreds of genes that cause recessive diseases at 1 time with 1 test. ECS allows for the detection of couples who are at risk for a greater spectrum of genetic disorders, as hundreds of conditions could be included over time. [Although] this approach is still evolving, the American College of Medical Genetics and Genomics (ACMG) has published guidance [that addresses] how disorders should be considered for inclusion in expanded carrier screening panels,[3] and the American College of Obstetrics and Gynecology (ACOG) has stated that "ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening."[4]

AJMC®: Who should incorporate carrier screening for genetic disorders into their practice?

RAMOS: Guidelines for carrier screening from professional medical societies consistently outline important requirements for appropriate population carrier screening:

- [Heathcare providers should discuss education about carrier screening] with all women, regardless of ethnicity.
- Testing and genetic counseling are optimally performed *prior to* pregnancy.
- It is appropriate to offer testing to a couple sequentially unless there are time sensitivities because of gestational age. In that case, [providers should test both partners] simultaneously to maximize prenatal diagnosis options.

To achieve the goal of screening all women prior to pregnancy, all primary care providers should be aware of genetic carrier screening practices, have a process for ensuring screening is offered to their patients who are of childbearing age, and have the ability to discuss and order testing and report results.

[Although] all primary care physicians should [implement] screening protocols, they can benefit from collaboration with genetic counselors and incorporate internal practices that would trigger a referral to a genetic counselor. Providers should be familiar with prepregnancy/prenatal genetic counseling services in their areas, nationwide networks of genetic counselors available via telephone/video, and genetic counseling resources provided by clinical testing laboratories to determine the best combination of services for their practices and patients.

There are several touch points during the carrier screening process when genetic counselors can add value. However, there are certain situations in which genetic counseling may be critical, particularly when carriers are identified during a pregnancy or the testing strategy has to be altered [because of] family history or circumstances. These are situations in which the optimal or routine approach to testing cannot be applied and test selection and strategy are particularly critical. In these cases, involving a genetic counselor may help to support better outcomes for the patient and the child. Some examples include when:

- Screening is performed in the context of any family history of the related disorder
- A partner is not available for testing during a pregnancy
- The patient is in the second trimester of pregnancy and desires prenatal diagnosis
- Testing for other genetic risks is being considered during pregnancy, like testing for chromosome abnormalities

AJMC®: Can you discuss challenges to and opportunities for improving access to carrier screening?

RAMOS: Many of the major payers are contracted with labs offering expanded and traditional carrier screening. However, patients must be identified before they can be tested. There is a strong awareness that advances in genetic sequencing technologies, including NGS, have the potential to increase existing health disparities.[5] It is critical that all providers are aware of the recommendations for universal screening and are held responsible for offering it in their practices.

Another complicating factor is that although most health plans have good coverage policies for genetic counseling, their members [may not be able to] easily find a genetic counselor. Many health plans do not credential genetic counselors, and most health plan physician and practitioner directories do not list genetic counselors as standalone practitioners. While the National Society of Genetic Counselors (NSGC) has a Find a Counselor tool (findageneticcounselor.com) that could be leveraged, most of the public will not know to access our website. As a result, health plan members often receive the service from nongenetics practitioners even when genetic counselors are available to them. Payers can improve access to genetic counselors by establishing defined certified genetic counselor networks and promoting them to their physicians and members.

AJMC®: How important is education when it comes to carrier screening, and what resources are available for increasing awareness and knowledge?

RAMOS: Physicians already manage routine population-level screening in their practices, so education should focus on approaches to testing and the test options and the genetic counseling resources available. In addition to pursuing on-demand continuing medical education,

professional societies should consider partnering with genetics specialists to offer regular training at national and local conferences.

There are multiple practice guidelines available for review regarding aspects of traditional and expanded carrier screening from the ACMG,[3,6,7] the ACOG,[4,8,9] and the NSGC.[10] Guidelines currently recommend population carrier screening for cystic fibrosis, spinal muscular atrophy, [disorders affecting the Ashkenazi Jewish population], which include Tay-Sachs and Canavan diseases and hemoglobinopathies. Additional guidelines recommend consideration of carrier screening for fragile X syndrome when there is a maternal history of a family history of fragile X–related disorders, unexplained [intellectual disability], developmental delay, autism, or premature ovarian insufficiency.[11–13]

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