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Committee on Genetics

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Genetics in collaboration with committee members Stephanie Romero, MD; Britton Rink, MD; Joseph R. Biggio Jr, MD; and Devereux N. Saller Jr, MD.

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Carrier Screening in the Age of Genomic Medicine

ABSTRACT: Carrier screening, whether targeted or expanded, allows individuals to consider their range of reproductive options. Ultimately, the goal of genetic screening is to provide individuals with meaningful information that they can use to guide pregnancy planning based on their personal values. Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Because all of these are acceptable strategies, each obstetrician–gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. Carrier screening will not identify all individuals who are at risk of the screened conditions. Patients should be counseled regarding the residual risk with any test result. Screening for any condition is optional and, after counseling, a patient may decline any or all carrier screening. If a patient requests a screening strategy other than the one used by the obstetrician–gynecologist or other health care provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives. Expanded carrier screening does not replace previous risk-based screening recommendations. The determination of the appropriate screening approach for any individual patient should be based on the patient's family history and personal values after counseling. Referral to an obstetrician–gynecologist or other health care provider with genetics expertise should be considered for risk assessment, evaluation, and consideration of diagnostic testing as indicated for any patient with a family history of a genetic condition or concern for a genetic diagnosis.

Recommendations

- Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each obstetrician–gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counseling, a patient may decline any or all carrier screening.
- If a patient requests a screening strategy other than the one used by the obstetrician–gynecologist or other health care provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives.
- All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome, or women with a personal history of ovarian insufficiency. Additional screening also may be indicated based on family history or specific ethnicity.
- Couples with consanguinity should be offered genetic counseling to discuss the increased risk of recessive conditions being expressed in their offspring and the limitations and benefits of carrier screening.
- Carrier screening will not identify all individuals who are at risk of the screened conditions. Patients should

be counseled regarding residual risk with any test result.

- Prenatal carrier screening does not replace newborn screening, nor does newborn screening diminish the potential benefit of prenatal carrier screening.
- If a woman is found to be a carrier for a specific condition, her reproductive partner should be offered screening to provide accurate genetic counseling for the couple with regard to the risk of having an affected child. Additional genetic counseling should be provided to discuss the specific condition, residual risk, and options for prenatal testing.
- If a carrier couple (ie, carriers for the same condition) is identified before pregnancy, genetic counseling is encouraged so that reproductive options (eg, donor gametes, preimplantation genetic diagnosis, prenatal diagnosis) can be discussed.
- Individuals with a family history of a genetic disorder may benefit from the identification of the specific familial mutation or mutations rather than carrier screening. Knowledge of the specific familial mutation may allow for more specific and rapid prenatal diagnosis.
- Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth.
- Carrier screening panels should not include conditions primarily associated with a disease of adult onset.

Introduction

Carrier screening is a term used to describe genetic testing performed on an asymptomatic individual to determine whether that person has a mutation or abnormal allele within a gene that is associated with a particular disorder. Carrier screening can be performed for one specific condition or for multiple disorders. The likelihood of identifying someone as a carrier for an inherited genetic condition reflects the **prevalence** of the condition in a particular population. In the absence of a family history, the more prevalent a condition the greater the likelihood of finding a carrier. This fact has historically guided practitioners to offer genetic screening to those individu-

als at highest risk of carrying particular disorders based on the individual's race, ethnicity, or family history.

Traditionally, carrier screening was targeted toward specific ethnic populations known to be at increased risk of particular disorders, commonly known as **ethnic-based screening**, such as screening those of **Ashkenazi Jewish** descent for Tay–Sachs disease. However, in the present multiracial society, it is increasingly difficult to define an individual's ancestry. Therefore, the pretest probability of being a carrier for a specific disorder may not be consistent with previous assumptions about the prevalence of that disorder in the various ethnic and racial groups with which a patient identifies (1). In addition, particular disorders are less likely to be confined only to a specific high-risk ethnic group because of the increasing frequency of ethnic admixture of reproductive partners. This has prompted consideration of **panethnic screening** (nondirective screening), in which carrier screening for a panel of disorders is offered to all individuals regardless of ethnicity rather than traditional ethnic-based screening.

The cost of DNA analysis and sequencing has decreased substantially in recent years. In addition, because genetic testing technology has evolved rapidly over the past decade, it is now possible to screen for a large number of conditions simultaneously. This testing strategy is known as **expanded carrier screening**. Expanded carrier screening panels offered by laboratories typically include options to screen from 5–10 conditions to as many as several hundred conditions (1). Traditionally, panethnic screening has been defined as making screening for specific recommended conditions available to all patients, regardless of ethnic or racial background. This approach largely has been supplanted by expanded carrier screening because of its efficiency and economy (2).

In the past, the American College of Obstetricians and Gynecologists has advocated for ethnic-based screening. Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Because all of these are acceptable strategies, each obstetrician–gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. If a patient requests a screening strategy other than the one used by the obstetrician–gynecologist or other health care provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives. Couples with **consanguinity** should be offered genetic counseling to discuss the increased risk of recessive conditions being expressed in their offspring and the limitations and benefits of carrier screening.

Screening for any condition is optional and, after counseling, a patient may decline any or all carrier screening. Prenatal carrier screening does not replace newborn screening, nor does newborn screening diminish the potential benefit of prenatal carrier screening because newborn carrier screening precludes the possibility of

making reproductive choices based on test results (3). Individuals with a family history of a genetic disorder may benefit from the identification of the specific familial mutation or mutations rather than carrier screening. Knowledge of the specific familial mutation may allow for more specific and rapid prenatal diagnosis. Insurance coverage for carrier screening may be variable. Some patients may wish to confirm insurance coverage or obtain preapproval before proceeding with carrier screening.

Carrier screening, whether targeted or expanded, allows individuals to consider their range of reproductive options. Prepregnancy carrier screening is ideal because it provides patients with the opportunity to learn their carrier status and allows reproductive partners to discover if they are both carriers of the same condition before pregnancy. Patients then can consider whether or not to conceive and whether to use advanced reproductive technologies such as preimplantation genetic diagnosis or donor gametes. Knowledge of carrier status during pregnancy allows patients to consider prenatal diagnosis; pregnancy management options; or postnatal management, such as potential treatment options or availability of palliative care (if appropriate), in the event of an affected fetus. It also may help decrease the time necessary to diagnose an affected child. If a woman is found to be a carrier of a specific condition, her reproductive partner should be offered screening to provide accurate genetic counseling for the couple with regard to the risk of having an affected child. Additional genetic counseling should be provided to discuss the specific condition, **residual risk**, and options for prenatal testing. If a carrier couple (ie, carriers for the same condition) is identified before pregnancy, genetic counseling is encouraged so that reproductive options (eg, donor gametes, preimplantation genetic diagnosis, prenatal diagnosis) can be discussed. Ultimately, the goal of genetic screening is to provide individuals with meaningful information that they can use to guide pregnancy planning based on their personal values.

In 2015, the American College of Obstetricians and Gynecologists and several other organizations released a joint statement about expanded carrier screening to provide guidance to practitioners, patients who are considering screening options, and laboratories preparing screening panels (2). This statement, “Expanded Carrier Screening in Reproductive Medicine,” emphasizes the necessity of informed consent in pretest and posttest counseling for any patient who is undergoing carrier screening (Box 1). This includes discussion of residual risk. Carrier screening will not identify all individuals who are at risk of the screened conditions because not every possible disease-producing mutation or allele is screened and because *de novo* mutations may arise. Patients should be counseled regarding residual risk with any test result. Further, obstetrician–gynecologists and other health care providers should make every effort to maintain confidentiality of genetic screening and diag-

Box 1. Counseling Patients Regarding Expanded Carrier Screening ↵

Pretest education and consent should broadly describe the types of conditions being screened as well as the limitations of screening. Educating patients before testing may be done verbally or by using other informational approaches such as pamphlets, videos, or online resources. Pretest counseling should address the following general concepts:

- Some of the conditions screened have less well-defined phenotypes.
- Because many conditions being screened are rare, disease prevalence, mutation frequencies, and detection rates may be imprecise and residual risk estimations may not be reliable.
- Screen-negative results reduce the likelihood of the carrier state for the conditions, but a residual risk of being a carrier always remains.
- Screening panels may change over time, and there may be differences between laboratories in the conditions screened. Despite this, carrier rescreening typically is not offered or recommended.

Modified from Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, 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):653–62.

nostic test results and to respect patients’ right to privacy with regard to all genetic information.

As carrier screening becomes more prevalent, it will be important to determine if patients have been screened previously for specific disorders to avoid repeat screens and unnecessary costs. Although screening technology inevitably will advance over time, in general, carrier screening for a specific genetic condition should be performed only once in a person’s lifetime. The decision to rescreen a patient should only be undertaken with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations.

Developing an Expanded Carrier Screening Panel

Expanded carrier screening panels may include many more conditions than currently are recommended on an individual basis. Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on

quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life (2). Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth. Similar to the genetic testing of children, carrier screening panels should not include conditions primarily associated with a disease of adult onset (such as mutations of the *BRCA* gene, which confers increased risk of hereditary breast cancer and ovarian cancer in adulthood) (2, 4, 5). For some conditions included on expanded carrier screening panels (eg, β -thalassemia and Tay–Sachs disease), the genetic testing method offered by the panel may not be the most sensitive method of carrier detection. The need for ancillary screening methods for such disorders should be considered.

Although there is no ideal threshold to determine which conditions to include on an expanded carrier screening panel, selection of conditions with a carrier frequency of 1 in 100 or greater, which corresponds with a disease incidence of 1 in 40,000, is a useful threshold. This approach aims to provide a balance between identifying carriers for more common conditions and minimizing anxiety associated with identifying carriers of extremely rare disorders (6). Some conditions are so rarely seen outside of a particular ethnic group that a population-wide carrier rate cannot be calculated and, therefore, only the ethnic-based carrier rate is known. Thus, for these conditions, a residual risk calculation is not possible.

Although it may seem appealing to screen for many disorders with one test, there are limitations and disadvantages to expanded carrier screening. As the number of disorders being screened increases, the likelihood of identifying a carrier state increases. Even with the low prevalence of the individual disorders, the large number of disorders being screened may result in more than one half of patients being found to be carriers for one or more disorders (1, 6–8). This could result in the need for additional testing for a woman's partner, extensive genetic counseling, and increased anxiety (6). To minimize the potential for harm, the number of conditions included in the screening panel needs to be considered in addition to the nature of the conditions.

Expanded carrier screening does not replace previous risk-based screening recommendations. If obstetrician–gynecologists or other health care providers do not offer expanded carrier screening in their practice, screening recommendations for individual disorders should follow guidelines for carrier screening as outlined in Committee Opinion No. 691, *Carrier Screening for Genetic Conditions*. All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and

spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome, or women with a personal history of ovarian insufficiency (see Committee Opinion No. 691, *Carrier Screening for Genetic Conditions*, and Practice Bulletin No. 78, *Hemoglobinopathies in Pregnancy*, for additional information). Additional screening also may be indicated based on family history or specific ethnicity, including screening for a limited number of specific diseases in individuals of Ashkenazi Jewish, African, Mediterranean, or Southeast Asian ancestry and screening individuals with a family history of or risk factors for genetic diseases (9).

Although predefined panels are marketed by commercial laboratories, obstetrician–gynecologists and other health care providers should carefully evaluate the conditions included and determine the appropriateness of the panels offered. As an alternative, some obstetrician–gynecologists and other health care providers might choose to work with companies that perform expanded carrier screening to create a panel that is customized to suit their practice. Table 1 provides examples of conditions that are considered reasonable for inclusion in an expanded carrier screening panel. After counseling regarding screening options, obstetrician–gynecologists or other health care providers and patients may elect to screen for fewer or more conditions than those listed. The availability of expanded carrier screening does not preclude the appropriateness of ethnic-based screening or screening based on family history.

The conditions listed in Table 1 were selected on the basis of the benefits of detection, the accuracy of current screening methods, and the aforementioned consensus-determined criteria. The general population carrier frequency may be unknown for some disorders that are more common in high-risk ethnic groups. This may make selection of disorders for inclusion in the screening panel more difficult, but decisions can be based on the severity of the disorder and the carrier rate in higher-risk ethnic groups.

Conclusion

The determination of the appropriate screening approach for any individual patient should be based on the patient's family history and personal values after counseling, either by her primary obstetrician–gynecologist or other health care provider or by a genetics professional. Referral to an obstetrician–gynecologist or other health care provider with genetics expertise should be considered for risk assessment, evaluation, and consideration of diagnostic testing as indicated for any patient with a family history of a genetic condition or concern for a genetic diagnosis.

Table 1. Example of an Expanded Carrier Screening Panel* ←

Condition	Carrier Frequency in General Population	Carrier Frequency in Specific Ethnic Groups
α -thalassemia	Unknown	African (particularly sub-Saharan): 1 in 3 Mediterranean: 1 in 30 Southeast Asian and Middle Eastern: 1 in 20
β -thalassemia	Unknown	African American: <1 in 8 Ashkenazi Jewish: Varied Asian: 1 in 20 Mediterranean: 1 in 7
Bloom syndrome	<1 in 500	Ashkenazi Jewish: 1 in 100
Canavan disease	<1 in 150	Ashkenazi Jewish: 1 in 41
Cystic fibrosis	Unknown	African American: 1 in 61 Asian: 1 in 94 Ashkenazi Jewish: 1 in 24 Caucasian: 1 in 25 Hispanic: 1 in 58
Familial dysautonomia	<1 in 500	Ashkenazi Jewish: 1 in 31
Familial hyperinsulinism	<1 in 150	Ashkenazi Jewish: 1 in 52
Fanconi anemia C	<1 in 790	Ashkenazi Jewish: 1 in 89
Fragile X syndrome [†]	1 in 259	
Galactosemia	1 in 87	Ashkenazi Jewish: 1 in 127
Gaucher disease	<1 in 100	Ashkenazi Jewish: 1 in 15
Glycogen storage disease type 1A	<1 in 150	Ashkenazi Jewish: 1 in 71
Joubert syndrome	<1 in 500	Ashkenazi Jewish: 1 in 92
Medium-chain acyl-CoA dehydrogenase deficiency	Unknown	Caucasian: 1 in 50
Maple syrup urine disease types 1A and 1B	1 in 240	Ashkenazi Jewish: 1 in 81 (type 1B) Mennonite: 1 in 10 (type 1A- <i>BCKDHA</i> p.Y438N)
Mucopolidosis IV	<1 in 500	Ashkenazi Jewish: 1 in 96
Niemann–Pick disease type A	<1 in 500	Ashkenazi Jewish: 1 in 90
Phenylketonuria	Unknown	Caucasian: 1 in 50 Irish: 1 in 34
Sickle cell anemia	Unknown	African American: 1 in 10
Smith–Lemli–Opitz syndrome	Unknown	Caucasian: 1 in 70
Spinal muscular atrophy	Unknown	African American: 1 in 66 Asian: 1 in 53 Ashkenazi Jewish: 1 in 41 Caucasian: 1 in 35 Hispanic: 1 in 117
Tay–Sachs disease [‡]	1 in 300	Ashkenazi Jewish: 1 in 30 French Canadian and Cajun: 1 in 30

*Conditions reasonable for inclusion in an expanded carrier screening panel as of 2016. After counseling regarding screening options, obstetrician–gynecologists or other health care providers and patients may elect to screen for fewer or more conditions than those listed here. The availability of expanded carrier screening does not preclude the appropriateness of ethnic-based screening or screening based on family history. Conditions were selected on the basis of the benefits of detection, the accuracy of current screening methods, and the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth.

[†]Included on this list despite a carrier frequency lower than 1 in 100 because, as an X-linked syndrome, fragile X syndrome is more prevalent than other conditions.

[‡]DNA testing alone will miss up to 10% of carriers of Tay–Sachs disease, especially in lower-risk groups and, therefore, enzyme-based testing may be a more appropriate choice for some patients.

Glossary

Ashkenazi Jewish: Individuals whose Jewish relatives originate from Eastern or Central Europe.

Carrier screening: Genetic testing that is performed on an individual who does not have any symptoms of a particular genetic disorder but may have one abnormal allele for the gene that is associated with the disorder.

Consanguinity: A union between two individuals who are second cousins or closer in family relationship.

Ethnic-based screening: Disease screening that is targeted at high-risk populations, such as screening individuals of Ashkenazi Jewish descent for Tay–Sachs disease.

Expanded carrier screening: Disease screening that evaluates an individual's carrier state for multiple conditions at once and regardless of ethnicity.

Panethnic screening: Individuals are screened regardless of their ethnic background. One example is the current recommendation for screening every pregnant woman for cystic fibrosis once during her lifetime.

Prevalence: The percentage of a population that is affected by a particular disease at a particular time.

Residual risk: A calculated risk that an individual carries an abnormal allele after a negative screening test result.

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/CarrierScreening.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's website, or the content of the resource. The resources may change without notice.

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