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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 Britton Rink, MD; Stephanie Romero, MD; Joseph R. Biggio Jr, MD; Devereux N. Saller Jr, MD; and Rose Giardine, MS.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Carrier Screening for Genetic Conditions

ABSTRACT: Carrier screening is a term used to describe genetic testing that is performed on an individual who does not have any overt phenotype for a genetic disorder but may have one variant allele within a gene(s) associated with a diagnosis. Information about carrier screening should be provided to every pregnant woman. Carrier screening and counseling ideally should be performed before pregnancy because this enables couples to learn about their reproductive risk and consider the most complete range of reproductive options. A patient may decline any or all screening. When an individual is found to be a carrier for a genetic condition, his or her relatives are at risk of carrying the same mutation. The patient should be encouraged to inform his or her relatives of the risk and the availability of carrier screening. If an individual is found to be a carrier for a specific condition, the patient's reproductive partner should be offered testing in order to receive informed genetic counseling about potential reproductive outcomes. If both partners are found to be carriers of a genetic condition, genetic counseling should be offered. What follows is a detailed discussion of some of the more common genetic conditions for which carrier screening is recommended in at least some segments of the population.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists (the College) makes the following recommendations and conclusions:

General Recommendations

- Information about genetic carrier screening should be provided to every pregnant woman. After counseling, a patient may decline any or all screening.
- Carrier screening and counseling ideally should be performed before pregnancy.
- If an individual is found to be a carrier for a specific condition, the individual's reproductive partner should be offered testing in order to receive informed genetic counseling about potential reproductive outcomes. Concurrent screening of the patient and her partner is suggested if there are time constraints for decisions about prenatal diagnostic evaluation.

- If both partners are found to be carriers of a genetic condition, genetic counseling should be offered. Prenatal diagnosis and advanced reproductive technologies to decrease the risk of an affected offspring should be discussed.
- When an individual is found to be a carrier for a genetic condition, the individual's relatives are at risk of carrying the same mutation. The patient should be encouraged to inform his or her relatives of the risk and the availability of carrier screening. The obstetrician–gynecologist or other health care provider should not disclose this information without permission from the patient.
- It is important to obtain the family history of the patient and, if possible, her partner as a screening tool for inherited risk. The family history should include the ethnic background of family members as well as any known consanguinity. Individuals with a

positive family history of a genetic condition should be offered carrier screening for the specific condition and may benefit from genetic counseling.

- Carrier screening for a particular condition generally should be performed only once in a person's lifetime, and the results should be documented in the patient's health record. Because of the rapid evolution of genetic testing, additional mutations may be included in newer screening panels. The decision to rescreen a patient should be undertaken only with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations.

- Prenatal carrier screening does not replace newborn screening, nor does newborn screening replace the potential value of prenatal carrier screening.

- If a patient requests carrier screening for a particular condition for which testing is readily available and which reasonably would be considered in another screening strategy, the requested test should be offered to her (regardless of ethnicity and family history) after counseling on the risks, benefits, and limitations of screening.

- The cost of carrier screening for an individual condition may be higher than the cost of testing through commercially available expanded carrier screening panels. When selecting a carrier screening approach, the cost of each option to the patient and the health care system should be considered.

Recommendations for Specific Conditions

Spinal Muscular Atrophy

- Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant.

- In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, *SMN1* deletion testing should be recommended for the low-risk partner.

Cystic Fibrosis

- Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant.

- Complete analysis of the *CFTR* gene by DNA sequencing is not appropriate for routine carrier screening.

- For couples in which both partners are unaffected but one or both has a family history of cystic fibrosis, genetic counseling and medical record review should be performed to determine if *CFTR* mutation analysis in the affected family member is available.

- If a woman's reproductive partner has cystic fibrosis or apparently isolated congenital bilateral absence of the vas deferens, the couple should be provided follow-up genetic counseling by an obstetrician–gynecologist or other health care provider with expertise in genetics for mutation analysis and consultation.

Hemoglobinopathies

- A complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. Ideally, this testing also should be offered to women before pregnancy.

- A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electrophoresis also should be performed.

Fragile X Syndrome

- 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 and who are considering pregnancy or are currently pregnant.

- If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an *FMR1* premutation.

- All identified individuals with intermediate results and carriers of a fragile X premutation or full mutation should be provided follow-up genetic counseling to discuss the risk to their offspring of inheriting an expanded full-mutation fragile X allele and to discuss fragile X-associated disorders (premature ovarian insufficiency and fragile X tremor/ataxia syndrome).

- Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation.

- DNA-based molecular analysis (eg, Southern blot analysis and polymerase chain reaction) is the preferred method of diagnosis of fragile X syndrome and of determining *FMR1* triplet repeat number (eg, premutations). In rare cases, the size of the triplet repeat and the methylation status do not correlate, which makes it difficult to predict the clinical phenotype. In cases of this discordance, the patient should be referred to a genetics professional.

Genetic Conditions in Individuals of Eastern and Central European Jewish Descent

- When only one partner is of Ashkenazi Jewish descent, that individual should be offered screening first. If it is determined that this individual is a carrier, the other partner should be offered screening. However, the couple should be informed that the carrier frequency and the detection rate in non-Jewish individuals are unknown for most of these disorders, except for Tay–Sachs disease and cystic fibrosis. Therefore, it is difficult to accurately predict the couple's risk of having a child with the disorder.

Tay–Sachs Disease

- Screening for Tay–Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French–Canadian, or Cajun descent. Those with a family history consistent with Tay–Sachs disease also should be offered screening.

- When one member of a couple is at high risk (ie, of Ashkenazi Jewish, French–Canadian, or Cajun descent or has a family history consistent with Tay–Sachs disease) but the other partner is not, the high-risk partner should be offered screening. If the high-risk partner is found to be a carrier, the other partner also should be offered screening.

- Enzyme testing in pregnant women and women taking oral contraceptives should be performed using leukocyte testing because serum testing is associated with an increased false-positive rate in these populations.

- If Tay–Sachs disease screening is performed as part of pan-ethnic expanded carrier screening, it is important to recognize the limitations of the mutations screened in detecting carriers in the general population. In the presence of a family history of Tay–Sachs disease, expanded carrier screening panels are not the best approach to screening unless the familial mutation is included on the panel.

- Referral to an obstetrician–gynecologist or other health care provider with genetics expertise may be helpful in instances of inconclusive enzyme testing results or in discussion of carrier testing of an individual with non-Ashkenazi Jewish ethnicity whose reproductive partner is a known carrier of Tay–Sachs disease.

Introduction

Carrier screening is a term used to describe genetic testing that is performed on an individual who does not have any overt phenotype for a genetic disorder but may have one variant allele within a gene(s) associated with a diagnosis. Information about genetic carrier screening should be provided to every pregnant woman. After counseling, a patient may decline any or all screening. Carrier screening and counseling ideally should be performed before pregnancy because this enables couples to learn about their reproductive risk and consider the most complete range of reproductive options, including whether or not to become pregnant and whether to use advanced reproductive technologies such as preimplantation genetic diagnosis or use of donor gametes. Knowledge during pregnancy allows patients to consider prenatal diagnosis and pregnancy management options in the event of an affected fetus.

If an individual is found to be a carrier for a specific condition, the individual's reproductive partner should be offered testing in order to receive informed genetic counseling about potential reproductive outcomes. Concurrent screening of the patient and her partner is suggested if there are time constraints for decisions about prenatal diagnostic evaluation. If both partners are found to be carriers of a genetic condition, genetic counseling should be offered. Prenatal diagnosis and advanced reproductive technologies to decrease the risk of an affected offspring should be discussed. Prenatal carrier screening does not replace newborn screening, nor does newborn screening replace the potential value of prenatal carrier screening.

When an individual is found to be a carrier for a genetic condition, the individual's relatives are at risk of carrying the same mutation. The patient should be encouraged to inform his or her relatives of the risk and the availability of carrier screening. The obstetrician–gynecologist or other health care provider should not disclose this information without permission from the patient.

It is important to obtain the family history of the patient and, if possible, her partner as a screening tool for inherited risk. The family history should include the ethnic background of family members as well as any known consanguinity (a union between two individuals who are second cousins or closer in family relationship) (1)*. Individuals with a positive family history of a genetic condition should be offered carrier screening for the specific condition and may benefit from genetic counseling. Ideally, information on the specific mutation will be available to aid testing and counseling.

Carrier screening for a particular condition generally should be performed only once in a person's lifetime, and the results should be documented in the patient's health record. Because of the rapid evolution of genetic testing, additional mutations may be included in newer screening panels. The decision to rescreen a patient should be undertaken only with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations.

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*For the purposes of this document, individuals are considered to be of Ashkenazi Jewish descent if their Jewish relatives originated from Eastern or Central Europe (2).

Although several different strategies for screening are available and reviewed in Committee Opinion No. 690, *Carrier Screening in the Age of Genomic Medicine*, this document seeks to provide information about the different conditions for which a patient may seek prepregnancy carrier screening. If a patient requests carrier screening for a particular condition for which testing is readily available and which reasonably would be considered in another screening strategy, the requested test should be offered to her (regardless of ethnicity and family history) after counseling on the risks, benefits, and limitations of screening. The cost of carrier screening for an individual condition may be higher than the cost of testing through commercially available expanded carrier screening panels. When selecting a carrier screening approach, the cost of each option to the patient and the health care system should be considered.

What follows is a detailed discussion of some of the more common genetic conditions for which carrier screening is recommended in at least some segments of the population. The different sections collect topics that had previously been discussed in separate Committee Opinions to show how the aforementioned general principles are used and reflected in carrier screening for specific genetic conditions.

Spinal Muscular Atrophy ⇐

Spinal muscular atrophy, also known as SMA, is an autosomal recessive disease characterized by degeneration of spinal cord motor neurons that leads to atrophy of skeletal muscle and overall weakness. The disorder is caused by a mutation in the gene known as the survival motor neuron gene (*SMN1*), which is responsible for the production of a protein essential to motor neuron function. Because of the severity and relatively high carrier frequency, there has been increasing interest in carrier screening for spinal muscular atrophy in the general prenatal population (3). The genetics of spinal muscular atrophy are complex and, because of limitations in the molecular diagnostic assays available, precise prediction of the phenotype in affected fetuses may not be possible.

The incidence of spinal muscular atrophy is approximately 1 in 6,000 to 1 in 10,000 live births, and the disease is reported to be the leading genetic cause of infant death. Carrier frequencies in most populations are estimated at 1 in 40 to 1 in 60, but carrier frequencies appear to be lower in the Hispanic population (1:117) (4). Carrier frequencies and residual risks are outlined by ethnicity in Table 1. Approximately 2% of cases of spinal muscular atrophy are the result of a new gene mutation. There is no effective treatment for the disease.

There are several types of spinal muscular atrophy based on age at symptom onset. Earlier onset is correlated with more severe manifestations. The most severe and most common form of the disease, type I (Werdnig–Hoffman), has symptomatic onset before 6 months of age and causes death from respiratory failure within the first 2 years of life. Type II spinal muscular atrophy is of intermediate severity, with typical onset before 2 years of age. Affected children are able to sit, but few are able to stand or walk unaided. Respiratory insufficiency is a frequent cause of death during adolescence; however, the lifespan of patients with spinal muscular atrophy type II varies from age 2 years to the third decade of life. More than 80% of cases of spinal muscular atrophy are type I or type II, both of which are lethal forms. A milder form, type III (Kugelberg–Welander), has typical symptomatic onset after 18 months of age. However, the symptom profile is quite variable. Affected individuals typically reach all major motor milestones, but function ranges from requiring wheelchair assistance in childhood to completely unaided ambulation into adulthood with minor muscular weakness. Many patients have normal life expectancies. Type IV has onset in adulthood. There is an additional Type 0 proposed, which has onset in the prenatal period.

Molecular Genetics

There are two nearly identical survival motor neuron genes present in humans, known as *SMN1* and S*MN2*. *SMN1* is considered the active gene for survival motor neuron protein production, and more than 98% of patients with spinal muscular atrophy have an abnormality in both *SMN1* genes, which can be caused by a deletion (95%) of exon 7, or other mutation. There is generally one copy of *SMN1* per chromosome, but

Table 1. Carrier Risk Based on Ethnicity and Residual Risk Assuming Negative Test Results ⇐

Ethnicity	Carrier Detection by Ethnicity (%)	Carrier Risk by Ethnicity	Residual Risk 2 Copies *SMN1*	Residual Risk 3 Copies *SMN1*
Caucasian	95	1:35	1:632	1:3,500
Ashkenazi Jewish	90	1:41	1:350	1:4,000
Asian	93	1:53	1:628	1:5,000
African American	71	1:66	1:121	1:3,000
Hispanic	91	1:117	1:1,061	1:11,000

Adapted with permission from BMJ Publishing Group Limited. Hendrickson BC, Donohoe C, Akmaev VR, Sugarman EA, Labrousse P, Boguslavskiy L, et al. Differences in *SMN1* allele frequencies among ethnic groups within North America. J Med Genet 2009;46:641–4.

occasionally two can be located on the same chromosome. A variable number of *SMN2* gene copies (ranging from zero to three) may be present, but the *SMN2* gene produces only a small amount of functional survival motor neuron protein. A higher number of *SMN2* copies correlates with generally milder clinical phenotypes, but accurate prediction of the spinal muscular atrophy phenotype based on *SMN2* copy number is not possible (5).

Diagnosis Versus Carrier Detection

For diagnosis of spinal muscular atrophy in a child or an adult, it is sufficient to simply detect the classic *SMN1* deletion using DNA analysis in both *SMN1* alleles. This is approximately 95% sensitive (100% specific) for patients with clinical features suspicious for spinal muscular atrophy. However, this approach is not sufficient to identify patients who are heterozygous, or carriers, for the *SMN1* deletion. Carrier testing requires a quantitative polymerase chain reaction assay that provides a measure of *SMN1* copy number. Detection of a single normal copy of *SMN1* would indicate the carrier state (Figure 1). There are limitations, however, to the use of this assay to determine carrier status. Approximately 3–4% of the general population have two *SMN1* copies on one chromosome and no copies on the other and will not be identified as being a carrier of spinal muscular atrophy using this approach. These individuals are carriers because one of their chromosomes is missing the *SMN1* allele. The missing *SMN1* allele appears to be more predominant in African Americans and lowers the carrier detection rate to approximately 71% in this group. In other ethnic groups, more than 90% of carriers are detected by dosage analysis of *SMN1*. Another 2% of the general population has *SMN1* mutations that are not detectable by dosage analysis. Therefore, the counseling of patients who are tested for carrier status must account for the residual risk present when carrier screening assay results are negative, particularly in patients from families affected by spinal muscular atrophy.

Carrier Screening

Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant and have had appropriate counseling about the possible range of severity, carrier rate, and detection rate. Posttest counseling should reiterate residual risk after negative screening based on the number of *SMN1* copies present. In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing to determine the residual risk for the patient with a negative screen. If the reports are not available, *SMN1* deletion testing should be recommended for the low-risk partner. If this individual is found to be a carrier, the couple should be referred for further genetic counseling and consideration of further genetic testing in the high-risk partner.

Cystic Fibrosis ⇐

Prepregnancy and prenatal carrier screening for cystic fibrosis, also known as CF, was introduced into routine obstetric practice in 2001 (6). The goal of cystic fibrosis carrier screening is to identify individuals at risk of having a child with classic cystic fibrosis, which is defined by significant pulmonary disease and pancreatic insufficiency. Cystic fibrosis is more common among the non-Hispanic white population compared with other racial and ethnic populations; however, because of the increasing difficulty in assigning a single ethnicity to individuals, in 2005, the American College of Obstetricians and Gynecologists recommended offering cystic fibrosis carrier screening to all patients.

Cystic fibrosis is the most common life-threatening, autosomal recessive condition in the non-Hispanic white

Figure 1. *SMN1* Gene in Normal, Carrier, and Affected States ⇐
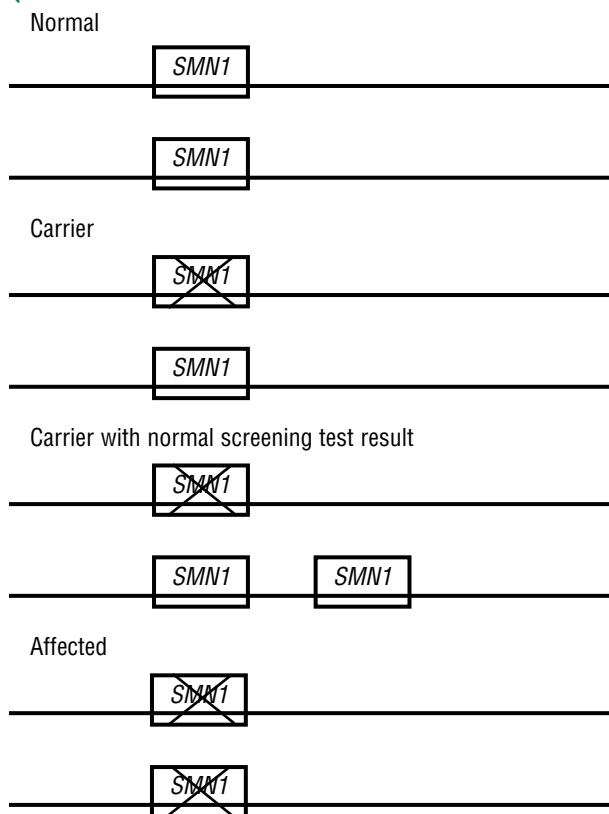
In the normal genotype, there are two normal copies of the *SMN1* gene—one on each chromosome. A carrier has a mutation that renders one of the genes inactive (as denoted by the "x"). It is possible for someone to be a carrier but have a normal result on a screening test; these individuals have both gene copies on the same chromosome. Although the carrier has enough genetic material to have a normal screening result, the carrier has a 50% chance of passing the chromosome with a single inactivated gene to his or her offspring. Affected individuals have two nonfunctioning genes. The copy number of *SMN2* alleles (not pictured here) may modify the phenotype in affected individuals.

population. The disease incidence is 1 in 2,500 individuals in the non-Hispanic white population and considerably less in other ethnic groups. It is a progressive, multisystem disease that primarily affects the pulmonary, pancreatic, and gastrointestinal systems butdoes not affect intelligence. The current median predicted survival is approximately 42 years, with respiratory failure as the most common cause of death (7). More than 95% of males with cystic fibrosis have primary infertility with obstructive azoospermia secondary to congenital bilateral absence of the vas deferens. Cystic fibrosis is caused by mutations in the *cystic fibrosis transmembrane regulator (CFTR)* gene, located on chromosome 7. Two copies of deleterious mutations in this gene cause cystic fibrosis.

The sensitivity of the screening test varies among ethnic groups (Table 2), ranging from less than 50% in those of Asian ancestry to 94% in the Ashkenazi Jewish population (8). Therefore, screening is most efficacious in non-Hispanic white and Ashkenazi Jewish populations. Because screening is offered for only the most common mutations, a negative screening test result reduces but does not eliminate the chance of being a cystic fibrosis carrier and having an affected offspring. Therefore, if a patient is screened for cystic fibrosis and has a negative test result, she still has a residual risk of being a carrier. The most common cystic fibrosis carrier frequencies, as well as the rates of residual carrier risk after a negative test result, are listed by racial and ethnic group in Table 2.

Screening Considerations for Cystic Fibrosis

As with all carrier screening, it is generally more cost effective and practical to perform initial carrier screening only for the patient. Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant. If the patient is a cystic fibrosis carrier, then her partner should be tested. During pregnancy, concurrent screening of the patient and her partner is suggested if there are time constraints for decisions regarding prenatal diagnostic evaluation. Given that cystic fibrosis screening has been a routine part of reproductive care for women since 2001, it is prudent to determine if the patient has been previously screened before ordering repeat cystic fibrosis screening. If a patient has been screened previously, cystic fibrosis screening results should be documented, but the test should not be repeated. Although some mutation panels have been expanded over the past decade, the incremental yield of the addition of those mutations is small for most patients. Before repeat testing, the clinical scenario should be discussed with an obstetrician–gynecologist or other health care provider with expertise in genetics.

The following are various carrier screening scenarios with associated management recommendations:

- **A woman is a carrier of a cystic fibrosis mutation and her partner is unavailable for testing or paternity is unknown**. Genetic counseling to review the risk of having an affected child and prenatal testing options and limitations is recommended.

- **Prenatal diagnosis is being performed for other indications and cystic fibrosis carrier status is unknown**. Cystic fibrosis screening can be performed concurrently on the patient and partner. Chorionic villi or amniocytes may be maintained in culture by the diagnostic laboratory until cystic fibrosis screening results are available for the patient or couple. If both partners are carriers, diagnostic testing for cystic fibrosis can be performed on the chorionic villi or amniocytes.

- **Both partners are cystic fibrosis carriers**. Genetic counseling is recommended to review prenatal testing and reproductive options. Prenatal diagnosis should be offered for the couple's specific, known mutations.

Table 2. Cystic Fibrosis Detection and Carrier Rates Before and After Testing ⇐

Racial or Ethnic Group	Detection Rate* (%)	Individual Carrier Risk Before Testing	Approximate Individual Carrier Risk After Negative Test Result[†]
Ashkenazi Jewish	94	1/24	1/380
Non-Hispanic white	88	1/25	1/200
Hispanic white	72	1/58	1/200
African American	64	1/61	1/170
Asian American	49	1/94	1/180

*Detection rate data based on use of a 23-mutation panel.

[†]Bayesian statistics used to calculate approximate carrier risk after a negative test result.

Modified from the American College of Medical Genetics and Genomics. Technical standards and guidelines for *CFTR* mutation testing. American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. Bethesda (MD): ACMG; 2011. Available at: http://www.acmg.net/docs/CFTR_Mutation_Testing_2011.pdf. Retrieved September 12, 2016.

- **Both partners are unaffected, but one or both has a family history of cystic fibrosis**. Genetic counseling and medical record review should be performed to determine if *CFTR* mutation analysis in the affected family member is available. Carrier screening should be offered for both partners, with attention to ensure that the familial mutation is included in the assessment.

- **A woman's reproductive partner has cystic fibrosis or apparently isolated congenital bilateral absence of the vas deferens**. The couple should be provided follow-up genetic counseling by an obstetrician–gynecologist or other health care provider with expertise in genetics for mutation analysis and consultation.

- **An individual has two cystic fibrosis mutations but has not previously received a diagnosis of cystic fibrosis**. The individual usually has a mild form of the disease and should be referred to a specialist for further evaluation. Genetic counseling is recommended.

CFTR Mutation Panels

To date, more than 1,700 mutations have been identified for cystic fibrosis (9). Current guidelines, revised by the American College of Medical Genetics and Genomics in 2004, recommend use of a panel that contains, at a minimum, the 23 most common mutations. The guidelines were developed after assessing the initial experiences following the implementation of cystic fibrosis screening into clinical practice (10). A number of expanded mutation panels are now commercially available and can be considered to enhance the sensitivity for carrier detection, especially in non-Caucasian ethnic groups. Cystic fibrosis screening also may identify the 5T/7T/9T variants in the *CFTR* gene. Although not disease-causing on their own, these variants can be associated with milder forms of disease and male infertility in individuals who are heterozygous for certain *CFTR* gene mutations. Genetic counseling is important to discern whether the combination of mutations and variants would cause classic or atypical cystic fibrosis.

Complete analysis of the *CFTR* gene by DNA sequencing is not appropriate for routine carrier screening. This type of testing generally is reserved for patients with cystic fibrosis, patients with negative carrier screening result but a family history of cystic fibrosis (especially if family test results are not available), males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening result when mutation testing (using the standard 23-mutation panel) has a negative result. Because carrier screening detects most mutations, sequence analysis should be considered only after discussion with a genetics professional to determine if it will add value to the standard screening that was performed previously.

All states include cystic fibrosis screening as part of their newborn screening panel. However, newborn screening panels do not replace prepregnancy or prenatal carrier screening. Because these screening programs generally identify affected newborns, a negative test result in an unaffected newborn provides no information about the carrier status of the parents. Thus, it is important that cystic fibrosis screening continues to be offered to women who are considering pregnancy or are currently pregnant.

Hemoglobinopathies ⇐

Hemoglobin Structure

Hemoglobin consists of four interlocking polypeptide chains, each of which has an attached heme molecule. Adult hemoglobin consists of two α-chains and either two β-chains (hemoglobin A), two γ-chains (hemoglobin F), or two δ-chains (hemoglobin A_2). Alpha-globin chain production begins in the first trimester and is an essential component of fetal hemoglobin F, hemoglobin A, and hemoglobin A_2. Hemoglobin F is the primary hemoglobin of the fetus from 12 weeks to 24 weeks of gestation. In the third trimester, production of hemoglobin F decreases as production of β-chains and hemoglobin A begins.

Sickle Cell Disease

Sickle cell disease refers to a group of autosomal recessive disorders that involve abnormal hemoglobin (hemoglobin S). Hemoglobin S differs from the normal hemoglobin A because of a single nucleotide substitution in the *β-globin* gene; this alteration causes a substitution of valine for glutamic acid in the number six position of the β-globin polypeptide. Asymptomatic individuals with heterozygous hemoglobin S genotypes (carriers) are said to have sickle cell trait. The most severe form of the disease, hemoglobin SS (homozygous hemoglobin S), is called sickle cell anemia.

Sickle cell disorders are found not only in patients who have the hemoglobin genotype SS, but also in those who have hemoglobin S and another abnormality of β-globin structure or β-globin production. The most common of these are hemoglobin SC disease and hemoglobin S/β-thalassemia. In hemoglobin C, the same nucleotide involved in the hemoglobin S mutation is altered, but the nucleotide change results in the amino acid substitution of lysine for glutamic acid. This and other abnormal hemoglobins, when inherited with hemoglobin S, may cause clinically significant vasoocclusive phenomena and hemolytic anemia similar to hemoglobin SS.

Sickle cell disease occurs most commonly in people of African origin. Approximately 1 in 10 African Americans has sickle cell trait (11). One in every 300–500 African-American newborns has some form of sickle cell disease. Hemoglobin S also is found in high frequency in other populations such as Greeks, Italians (particularly

Sicilians), Turks, Arabs, Southern Iranians, and Asian Indians (12).

The classical clinical feature of patients with sickle cell disease is seen under conditions of decreased oxygen tension, in which the red blood cells become distorted into various shapes, some of which resemble sickles. The distorted red cells lead to increased viscosity, hemolysis, and anemia and a further decrease in oxygenation. When sickling occurs within small blood vessels, it can interrupt blood supply to vital organs (vasoocclusive crisis). Repeated vasoocclusive crises result in widespread microvascular obstruction with interruption of normal perfusion and function of several organs, including the spleen, lungs, kidneys, heart, and brain. These crises are extremely painful and typically require hospitalization and medical management. Over the course of their lifetimes, patients with sickle cell disease who have repeated crises often build up tolerance to opioid medications and may require large doses in order to achieve relief from the pain of an acute vasoocclusive crisis. Also, these patients often have an element of chronic pain and they may require daily pain medication even in the absence of an acute crisis. Adults with hemoglobin SS are functionally asplenic, having undergone autosplenectomy by adolescence. Absence of the spleen contributes to the increased incidence and severity of infection in patients with sickle cell disease.

The most significant threat to patients with sickle cell disease is acute chest syndrome. Acute chest syndrome is characterized by a pulmonary infiltrate with fever that leads to hypoxemia and acidosis. The infiltrates are not infectious in origin but rather are due to vasoocclusion from sickling or embolization of marrow from long bones affected by sickling (13).

The diagnosis of hemoglobinopathies, including sickle cell disorders, is made by hemoglobin electrophoresis. In the homozygous form of sickle cell disease, nearly all the hemoglobin is hemoglobin S with small amounts of hemoglobin A_2 and hemoglobin F. Heterozygous sickle cell trait (hemoglobin AS) is identified by a larger per-centage of hemoglobin A and an asymptomatic course. Solubility tests alone are inadequate for diagnosis of sickle cell disorders because they cannot distinguish between the heterozygous AS and homozygous SS genotypes. Solubility tests are not useful for screening because of the inability to identify other pathologic variants such as hemoglobin C, hemoglobin E, and β-thalassemia trait.

The Thalassemias

The thalassemias represent a wide spectrum of hematologic disorders that are characterized by a reduced synthesis of globin chains, which results in microcytic anemia. Thalassemias are classified according to the globin chain affected, with the most common types being α-thalassemia and β-thalassemia (14).

Alpha-Thalassemia

Alpha-thalassemia usually results from a gene deletion of two or more copies of the four *α-globin* genes. Deletion of one *α-globin* gene (α-/αα) is clinically unrecognizable, and laboratory testing yields normal results. Deletion of two *α-globin* genes causes α-thalassemia trait, a mild asymptomatic microcytic anemia. The deletions can be on the same chromosome or in *cis* (αα/--), or on each chromosome or in *trans* (α-/α-).

Individuals with these gene deletions are referred to as carriers and are at an increased risk of having children with a more severe form of thalassemia caused by deletions of three or four copies of the *α-globin* gene (α-thalassemia major). The possible genetic combinations are summarized in Table 3.

Alpha-thalassemia trait (α-thalassemia minor) is common among individuals of Southeast Asian, African, and West Indian descent and in individuals with Mediterranean ancestry. Individuals with Southeast Asian ancestry are more likely to carry two gene deletions in *cis* or on the same chromosome (--/αα) and are at an increased risk of offspring with hemoglobin Bart or hemoglobin H disease. Hemoglobin H disease, which

Table 3. Classification of Alpha-Thalassemias ⇐

Number of Globin Genes	Genotype	Description	Clinical Features
4	αα/αα	Normal	Normal
3	α-/αα	Heterozygous α$^+$-thalassemia	Asymptomatic
2	α-/α-	Homozygous α$^+$-thalassemia	Mild microcytic anemia
	αα/--	Heterozygous α^0-thalassemia	Mild microcytic anemia
1	α-/--	Hemoglobin H disease	Hemolytic anemia, splenomegaly, variable bone changes, iron overload
0	--/--	Hemoglobin Bart disease	Hydrops fetalis

Modified from Hemoglobinopathies in pregnancy. ACOG Practice Bulletin No. 78. American College of Obstetricians and Gynecologists. Obstet Gynecol 2007;109:229–37.

is caused by the deletion of three *α-globin* genes, usually is associated with mild-to-moderate hemolytic anemia. Alpha-thalassemia major (hemoglobin Bart) results in the absence of *α-globin* (--/--), which is associated with hydrops fetalis, intrauterine death, and preeclampsia (12).

Beta-Thalassemia

Beta-thalassemia is the result of a mutation in the *β-globin* gene that causes deficient or absent β-chain production, which in turn causes an absence of hemoglobin A. Individuals of Mediterranean, Asian, Middle Eastern, Hispanic, and West Indian descent are more likely to carry β-thalassemia mutations. Classification of β-thalassemias is based on a description of the molecular mutation or on clinical manifestations. Individuals who are heterozygous for this mutation have β-thalassemia minor. Those who are homozygous have β-thalassemia major (Cooley's anemia) or a milder form called thalassemia intermedia. There are numerous mutations associated with β-thalassemia, and each mutation can have a different effect on the amount of β-chain produced. Because of the many different mutations, many individuals with β-thalassemia major are actually compound heterozygotes carrying two different mutations. Beta-thalassemia major is characterized by severe anemia with resultant extramedullary erythropoiesis, delayed sexual development, and poor growth. Elevated levels of hemoglobin F in individuals with β-thalassemia major partially compensate for the absence of hemoglobin A; however, death usually occurs by age 10 years unless treatment is begun early with periodic blood transfusions. With transfusion, the severe anemia is reversed and extramedullary erythropoiesis is suppressed. In homozygotes with the less severe β+-thalassemia mutations, often referred to as β-thalassemia intermedia, variable but decreased amounts of β-chains are produced and as a result variable amounts of hemoglobin A are produced. Some individuals can inherit a hemoglobin S mutation from one parent and a β-thalassemia mutation from the other. The expression of the resulting hemoglobin S/β-thalassemia is determined by the type of β-thalassemia mutation (15).

Screening

A combination of laboratory tests may be required to provide the information necessary to counsel couples who are carriers of one of the thalassemias or sickle cell disease. To ensure accurate hemoglobin identification, which is essential for genetic counseling, a complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electrophoresis also should be performed. A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). Ideally, this testing also should be offered to women before pregnancy. If the results of a prior hemoglobin electrophoresis are available, repeat hemoglobin electrophoresis is not necessary to evaluate status.

Several tests, including solubility testing (such as a test for the presence of hemoglobin S), isoelectric focusing, and high-performance liquid chromatography, have been used for primary screening. However, solubility tests are inadequate for screening and fail to identify important transmissible hemoglobin gene abnormalities that affect fetal outcome (eg, hemoglobin C trait, β-thalassemia trait, hemoglobin E trait). Many individuals with these genotypes are asymptomatic, but if their partners have the sickle cell trait or other hemoglobinopathies, they may produce offspring with more serious hemoglobinopathies, such as hemoglobin S/β-thalassemia and hemoglobin sickle cell disease.

Determination of mean corpuscular volume is recommended to assess risk of α-thalassemia or β-thalassemia. Patients who have a low mean corpuscular volume (less than 80 fL) may have one of the thalassemia traits, and hemoglobin electrophoresis should be performed if it was not done previously. These individuals also may have iron deficiency anemia, and measurement of serum ferritin levels is recommended. Beta-thalassemia is associated with elevated hemoglobin F and elevated hemoglobin A_2 levels (more than 3.5%). Neither hemoglobin electrophoresis nor solubility testing can identify individuals with α-thalassemia trait; only molecular genetic testing can identify this condition. If the mean corpuscular volume is below normal, iron deficiency anemia has been excluded, and the hemoglobin electrophoresis is not consistent with β-thalassemia trait (ie, there is no elevation of Hb A_2 or Hb F), then DNA-based testing should be used to detect *α-globin* gene deletions characteristic of α-thalassemia. The hematologic features of some of the common hemoglobinopathies are shown in Table 4. If both partners are identified as carriers of a gene for abnormal hemoglobins, genetic counseling is recommended.

Prenatal Genetic Testing Options

Couples at risk of having a child with a hemoglobinopathy may benefit from genetic counseling to review their risk, the natural history of these disorders, prospects for treatment and cure, availability of prenatal genetic testing, and reproductive options. Prenatal diagnostic testing for the mutation responsible for sickle cell disease is widely available. Testing for α-thalassemia and β-thalassemia is possible if the mutations and deletions have been previously identified in both parents. These DNA-based tests can be performed using chorionic villi obtained by chorionic villus sampling or using cultured amniotic fluid cells obtained by amniocentesis. For some couples, preimplantation genetic diagnosis in combination

Table 4. Hematologic Features of Main Hemoglobinopathies ⇦

Disorder	Heterozygous State	Homozygous State
α^+Thalassemia ($-\alpha$)	0–2% Hb Bart at birth	5–10% Hb Bart in the neonatal period, low MCV
α^0Thalassemia (--)	5–10% Hb Bart in the neonatal period, low MCV, normal Hb A$_2$	Hb Bart's hydrops fetalis
β^0Thalassemia	Low MCH & MCV, Hb A$_2$ 3.5–7.0%	Thalassemia major: Hb F 98% Hb A$_2$ 2%
β^+Thalassemia (severe)	Low MCH & MCV, Hb A$_2$ 3.5–7.0%	Thalassemia major: Hb F 70–95%
β^+Thalassemia (mild)	Low MCH & MCV, Hb A$_2$ 3.5–7.0%	Thalassemia intermedia: Hb F 20–40%
Hb S	Hb A, Hb S, Hb A$_2$	Hb S, Hb F (1–15%), Hb A$_2$
Hb S/β-Thalassemia	—	If β^0Thalassemia, severe sickle cell anemia; if β^+Thalassemia, less severe
Hb E/β-Thalassemia	—	Thalassemia major or intermedia: Hb E 60–70%, Hb F 30–40%

Abbreviations: Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume.

Modified from Old JM. Prenatal diagnosis of the hemoglobinopathies. In: Milunsky A, Milunsky JM, editors. Genetic disorders and the fetus: diagnosis, prevention, and treatment. 7th ed. Hoboken (NJ): Wiley Blackwell; 2016. p. 718–54.

with in vitro fertilization may be a desirable alternative to avoid termination of an affected pregnancy. Preimplantation genetic diagnosis has been successfully performed for sickle cell disease and most types of β-thalassemia.

Fragile X Syndrome ⇦

Fragile X syndrome is the most common inherited form of intellectual disability. The syndrome occurs in approximately 1 in 3,600 males and 1 in 4,000–6,000 females from a variety of ethnic backgrounds. Intellectual disability or impairment ranges from borderline, including learning disabilities, to severe, presenting with cognitive and behavioral disabilities, including autism with intellectual disability; attention deficit–hyperactivity disorder; or both. Most affected males have significant intellectual disability. Fragile X syndrome is a common known cause of autism or autism spectrum disorder behaviors with intellectual disability, with the diagnosis occurring in approximately 25% of affected individuals (16). Other associated phenotypic abnormalities include distinctive facial features in males (including a long, narrow face and prominent ears), enlarged testicles (macroorchidism), joint and skin laxity, hypotonia, mitral valve prolapse, delay in speech, and delay in gross and fine motor skills. The abnormal facial features are subtle in infancy and become more noticeable with age, making phenotypic diagnosis difficult, especially in the newborn. Affected females may have a milder phenotype, and it is sometimes hard to establish the diagnosis based on clinical findings alone.

Fragile X syndrome is transmitted as an X-linked disorder. However, the molecular genetics of the syndrome are complex. The disorder is caused by expansion of a repeated trinucleotide segment of DNA, cytosine–guanine–guanine that leads to altered transcription of the fragile X gene *FMR1*. The number of cytosine–guanine–guanine repeats varies among individuals and has been classified into four groups depending on the repeat size: 1) unaffected (5–44 repeats), 2) intermediate (45–54 repeats), 3) premutation (55–200 repeats), and 4) full mutation (greater than 200 repeats) (17, 18) (see Table 5).

A person with 55–200 repeats does not have features associated with fragile X syndrome but is at increased risk of fragile X-associated tremor/ataxia syndrome (also known as FXTAS) and *FMR1*-related premature ovarian failure. When more than 200 repeats are present, an individual has a full mutation that results in the full expression of fragile X syndrome in males and variable expression in females. The large number of repeats in a full mutation allele causes the *FMR1* gene to become methylated and inactivated.

Transmission of a disease-producing mutation to a fetus depends on the sex of the parent transmitting the mutation and the number of cytosine–guanine–guanine repeats present in the parental gene. Repeats very rarely expand during spermatogenesis in the male, such that only an affected male can transmit the full mutation to his female offspring. However, repeats in the female may expand during oogenesis, such that women with the premutation may transmit a full mutation, which results in an affected child. The larger the size of the premutation

repeat, the more likely that there will be expansion to a full mutation (Table 5). Women with an intermediate number of triplet repeats (45–54) do not transmit a full mutation to their male and female offspring, although there may be expansion to a premutation allele in their offspring. Diagnosis of mutation size may vary by as many as 3 or 4 repeats. The frequency of premutation allele carriers (repeat size greater than 54) in the population has been reported to be as high as 1 in 157 in a large Israeli study of women (more than 36,000 individuals) without a family history of intellectual disability or developmental abnormalities (19). The most recent prevalence data from the United States reported a carrier frequency of 1 in 86 for those with a family history of intellectual disability and 1 in 257 for women with no known risk factors for fragile X syndrome (20).

Prepregnancy or Prenatal Carrier Screening

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 and who are considering pregnancy or are currently pregnant. If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an *FMR1* premutation. Although following these guide-

Table 5. Full Mutation Expansion From Maternal Premutation Allele ⇐

Maternal Number of Triplet Repeats (Cytosine–Guanine–Guanine)	Status of Individual	Full Mutation Expansion* (%)
Less than 45	Unaffected	
45–54	Intermediate (also called "gray zone")	
55–59	Premutation	4
60–69	Premutation	5
70–79	Premutation	31
80–89	Premutation	58
90–99	Premutation	80
100–200	Premutation	98
More than 200	Full mutation	100

* The likelihood of expansion to a full mutation also may be affected by other factors, including the presence of AGG interrupters that reduce the risks of expansion.

Modified from Nolin SL, Brown WT, Glicksman A, Houck GE Jr, Gargano AD, Sullivan A, et al. Expansion of the fragile X CGG repeat in females with premutation or intermediate alleles. Am J Hum Genet 2003;72:454–64 with permission from Elsevier and data from Pesso R, Berkenstadt M, Cuckle H, Gak E, Peleg L, Frydman M, et al. Screening for fragile X syndrome in women of reproductive age. Prenat Diagn 2000;20:611–4.

lines will not detect most premutation carriers in the population, the guidelines do target a higher prevalence group based on current data with regard to carrier frequency. If a patient with no family history requests fragile X screening, it is reasonable to offer screening after informed consent. All identified individuals with intermediate results and carriers of a fragile X premutation or full mutation should be provided follow-up genetic counseling to discuss the risk to their offspring of inheriting an expanded full-mutation fragile X allele and to discuss fragile X-associated disorders (premature ovarian insufficiency and fragile X tremor/ataxia syndrome).

Prenatal Diagnostic Testing

Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation. Fetal DNA analysis from amniocentesis or chorionic villus sampling reliably determines the number of triplet repeats. However, there are caveats in interpretation of chorionic villus sampling results: in some cases, an analysis of *FMR1* gene methylation in full mutations from samples of chorionic villi may not be accurate, and a follow-up amniocentesis is necessary to accurately determine the methylation status of the gene (21). These limitations should be discussed with an obstetrician–gynecologist or other health care provider with the requisite genetics expertise before ordering any testing. DNA-based molecular analysis (eg, Southern blot analysis and polymerase chain reaction) is the preferred method of diagnosis of fragile X syndrome and of determining *FMR1* triplet repeat number (eg, premutations). In rare cases, the size of the triplet repeat and the methylation status do not correlate, which makes it difficult to predict the clinical phenotype. In cases of this discordance, the patient should be referred to a genetics professional.

Genetic Conditions in Individuals of Eastern and Central European Jewish Descent ⇐

A number of clinically significant, autosomal recessive disease conditions are more prevalent in individuals of Ashkenazi Jewish (Eastern European and Central European) descent. Most individuals of Jewish ancestry in North America are descended from Ashkenazi Jewish communities and, thus, are at increased risk of having offspring with one of these conditions. When only one partner is of Ashkenazi Jewish descent, that individual should be offered screening first. If it is determined that this individual is a carrier, the other partner should be offered screening. However, the couple should be informed that the carrier frequency and the detection rate in non-Jewish individuals are unknown for most of these disorders, except for Tay–Sachs disease and cystic fibrosis. Therefore, it is difficult to accurately predict the couple's risk of having a child with the disorder.

The American College of Obstetricians and Gynecologists has previously recommended offering carrier screening for four conditions in the Ashkenazi population:

1. Canavan disease is a severe degenerative neurologic disease. The phenotype is quite variable, but patients typically present in the first few months of life with delayed motor milestones (eg, head control and sitting). They will manifest macrocephaly, hypotonia, and intellectual disability. Life expectancy is variable, but many individuals die in childhood or adolescence. Treatment is primarily supportive because there is no cure. The disease is caused by mutations in the gene for aspartoacylase, which is involved in the metabolism of N-acetyl-L aspartic acid.

2. Cystic fibrosis is discussed elsewhere in this document.

3. Familial dysautonomia, a disorder of the sensory and autonomic nervous system, is associated with significant morbidity. Clinical features include abnormal suck and feeding difficulties, episodic vomiting, abnormal sweating, pain and temperature insensitivity, labile blood pressure levels, absent tearing, and scoliosis. Treatment is available that can improve the length and quality of life, but there currently is no cure. In 2001, the gene for familial dysautonomia was identified. At least two mutations in the familial dysautonomia gene, *IKBKAP*, have been identified in patients of Ashkenazi Jewish descent with familial dysautonomia. One of the mutations, IVS20(+6T->C), is found in more than 99% of patients with familial dysautonomia. It occurs almost exclusively in individuals of Ashkenazi Jewish descent; the carrier rate (1 in 32) is similar to Tay–Sachs disease and cystic fibrosis (22).

4. Tay–Sachs disease is discussed elsewhere in this document.

Some experts have advocated for a more comprehensive screening panel for those of Ashkenazi descent, including tests for several diseases that are less common (carrier rates 1 in 15 to 1 in 168). The following is a list of autosomal recessive conditions for which screening should be considered in individuals of Ashkenazi descent:

- Bloom syndrome is characterized by short stature, skin rash with sun exposure, and increased risk of cancer of any type. Affected individuals often have a high-pitched voice, distinctive facial features, learning disabilities, increased risk of diabetes, and chronic obstructive pulmonary disease. It is caused by mutations in the *BLM* gene, which codes for a protein family known as the RecQ helicases.

- Familial hyperinsulinism is a condition in which the pancreas produces too much insulin, which results in low blood sugar caused by mutations in the *ABCC8* gene.

- Fanconi anemia can be caused by mutations in at least 15 different genes, but 80–90% of cases are due to mutation in one of three genes: 1) *FANCA*, 2) *FANCC*, and 3) *FANCG*. Affected individuals can experience bone marrow failure; increased risk of cancer, including leukemia and solid tumors; and structural defects such as short stature, skin pigment changes, nervous system abnormalities (including central nervous system malformations), eye and ear malformations and hearing loss, skeletal abnormalities in particular affecting the thumb or forearms, gastrointestinal abnormalities (including effects on the oral cavity), and others. Of note, 25–40% of affected individuals do not have any physical abnormalities (23).

- Gaucher disease is caused by mutations in the *GBA* gene, which codes for the enzyme beta-glucocerebrosidase; this enzyme is responsible for the metabolism of glucocerebroside into glucose and ceramide. There are multiple types. Type 1 is the most common and does not affect the central nervous system. The symptoms can range from mild to severe and may not present until adulthood. Individuals present with hepatosplenomegaly, anemia, thrombocytopenia, lung disease, and bone abnormalities. Type 2 and type 3 Gaucher disease cause the aforementioned symptoms and signs and affect the central nervous system, including abnormal eye movement, seizures, and brain damage. Individuals with Type 2 can experience life-threatening issues early in life. There is also a perinatal lethal form, which can cause complications that manifest before birth or early in infancy. Finally, there is a cardiovascular type, which is characterized by calcification of the cardiac valves.

- Glycogen storage disease type I (also known as von Gierke disease) is caused by the buildup of glycogen in body cells, particularly the liver, kidneys, and small intestine, and leads to malfunction of these organs. The signs and symptoms present early in life, approximately age 3–4 months.

- Joubert syndrome is caused by mutations in genes related to the structure and function of cilia. Manifestations include the "molar tooth" sign on magnetic resonance imaging of the brain, which indicates abnormal development of the brainstem and cerebellar vermis; infants also can have hypotonia and ataxia, unusually fast or slow breathing, intellectual disability, and developmental delays.

- Maple syrup urine disease is caused by mutations in the *BCKDHA, BCKDHB*, and *DBT* genes, which encode proteins that are essential for breaking down the amino acids leucine, isoleucine, and valine. The urine of affected infants has a distinctive sweet odor. Affected individuals manifest poor feeding, lethargy, and developmental delays. Without treatment, this condition can be lethal.

- Mucolipidosis type IV is caused by mutations in the *MCOLN1* gene, which is involved in the function of lysosomes; dysfunction of this gene leads to accumulation of lipids and proteins in lysosomes. Affected individuals have severe psychomotor delays and visual impairment.

- Niemann–Pick disease can present in a variety of ways, with affected individuals exhibiting a range of severity. There are four main types: 1) A, 2) B, 3) C1, and 4) C2. Those with type A have a cherry-red spot in the eye; they often have failure to thrive, and at approximately age 1 year begin to exhibit psychomotor regression and widespread lung damage. Most do not survive beyond early childhood. Type A is the most common form in the Jewish population. Types B, C1, and C2 are not as severe as type A and present later in childhood, although all three can manifest with lung disease. Individuals with types C1 and C2 develop neurologic compromise that eventually interferes with feeding ability and intellectual function.

- Usher syndrome is characterized by impairments in vision, balance, and hearing. Retinitis pigmentosa is the major cause of loss of vision in these patients. Type 1F and Type III appear to be the most common in the Jewish population.

The prevalence of these disorders in non-Jewish populations, except for Tay–Sachs disease and cystic fibrosis, is unknown, and the sensitivity of these carrier tests in non-Jewish populations has not been established. Because the mutations in other populations may vary, counseling on the residual risks after negative carrier screening can be complicated in non-Jewish individuals. For couples in which one partner is a carrier and the other is of non-Jewish ancestry, genetic counseling may be useful in determining the best approach to risk estimation. Some people advocate screening for additional conditions in the Ashkenazi Jewish population, but inclusion in this list is limited to conditions that meet the criteria established in Committee Opinion 690, *Carrier Screening in the Age of Genomic Medicine*.

Tay–Sachs Disease ⇦

Tay–Sachs disease is a severe, progressive neurodegenerative disease. It is an autosomal recessive lysosomal storage disease in which GM2 gangliosides accumulate throughout the body due to functional deficiency in the enzyme hexosaminidase A. The accumulation of these gangliosides in the central nervous system causes death in early childhood. Because carriers for this severe disease are more prevalent in populations of Ashkenazi Jewish descent, it is well accepted for ethnic-based carrier screening. Three hexosaminidase A mutations account for the majority (up to 98%) of Tay–Sachs disease alleles in this population (24).

The Tay–Sachs disease carrier rate in Jewish individuals of Eastern or Central European descent (Ashkenazi) is approximately 1 in 30; the carrier rate for non-Jewish individuals is estimated to be 1 in 300. However, individuals of French–Canadian and Cajun descent also have a carrier frequency higher than that in the general population (approximately 1 in 50) (25). Screening for Tay–Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French–Canadian, or Cajun descent. Those with a family history consistent with Tay–Sachs disease also should be offered screening. When one member of a couple is at high risk (ie, of Ashkenazi Jewish, French–Canadian, or Cajun descent or has a family history consistent with Tay–Sachs disease) but the other partner is not, the high-risk partner should be offered screening. This is particularly important if there is uncertainty about ancestry or if there is a family history consistent with Tay–Sachs disease. If the high-risk partner is found to be a carrier, the other partner also should be offered screening. If Tay–Sachs disease screening is performed as part of pan-ethnic expanded carrier screening, it is important to recognize the limitations of the mutations screened in detecting carriers in the general population. In the presence of a family history of Tay–Sachs disease, expanded carrier screening panels are not the best approach to screening unless the familial mutation is included on the panel.

Carrier testing can be performed using DNA-based testing (mutation analysis) or hexosaminidase enzymatic activity testing in serum or leukocytes (26). Laboratories report Hexosaminidase A levels as a percentage of total hexosaminidase activity. Hexosaminidase A levels can be used to distinguish affected individuals, carriers, and noncarriers. The enzyme assay detects approximately 98% of carriers, regardless of ethnicity. Enzyme testing in pregnant women and women taking oral contraceptives should be performed using leukocyte testing because serum testing is associated with an increased false-positive rate in these populations. Although molecular testing is highly effective in the ethnic groups at highest risk, the detection rate for carriers in the general population is more limited because of the potential for rare mutations. Referral to an obstetrician–gynecologist or other health care provider with genetics expertise may be helpful in instances of inconclusive enzyme testing results or in discussion of carrier testing of an individual with non-Ashkenazi Jewish ethnicity whose reproductive partner is a known carrier of Tay–Sachs disease.

If both partners are found to be carriers of Tay–Sachs disease, genetic counseling and prenatal diagnosis should be offered. Tay–Sachs disease can be diagnosed prenatally by measuring hexosaminidase activity in samples obtained by amniocentesis, chorionic villus sampling, or mutation analysis.

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.

References

1. Family history as a risk assessment tool. Committee Opinion No. 478. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:747–50. [PubMed] [*Obstetrics & Gynecology*] ⇐

2. Hereditary cancer syndromes and risk assessment. Committee Opinion No. 634. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;125:1538–43. [PubMed] [*Obstetrics & Gynecology*] ⇐

3. Prior TW. Carrier screening for spinal muscular atrophy. Professional Practice and Guidelines Committee. Genet Med 2008;10:840–2. [PubMed] [Full Text] ⇐

4. Prior TW, Snyder PJ, Rink BD, Pearl DK, Pyatt RE, Mihal DC, et al. Newborn and carrier screening for spinal muscular atrophy. Am J Med Genet A 2010;152A:1608–16. [PubMed] ⇐

5. Mailman MD, Heinz JW, Papp AC, Snyder PJ, Sedra MS, Wirth B, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by *SMN2*. Genet Med 2002;4:20–6. [PubMed] [Full Text] ⇐

6. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel [published errata appear in Genet Med 2005;7:286; Genet Med 2004;6:548]. Genet Med 2004;6:387–91. [PubMed] [Full Text] ⇐

7. Cystic Fibrosis Foundation. 2015 patient registry annual data report. Bethesda (MD): CFF; 2016. Available at: https://www.cff.org/Our-Research/CF-Patient-Registry/2015-Patient-Registry-Annual-Data-Report.pdf. Retrieved February 6, 2017. ⇐

8. American College of Medical Genetics and Genomics. Technical standards and guidelines for *CFTR* mutation testing. American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. Bethesda (MD): ACMG; 2011. Available at: http://www.acmg.net/docs/CFTR_Mutation_Testing_2011.pdf. Retrieved September 12, 2016. ⇐

9. Cystic Fibrosis Centre, Hospital for Sick Children. Cystic fibrosis mutation database. Available at: http://www.genet.sickkids.on.ca/*CFTR*/app. Retrieved September 12, 2016. ⇐

10. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med 2004;6:387–91. [PubMed] [Full Text] ⇐

11. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med 2010;38:S512–21. [PubMed] [Full Text⇒] ⇐

12. Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C. Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research. Health Technol Assess 2000;4:i-v, 1–99. [PubMed] ⇐

13. Duffy TP. Hematologic aspects of pregnancy. In: Burrow GN, Duffy TP, Copel JA, editors. Medical complications during pregnancy. Philadelphia (PA): Elsevier Saunders; 2004. p. 69–86. ⇐

14. Kazazian HH Jr. The thalassemia syndromes: molecular basis and prenatal diagnosis in 1990. Semin Hematol 1990;27:209–28. [PubMed] ⇐

15. Serjeant GR, Serjeant BE. Sickle cell disease. 3rd ed. New York (NY): Oxford University Press; 2001. ⇐

16. Hatton DD, Sideris J, Skinner M, Mankowski J, Bailey DB Jr, Roberts J, et al. Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP. Am J Med Genet A 2006;140A:1804–13. [PubMed] ⇐

17. Kronquist KE, Sherman SL, Spector EB. Clinical significance of tri-nucleotide repeats in Fragile X testing: a clarification of American College of Medical Genetics guidelines. Genet Med 2008;10:845–7. [PubMed] [Full Text] ⇐

18. Monaghan KG, Lyon E, Spector EB. ACMG Standards and Guidelines for fragile X testing: a revision to the disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics and Genomics. Genet Med 2013;15:575–86. [PubMed] [Full Text] ⇐

19. Pesso R, Berkenstadt M, Cuckle H, Gak E, Peleg L, Frydman M, et al. Screening for fragile X syndrome in women of reproductive age. Prenat Diagn 2000;20:611–4. [PubMed] ⇐

20. Cronister A, Teicher J, Rohlfs EM, Donnenfeld A, Hallam S. Prevalence and instability of fragile X alleles: implications for offering fragile X prenatal diagnosis. Obstet Gynecol 2008;111:596–601. [PubMed] [*Obstetrics & Gynecology*] ⇐

21. Willemsen R, Bontekoe CJ, Severijnen LA, Oostra BA. Timing of the absence of FMR1 expression in full mutation chorionic villi. Hum Genet 2002;110:601–5. [PubMed] ⇐

22. Dong J, Edelmann L, Bajwa AM, Kornreich R, Desnick RJ. Familial dysautonomia: detection of the IKBKAP IVS20(+6T --> C) and R696P mutations and frequencies among Ashkenazi Jews. Am J Med Genet 2002;110:253–7. [PubMed] ⇐

23. Fanconi Anemia Research Fund. Fanconi anemia: guidelines for diagnosis and management. 4th ed. Eugene (OR): FARF; 2014. Available at: http://fanconi.org/images/uploads/other/FA_Guidelines_4th_Edition_Revised_Names_in_Appendix.pdf. Retrieved September 12, 2016. ⇐

24. Hoffman JD, Greger V, Strovel ET, Blitzer MG, Umbarger MA, Kennedy C, et al. Next-generation DNA sequencing of HEXA: a step in the right direction for carrier screening.

Mol Genet Genomic Med 2013;1:260–8. [PubMed] [Full Text] ⇐

25. van Bael M, Natowicz MR, Tomczak J, Grebner EE, Prence EM. Heterozygosity for Tay–Sachs disease in non-Jewish Americans with ancestry from Ireland or Great Britain. J Med Genet 1996;33:829–32. [PubMed] [Full Text] ⇐

26. Schneider A, Nakagawa S, Keep R, Dorsainville D, Charrow J, Aleck K, et al. Population-based Tay–Sachs screening among Ashkenazi Jewish young adults in the 21st century: Hexosaminidase A enzyme assay is essential for accurate testing. Am J Med Genet A 2009;149A:2444–7 ⇐