ACOG COMMITTEE OPINION

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Preconception and Prenatal Carrier Screening for Genetic Diseases in Individuals of Eastern European Jewish Descent

Committee on Genetics

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.

ABSTRACT: Certain autosomal recessive disease conditions are more prevalent in individuals of Eastern European Jewish (Ashkenazi) descent. Previously, the American College of Obstetricians and Gynecologists recommended that individuals of Eastern European Jewish ancestry be offered carrier screening for Tay–Sachs disease, Canavan disease, and cystic fibrosis as part of routine obstetric care. Based on the criteria used to justify offering carrier screening for Tay–Sachs disease, Canavan disease, and cystic fibrosis, the American College of Obstetricians and Gynecologists' Committee on Genetics recommends that couples of Ashkenazi Jewish ancestry also should be offered carrier screening for familial dysautonomia. Individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening for other disorders. Carrier screening is available for mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease.

Carrier screening for specific genetic conditions often is determined by an individual's ancestry. Certain autosomal recessive disease conditions are more prevalent in individuals of Eastern European Jewish (Ashkenazi) descent. Most individuals of Jewish ancestry in North America are descended from Ashkenazi Jewish communities and, thus, are at increased risk for having offspring with one of these conditions. Many of these disorders are lethal in childhood or are associated with significant morbidity.

Screening options continue to evolve. The American College of Medical Genetics has recently recommended additional carrier screening for the Ashkenazi Jewish population. The basis for these recommendations seems to be the high detection rate (Table 1). The Committee on Genetics reaffirms support for screening for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia.

Tay–Sachs disease (TSD) was one of the first disorders available for carrier screening. As a result of carrier screening programs established in the 1970s, the incidence of TSD in the North American Ashkenazi Jewish population has decreased by more than 90%. Carrier screening also is recommended for individuals of French Canadian and Cajun descent. Initially, carrier screening was based on the measurement of hexosaminidase A levels (the enzyme deficient in TSD) in serum or leukocytes. As the genes for TSD and other diseases more prevalent in Ashkenazi Jews were identified, DNA carrier tests were developed. Because each of these disorders is caused by a small number of common mutations, the carrier tests are very sensitive (94–99% detection rates). Previously, the American College of Obstetricians and Gynecologists recommended that individuals of Eastern European Jewish ancestry be offered carrier screening for TSD, Canavan disease, and cystic fibrosis as part of routine obstetric care. Because of recent advances in genetics, additional carrier tests are now available (Table 1).

In 2001, the gene for familial dysautonomia was identified. At least 2 mutations in the

The American College of Obstetricians and Gynecologists

Women's Health Care Physicians

Table 1. Recessive Genetic Diseases Frequent Among Individuals of Eastern European Jewish Descent Amenable to Carrier Screening

Disorder	Disease Incidence	Carrier Frequency*	Detection Rate*
Tay–Sachs disease	1/3,000	1/30	98% by hexosaminidase A test, 94% by DNA-based test
Canavan disease	1/6,400	1/40	98%
Cystic fibrosis	1/2,500–3,000	1/29	97%
Familial dysautonomia	1/3,600	1/32	99%
Fanconi anemia group C	1/32,000	1/89	99%
Niemann-Pick disease type A	1/32,000	1/90	95%
Mucolipidosis IV	1/62,500	1/127	95%
Bloom syndrome	1/40,000	1/100	95–97%
Gaucher disease	1/900	1/15	95%

*Non-Jewish carrier frequency and detection rates are unknown except for Tay–Sachs disease and cystic fibrosis. Carrier frequency for Tay–Sachs disease is 1 in 30 if French Canadian or Cajun ancestry and 1 in 300 for others with a 98% carrier detection rate by hexosaminidase A test.

Modified from March of Dimes. Genetic screening pocket facts. White Plains (NY): MOD; 2001.

familial dysautonomia gene, *IKBKAP*, have been identified in patients with familial dysautonomia of Ashkenazi Jewish descent. 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 TSD and cystic fibrosis. 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, which can improve the length and quality of life, but there currently is no cure. Based on the criteria used to justify offering carrier screening for TSD, Canavan disease, and cystic fibrosis, the ACOG Committee on Genetics recommends that couples of Ashkenazi Jewish ancestry also should be offered carrier screening for familial dysautonomia.

Carrier screening tests are available for several diseases that are less common (carrier rates 1 in 89 to 1 in 127), including Fanconi anemia group C, Niemann-Pick disease type A, Bloom syndrome, and mucolipidosis IV. These conditions are associated with significant neurologic or medical problems and very limited treatment options (see Box 1). Carrier screening also is available for Gaucher disease, the most common disorder in Eastern European Jews. Although Gaucher disease affects 1 in 900 individuals, the age of onset (from a few months to 90 years) and severity are variable (see Box 1). Gaucher disease can be very mild, and treatment is available.

All of these tests have a high sensitivity in the Jewish population. The prevalence of these disorders in non-Jewish populations, except for TSD and cystic fibrosis, is unknown. The sensitivity of these carrier tests in non-Jewish populations has not been established. The mutations may be different and more diverse. Consequently, when only one partner is Jewish, it is difficult to assess the risk of having an affected offspring. Therefore, carrier screening of the non-Jewish partner is of limited value.

Based on these developments, the ACOG Committee on Genetics makes the following seven recommendations:

1. The family history of individuals considering pregnancy, or who are already pregnant, should determine whether either member of the couple is of Eastern European (Ashkenazi) Jewish ancestry or has a relative with one or more of the genetic conditions listed in Table 1.
2. Carrier screening for TSD, Canavan disease, cystic fibrosis, and familial dysautonomia should be offered to Ashkenazi Jewish individuals before conception or during early pregnancy so that a couple has an opportunity to consider prenatal diagnostic testing options. If the woman is already pregnant, it may be necessary to screen both partners simultaneously so that the results are obtained in a timely fashion to ensure that prenatal diagnostic testing is an option.
3. Individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening for other disorders. Carrier screening is available for mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease. Patient education materials can be made available so that interested patients can make an informed decision about having additional screening tests . Some patients may benefit from genetic counseling.
4. When only one partner is of Ashkenazi Jewish descent, that individual should be screened 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 fre-

quency and the detection rate in non-Jewish individuals is unknown for all of these disorders, except for TSD and cystic fibrosis. Therefore, it is difficult to accurately predict the couple's risk of having a child with the disorder.

5. Individuals with a positive family history of one of these disorders should be offered carrier screening for the specific disorder and may benefit from genetic counseling.
6. When both partners are carriers of one of these disorders, they should be referred for genetic counseling and offered prenatal diagnosis. Carrier couples should be informed of the disease manifestations, range of severity, and available treatment options. Prenatal diagnosis by DNA-based testing can be performed on cells obtained by chorionic villus sampling and amniocentesis.
7. When an individual is found to be a carrier, his or her relatives are at risk for 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 provider does not need to contact these relatives because there is no provider–patient relationship with the relatives, and confidentiality must be maintained.

Carrier screening is voluntary. Informed consent and assurance of confidentiality are required. For all of these disorders, a negative screening test result for one or both partners significantly reduces the possibility of an affected offspring. However, it does not exclude the possibility because the test sensitivity is less than 100% so not all carriers can be identified.

The number and choice of genetic tests available to patients is likely to increase as a result of the Human

Box 1. Clinical Features of Autosomal Recessive Genetic Diseases Frequent Among Individuals of Eastern European Jewish Descent

Bloom syndrome is a genetic condition associated with increased chromosome breakage, a predisposition to infections and malignancies, prenatal and postnatal growth deficiency, skin findings (such as facial telangiectasias or abnormal pigmentation), and in some cases learning difficulties and mental retardation. The mean age of death is 27 years and usually is related to cancer. No effective treatment currently is available.

Canavan disease is a disorder of the central nervous system characterized by developmental delay, hypotonia, large head, seizures, blindness, and gastrointestinal reflux. Most children die within the first several years of life. Canavan disease is caused by a deficiency of the aspartoacylase enzyme. No treatment currently is available.

Familial dysautonomia is a neurologic disorder characterized by abnormal suck and feeding difficulties, episodic vomiting, abnormal sweating, pain and temperature insensitivity, labile blood pressure levels, absent tearing, and scoliosis. There currently is no cure for familial dysautonomia, but some treatments are available that can improve the length and quality of a patient's life.

Fanconi anemia group C usually presents with severe anemia that progresses to pancytopenia, developmental delay, and failure to thrive. Congenital anomalies are not uncommon, including limb, cardiac, and genital–urinary defects. Microcephaly and mental retardation may be present. Children are at increased risk for leukemia. Some children have been successfully treated with bone marrow transplantation. Life expectancy is 8–12 years.

Gaucher disease is a genetic disorder that mainly affects the spleen, liver, and bones; it occasionally affects the lungs, kidneys, and brain. It may develop at any age. Some individuals are chronically ill, some are moderately affected, and others are so mildly affected that they may not know that they have Gaucher disease. The most common symptom is chronic fatigue caused by anemia. Patients may experience easy bruising, nosebleeds, bleeding gums, and prolonged and heavy bleeding with their menses and after childbirth. Other symptoms include an enlarged liver and spleen, osteoporosis, and bone and joint pain. Gaucher disease is caused by the deficiency of the β-glucosidase enzyme. Treatment is available through enzyme therapy, which results in a vastly improved quality of life.

Mucolipidosis IV is a neurodegenerative lysosomal storage disorder characterized by growth and psychomotor retardation, corneal clouding, progressive retinal degeneration, and strabismus. Most affected infants never speak, walk, or develop beyond the level of a 1–2 year old. Life expectancy may be normal, and there currently is no effective treatment.

Niemann-Pick disease type A is a lysosomal storage disorder typically diagnosed in infancy and marked by a rapid neurodegenerative course similar to Tay–Sachs disease. Affected children die by age 3–5 years. Niemann-Pick disease type A is caused by a deficiency of the sphingomyelinase enzyme. There currently is no treatment.

Tay–Sachs disease (TSD) is a severe, progressive disorder of the central nervous system leading to death within the first few years of life. Infants with TSD appear normal at birth but by age 5–6 months develop poor muscle tone, delayed development, loss of developmental milestones, and mental retardation. Children with TSD lose their eyesight at age 12–18 months. This condition usually is fatal by age 6 years. Tay–Sachs disease is caused by a deficiency of the hexosaminidase A enzyme. No effective treatment currently is available.

Genome Project and advances in technology. For some patients, it can be difficult to decide whether to have a specific test. There are many factors patients may consider, including the prevalence of the disease, the carrier risk, the disease severity and treatment options, cost, and reproductive choices. Counseling by a genetic counselor, geneticist, or physician with expertise in these diseases may assist patients in making an informed decision about carrier testing.

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