

Ashkenazi Jewish Carrier Testing

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Key Points

- Carrier screening to determine reproductive risks for certain genetics diseases is offered to pregnant couples and/or those planning a pregnancy based on ethnic background.
- Individuals of Eastern European (Ashkenazi) Jewish background are at increased risk to be carriers for certain recessive genetic diseases for which carrier testing is available.
- There are few established standard practice guidelines for Ashkenazi Jewish carrier screening and providers are responsible for determining which tests to offer their patients.

Learning Objectives

Participants will be able to:

- Identify the genetic diseases for which carrier screening is commercially available to individuals of Ashkenazi Jewish descent;
- Discuss the current status, benefits and limitations of Ashkenazi Jewish carrier screening.

Family History Issues

The diseases that are included in testing the Ashkenazi Jewish population are inherited in an autosomal recessive manner. In autosomal recessive inheritance a pregnancy is at risk only if both parents are carriers. Siblings of affected individuals have a 25% chance of being affected.

Red Flags



If one or both members of a couple who are planning a pregnancy are of Ashkenazi Jewish background, carrier testing should be discussed.

Case 38. Carrier Testing for Individuals with Ashkenazi Jewish Background

One of your patients, Mrs. K, a thirty-one year old woman, has scheduled a pre-pregnancy consultation to discuss reproductive health issues. Her main concern is the risk of genetic diseases in her future offspring. She just attended a symposium on Ashkenazi (Eastern European) Jewish genetic diseases at her synagogue. She already knew about carrier testing for Tay-Sachs disease, but she learned at the symposium that several other genetic diseases are more common in Ashkenazi Jewish individuals. Because she and her husband both have Ashkenazi Jewish background, she is requesting testing for as many diseases as possible.

Clinical Care Issues

History of carrier screening in the Ashkenazi Jewish population

Screening for genetic diseases to identify reproductive risks in members of the Ashkenazi Jewish population began after the underlying cause of Tay-Sachs disease was identified in 1969. Tay-Sachs disease is an autosomal recessive neurodegenerative condition which results in the loss of motor skills in infancy, with progressive deterioration, including seizures, blindness, and eventual total incapacitation and death, usually by age four years. Approximately one out of 30 Ashkenazi Jewish individuals is a carrier for this condition. An effort was made to identify couples in which both members are carriers and are thus at 25% risk to have an affected child. These couples can be offered prenatal testing for Tay-Sachs disease. Large-scale population screening programs were developed, identifying couples at risk. These programs have resulted in a greater than 90% reduction in Tay-Sachs births among screened populations. Tay-Sachs screening is viewed as a prototypic program of public education, carrier testing, and reproductive counseling for avoiding an inherited fatal childhood disease.

Carrier testing later became available for other diseases that are also prevalent in the Ashkenazi Jewish population, notably Canavan disease and Gaucher disease. The prevalence of Canavan disease carriers among Ashkenazi Jews (1/40-1/57) is somewhat lower than Tay-Sachs, but Canavan disease is clinically similar to Tay-Sachs in that it is also a progressive and fatal neurological disease. Gaucher disease has a higher carrier frequency (1/10-1/15) but its clinical course is highly variable, which

complicates its inclusion in the Ashkenazi Jewish carrier testing panel (see [Ethical/Legal/Social/Cultural Issues](#)).

In the late 1990s, the capability to test for more genetic diseases led some laboratories to develop expanded Ashkenazi Jewish test panels for up to nine diseases. Some of these diseases are exceedingly rare. Laboratories may offer a discounted price for carrier testing for several diseases (a panel), so an individual may decide to proceed with testing for the entire panel even if he or she only sought testing for one of the diseases in the panel.

Risk Assessment

Risk of Ashkenazi Jewish genetic diseases

Among the Jewish population in North America, approximately 90% is Ashkenazi Jewish. In general, if a Jewish individual or couple is unsure of their family's origin, but they know their ancestors lived in Eastern Europe, it is prudent to consider them to be of Ashkenazi descent. Carrier testing is now available for several conditions that affect individuals of Ashkenazi Jewish background (see [Table 1](#)). As with any decision to undergo genetic testing, pre-test counseling should be provided as soon as possible. For tests related to reproductive decision making, counseling and testing ideally are provided prior to conception. In pre-test counseling, discussion about the risks, benefits, and limitations of carrier testing should be undertaken and descriptions of the clinical manifestations of the disease provided. Because these conditions are autosomal recessive, both parents must be carriers of the disease for pregnancies to be at risk.

Table 1. Diseases Included in Ashkenazi Jewish Carrier Testing Panels ¹

Disease	Incidence	Carrier Frequency in Individuals of Ashkenazi Jewish Background	Detection Rate ²	Disease Description

Gaucher disease	1/900	1/15	95%	Enlargement of the spleen and liver; anemia, easy bruising, and impaired clotting; bone and joint pain and an increased susceptibility to bone fracture. The age of onset is variable, some have onset in childhood and others remain relatively symptom-free into their 50s or 60s. The severity of symptoms varies among patients. Enzyme replacement therapy is effective in reversing some symptoms and reducing the severity of others.
Cystic fibrosis	1/2,500-3,000	1/26-29	98% ³	Thick mucus accumulation in the lungs, leading to breathing difficulty and infection. Pancreatic insufficiency, male infertility. Supportive treatments improve quality of life, median lifespan about 30 years.

Tay-Sachs disease	1/3,000	1/30	94-98% ⁴	CNS degeneration. Onset at 6 months with regression of developmental milestones, and eventual paralysis, blindness, seizures. No treatment; average life expectancy is 3-5 years.
Familial dysautonomia	1/3,700	1/32	99%	Disease of the autonomic nervous system affecting swallowing, sweating, control of blood pressure, and ability to cry tears and to sense pain. Severe GI problems, frequent pneumonia, ataxic gait. Life expectancy is decreased.
Canavan disease	1/6,400	1/40-1/57	98%	Progressive CNS disease beginning in infancy, with weakness, seizures, regression of developmental milestones, and severe mental retardation. Fatal in childhood; no treatment.
Niemann-Pick (Type A)	1/32,000	1/89	95%	Neurodegenerative condition, onset at 6 months, loss of brain function and enlargement of the liver and spleen. No treatment; average life expectancy is 2-3 years of age.

Fanconi anemia (type C)	1/32,000	1/90	95%	Bone marrow failure, predisposition to leukemia, short stature, congenital malformations. Learning disabilities are variable.
Bloom syndrome	1/40,000	1/100	95-98%	Poor growth, frequent infections, and possible learning disabilities. Predisposition to develop cancer such as breast cancer, colon cancer, and leukemia.
Mucopolysaccharidosis type IV	1/62,000	1/125	96%	Severe neurodegenerative condition, growth and psychomotor retardation. Abnormalities of the cornea and retina. Remain at the developmental level of 1 to 2 years of age.

1. Ordered by incidence; numbers may not be exact; for clinical comparison only.
2. Detection rate for mutation analysis of the most common mutations in the Ashkenazi Jewish population only. In non-Ashkenazi individuals, alternative methods of carrier testing should be used.
3. Mutation analysis for the detection of cystic fibrosis carriers is variable among different ethnic populations, but is generally much less than the Ashkenazi Jewish detection rate (see [GeneReview: CFTR-Related Disorders, Table 1](#))
4. Detection of Tay-Sachs carriers by HEX A enzymatic activity in serum or leukocytes identifies approximately 98% of carriers in both Ashkenazi Jewish and non-Ashkenazi Jewish individuals.

Genetic Counseling and Testing

Should this patient be offered genetic testing?

Since the couple has Ashkenazi Jewish background, it is appropriate to offer them carrier testing for genetic diseases that are more common in the Ashkenazi Jewish population. Many laboratories offer a panel of tests that include testing for some or all of the diseases in the Table. Some couples choose to have screening for only Tay-Sachs disease while others choose to have testing for additional diseases. Because many of the diseases are extremely rare, some couples may not wish to pursue testing for all of them. Some experts argue against the inclusion of tests for very rare conditions, because the identification of two-carrier couples is very rare, and may not justify the cost of testing, while generating unnecessary anxiety. In addition, testing for Gaucher disease (GD) has been questioned because it typically has a late onset, clinical severity is variable, and treatment is available (see [Ethical/Legal/Social/Cultural Issues](#)). Additionally, insurance companies may or may not cover the cost of testing for all of the diseases on the panel.

Few practice standards or recommendations exist for screening in the Ashkenazi Jewish population. Although CF and Tay-Sachs carrier testing is generally offered and carrier testing for Canavan disease and familial dysautonomia has been recommended (American College of Medical Genetics, American College of Obstetricians and Gynecologists), practice standards vary between different medical centers and health care providers regarding the other diseases. In geographic areas with a high percentage of Ashkenazi Jewish individuals, carrier testing for all diseases may be routinely offered, while in areas with fewer Ashkenazi Jewish individuals, only Tay-Sachs carrier testing may be routinely offered.

Many centers design their clinical practice based on the demand for commercially available testing. Genetic counseling prior to screening is designed to discuss the carrier frequencies and detection rate, as well as the natural history of each condition. In that way, the patient, rather than the practitioner, can choose the conditions for which they wish to have carrier testing.

Another important aspect of genetic counseling is to inform the patient/couple that the carrier detection rate varies among the conditions and that ALL tests are less than 100% accurate. That is, while a negative carrier test result for these conditions may greatly reduce the risk to have offspring affected with one of these conditions, the risk cannot be eliminated entirely.

What is the optimal testing strategy?

Since Mrs. K is not yet pregnant, a possible testing strategy would be to

offer carrier testing to Mrs. K prior to testing Mr. K. Given the high carrier detection rate for all of these conditions in the Ashkenazi Jewish population, we can assume that if a mutation is not identified in Mrs. K, her risk to be a carrier is significantly decreased. However, because none of the tests in the panel have 100% detection rate, screening both parents together increases the specificity of the carrier screening, particularly if both screen negative.

If a couple is already pregnant, both partners may wish to be tested simultaneously so that results will be available in a more timely fashion, because results typically take up to three weeks.

If one member of the couple is Ashkenazi Jewish and the other is not, it is prudent to screen the Ashkenazi Jewish member first. This approach takes into account the decreased sensitivity and specificity of most of these tests in the non-Ashkenazi Jewish population.

Patients of Moroccan Sephardic Jewish descent or French Canadian descent are also candidates for Tay-Sachs carrier screening. The Tay-Sachs carrier frequency has been reported as 1/60 and 1/30 respectively in these groups [[Bonne-Tamir & Adam 1992](#)]. These individuals should be screening with HEX A testing (that is, testing for level of activity of the HEX A enzyme, which is reduced in carriers and virtually absent in affected individuals), because they are unlikely to have one of the common Ashkenazi Jewish mutations and DNA testing is unlikely to identify carriers.

Interventions

If both Mrs. K and her husband are identified as carriers of one of these conditions, options for their reproductive decision making should be provided. Some couples choose to adopt a child or to achieve a pregnancy with a sperm or egg donor. Other couples who wish to have their own biological children or who are already pregnant can consider prenatal diagnostic options such as chorionic villus sampling (CVS) or amniocentesis to determine if a fetus is affected. CVS is usually performed at about 10-12 weeks' pregnancy and amniocentesis is usually performed after 15 weeks' pregnancy. Another option for couples who wish to plan a pregnancy is preimplantation genetic diagnosis (PGD). This procedure, which is available in a limited number of centers, requires in vitro fertilization, genetic diagnosis of the embryo, and implantation of embryos unaffected by the disorder in question. Because such testing is very expensive, it may not be a realistic option for many families.

Ethical/Legal/Social/Cultural Issues

Screening for Gaucher disease. Carrier testing for Gaucher disease is controversial because most Ashkenazi Jews with this condition develop only mild symptoms and many do not have symptoms of the disease until adulthood, if at all. Intelligence is not affected by Gaucher disease. Additionally, treatment of Gaucher disease by enzyme replacement therapy (ERT) has become effective in recent years. Thus, Gaucher disease is a very different disorder from Tay-Sachs disease, which is uniformly fatal in early childhood. Of note, the early lethality of Tay-Sachs disease was the reason for initiating carrier testing in the Ashkenazi Jewish population. Yet Gaucher disease is the most common of the genetic diseases among the Ashkenazi Jewish population, with a carrier frequency of about 1/15. Therefore, if Gaucher disease is included in the screening panel, couples are more likely to find they are both carriers of Gaucher disease than any of the other diseases. To some extent, it is possible to predict the severity of Gaucher disease by which mutations are involved, but the extreme variability of the condition and the potential success of enzyme replacement treatment make it possible that individuals with Gaucher disease will have a relatively mild course of the disease. Couples who are found to be carriers for Gaucher disease may not wish to base reproductive decisions on this information. Some individuals who undergo carrier testing may learn that they have two mutations for Gaucher disease, indicating they are actually affected with the condition, despite the lack of symptoms. This finding speaks to the relatively mild clinical course that can be associated with Gaucher disease, but these individuals face the possibility of becoming symptomatic in the future. Many centers include a caveat regarding the potential diagnosis of Gaucher disease in their informed consent for Ashkenazi Jewish carrier screening. These issues underscore the need for pre-test counseling prior to undergoing genetic testing.

Some diseases are typically not included in testing panels. While most of the diseases discussed above can have very severe health manifestations and arguments can be made for including them in Ashkenazi Jewish panels, some experts are concerned that Ashkenazi Jewish panels may expand to include testing for additional diseases without serious consideration for the ethical implications of adding each disease. For example, carrier screening for a form of autosomal recessive, nonsyndromic deafness (**DFNB1**) is now available by testing for mutations in the *GJB2* gene, which encodes the connexin 26 protein. Ashkenazi Jewish individuals have a 4% risk of being carriers for a mutation in this gene. Prospective parents who learn that they carry a *GJB2* mutation will be faced with making reproductive decisions based on a 25% chance of isolated deafness in an otherwise healthy child. If

such testing is included among many diseases in an Ashkenazi Jewish carrier screening panel, parents undergoing testing may not have had the opportunity to consider whether they wanted such information before undergoing testing and receiving their results.

A completely different type of genetic test in the Ashkenazi Jewish population is testing for specific mutations in *BRCA1* and *BRCA2*, two genes associated with hereditary breast and ovarian cancer. Ashkenazi Jewish individuals have a 2-2.5% chance of having a mutation in one of these two genes, which would increase a woman's lifetime risk of breast cancer to 35-85% and ovarian cancer risk to 10-40%. A mutation in either gene also increases a man's risk for breast, prostate, and other cancers. Because testing has significant implications for an individual's current and future health and could lead to serious issues such as insurance discrimination, it is generally accepted that such testing should be done separately from an Ashkenazi Jewish panel aimed at determining reproductive risks.

Use of health care resources for carrier testing. Although agreement exists about carrier testing for Tay-Sachs disease, some experts argue that carrier testing for other extremely rare diseases may waste valuable health care resources. To date, the cost implications of carrier testing in the Ashkenazi Jewish population have not been fully investigated. In recommending the offer of four carrier tests to Ashkenazi Jewish women (for Tay-Sachs, cystic fibrosis, Canavan disease, and familial dysautonomia), the American College of Obstetrics and Gynecology utilized criteria related to disease severity and prevalence; ACOG Committee on Genetics noted that other carrier tests might be made available to interested individuals [[ACOG 2004](#)].

Resources

- **Mount Sinai School of Medicine Center for Jewish Genetic Diseases**
Box 1497
One Gustave L Levy Place
New York, NY 10029
Phone: 212-659-6774
- **Chicago Center for Jewish Genetic Disorders**

Ben Gurion Way
One South Franklin Street, Fourth Floor
Chicago, IL 60606
Phone: 312-357-4718
Fax: 312-855-3295
Email: jewishgeneticsctr@juf.org

For information about support groups related to genetic disease:

- **Genetic Alliance**
4301 Connecticut Avenue, NW, #404
Washington, DC 20008
Phone: 202-966-5557; 800-336-GENE

For information about other rare genetic conditions:

- **National Organization for Rare Disorders, Inc (NORD)**
PO Box 8923
New Fairfield, CT 06812
Phone: 203-746-6518; 800-999-6673

Foundations that focus on specific diseases:

- **Bloom's Syndrome Registry**
James L. German III, MD
Professor, Departments of Pediatrics and Microbiology
Cornell University Medical College
1300 York Avenue
New York, NY 10021
Phone: 212-746-3956
- **The Canavan Foundation**
600 West 111th Street
New York, NY 10025
Phone: 212-316-6488
- **Cystic Fibrosis Foundation**
6931 Arlington Road, 2nd Floor
Bethesda, MD 20814-5200
Phone: 800-FIGHTCF (800-344-4823); 301-951-4422
Fax: 301-951-6378
Email: info@cff.org

- **Dysautonomia Foundation, Inc**
633 Third Ave, 12th Floor
New York, NY 10017-6706
Phone: 212-949-6644
Fax: 212-682-7625
Email: info@familialdysautonomia.org
- **Fanconi Anemia Research Fund, Inc**
1902 Jefferson Street, Suite 2
Eugene, OR 97405
Phone: 541-687-4658
- **Mucopolysaccharidosis IV Foundation**
Randy Yudenfriend Glaser, President
719 East 17th Street
Brooklyn, NY 11230
Phone: 718-434-5067
- **National Gaucher Foundation**
11140 Rockville Pike, Suite 350
Rockville, MD 20852
Phone: 301-816-1515; 800-925-8885
- **National Niemann-Pick Disease Foundation**
Barb Vorpahl, Director of Support Services
3734 East Olive Avenue
Gilbert, AZ 85234
Phone: 920-563-8677; 877-287-3672
- **National Tay-Sachs and Allied Diseases Association, Inc**
2001 Beacon Street, Suite 204
Brighton, MA 02135
Phone: 800-906-8723; 617-277-4463
Fax: 617-277-0134
Email: info@ntsad.org
- **National Library of Medicine Genetics Home Reference**
[Bloom syndrome](#)
[Canavan disease](#)
[Cystic fibrosis](#)

Familial dysautonomia
Gaucher disease
Niemann-Pick disease
Tay-Sachs disease

- **GeneTests Online Medical Genetics Information Resource**
- **GeneReviews, GeneTests Online Medical Genetics Information Resource**

References

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