Test Definition: AJPO

Ashkenazi Jewish Panel Without CF

Overview

Useful For

Carrier screening in individuals of Ashkenazi Jewish ancestry for Bloom syndrome, Canavan disease, *FANCC*-related Fanconi anemia, familial dysautonomia, Gaucher disease, mucolipidosis IV, Niemann-Pick disease types A and B, and Tay-Sachs disease

Genetics Test Information

Panel includes the following disorders Bloom syndrome, Canavan disease, *FANCC*-related Fanconi anemia, familial dysautonomia, Gaucher disease, mucolipidosis IV, Niemann-Pick disease types A and B, and Tay-Sachs disease. Specific detection rates for the Ashkenazi Jewish population are provided.

Additional Tests

Test ID	Reporting Name	Available Separately	Always Performed
NAGAJ	Hexosaminidase A and Tot, WBC/AJ	No, (Bill Only)	Yes

Testing Algorithm

When this test is ordered, hexosaminidase A and total, white blood cells will always be performed at an additional charge.

See Tay-Sachs Disease Carrier Testing Protocol in Special Instructions

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Tay-Sachs Disease Carrier Testing Protocol
- Informed Consent for Genetic Testing (Spanish)

Method Name

AJPO: Polymerase chain reaction (PCR) analysis is used to test for mutations associated with 8 disorders prevalent in the Ashkenazi Jewish population.

NAGAJ: Heat Inactivation, Fluorometric, Semiautomated

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within72 hours of draw.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:

Preferred: Yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 2 full tubes

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tubes.

Additional Information:A patient education brochure (T561) is available upon request.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Biochemical Disorders Patient Information(T527) in Special Instructions

Specimen Minimum Volume

6 mL

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical and Interpretive

Clinical Information

Certain genetic diseases are more common in individuals of Ashkenazi Jewish heritage (Jewish individuals of Eastern European ancestry) compared to the non-Jewish population. The majority of these conditions are inherited in an autosomal recessive manner. This group of diseases includes Gaucher, Tay-Sachs, familial dysautonomia, Canavan, mucolipidosis IV, Niemann-Pick Type A and B, *FANCC*-related Fanconi anemia, and Bloom syndrome. While these conditions are observed outside of the Ashkenazi Jewish population, they occur at a lower frequency. It is estimated that an individual of Ashkenazi Jewish ancestry has a 20% to 25% chance of being a carrier of 1 of these diseases.

Gaucher Disease:

Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of acid beta-glucocerebrosidase. Mutations in the beta-glucocerebrosidase gene, *GBA*, cause the clinical manifestations of Gaucher disease. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). Type 1 accounts for over 95% of all cases of Gaucher disease and is the presentation commonly found among Ashkenazi Jewish patients. Type 1 disease does not involve nervous system dysfunction; patients display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. There is a broad spectrum of disease in type 1, with some patients exhibiting severe symptoms and others very mild disease. Types 2 and 3 are associated with neurological disease of variable onset and progression, though type 2 tends to be more severe. Eight common *GBA* mutations, including the N370S mutation most commonly found in the Ashkenazi Jewish population, are included in this test: delta55bp, V394L, N370S, IVS2+1G>A, 84G>GG, R496H, L444P, and D409H.

Tay-Sachs:

Tay-Sachs disease is caused by an absence of hexosaminidase (HexA) enzyme activity, which results in the accumulation of the sphingolipid GM2 ganglioside. Mutations in the *HEXA* gene cause the clinical manifestations of Tay-Sachs disease (TSD). The most common form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations of this condition include progressive neurodegeneration, seizures, and blindness, leading to total incapacitation and death. This panel tests for the 3 common mutations in the Ashkenazi Jewish population: 1278insTATC, G269S, and IVS12+1G>C. Also included in this assay are the mutations IVS9+1G>A and delta7.6kb mutations along with the R247W and R249W polymorphisms associated with pseudodeficiency.

Familial Dysautonomia:

Familial dysautonomia affects sensory, parasympathetic, and sympathetic neurons. Patients experience gastrointestinal dysfunction, pneumonia, vomiting episodes, altered sensitivity to pain and temperature, and cardiovascular problems. Progressive neuronal degeneration continues throughout the lifespan. Mutations in the *IKBKAP* gene cause the clinical manifestations of familial dysautonomia. Two mutations in the *IKBKAP* gene are common in the Ashkenazi Jewish population: IVS20(+6)T>C and R696P.

Canavan Disease:

Canavan disease is a severe leukodystrophy resulting from a deficiency of the enzyme aspartoacylase. Mutations in the *ASPA* gene cause the clinical manifestations of Canavan disease. The deficiency of aspartoacylase leads to spongy degeneration of the brain, and the disease is characterized by delayed development beginning at age 3 to 6 months, head lag, macrocephaly, and hypotonia. Death usually occurs in the first decade of life. Four *ASPA* mutations are included in this test: 433(-2)A>G, A305E, E285A, and Y231X.

Mucolipidosis IV:

Mucolipidosis IV is a lysosomal storage disease characterized by mental retardation, hypotonia, corneal clouding, and retinal degeneration. Mutations in the *MCOLN1* gene are responsible for the clinical manifestations of mucolipidosis IV. Two mutations in the *MCOLN1* gene account for the majority of mutations in the Ashkenazi Jewish population: IVS3(-2)A>G and delta6.4kb.

Niemann-Pick Disease Types A and B:

Niemann-Pick disease (types A and B) is a lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is milder, though variable in its clinical presentation. Most individuals with type B do not have neurologic involvement and survive to adulthood. Mutations in the *SMPD1* gene are known to cause Niemann-Pick disease types A and B. There are 3 common mutations causing Niemann-Pick type A in the Ashkenazi Jewish population: L302P, R496L, and fsP330. The deltaR608 mutation accounts for approximately 90% of the type B mutant alleles in individuals from the Maghreb region of North Africa and 100% of the mutation alleles in Gran Canaria Island.

Fanconi Anemia:

Fanconi anemia is an aplastic anemia that leads to bone marrow failure and myelodysplasia or acute myelogenous leukemia. Physical findings include short stature; upper limb, lower limb, and skeletal malformations; and abnormalities of the eyes and genitourinary tract. Mutations in several genes have been associated with Fanconi anemia, although 1 mutation, IVS4(+4)A>T, in the *FANCC* gene is common in the Ashkenazi Jewish population. A second mutation, 322delG, is over represented in *FANCC* patients of Northern European ancestry.

Bloom Syndrome:

Bloom syndrome is characterized by short stature, sun sensitivity, susceptibility to infections, and a predisposition to cancer. Mutations in the *BLM* gene lead to genetic instability (increased chromosomal breakage and sister chromatid exchange) and cause the clinical manifestations of Bloom syndrome. The protein encoded by the *BLM* gene is a helicase involved in maintaining DNA integrity. There is a common mutation in the Ashkenazi Jewish population: 2281delATCTGAinsTAGATTC (2281del6/ins7).

Because of the high sensitivity of carrier testing in the Ashkenazi Jewish population, the American College of Medical Genetics and Genomics (ACMG) recommends that carrier screening for cystic fibrosis (CF), Canavan, Tay-Sachs, familial dysautonomia, Niemann-Pick type A, Fanconi anemia (*FANCC*), Bloom syndrome, mucolipidosis IV, and Gaucher disease be offered to individuals of Ashkenazi Jewish ancestry. The mutation detection rates and carrier frequencies for the diseases included in this panel are listed below. Of note, testing for CF is not included in this panel. If testing for this disorder is desired, please see details and ordering information under CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel.

Disease	Carrier Rate in the AJ Population	Mutation Detection Rate
Gaucher	1/18	95%
Tay-Sachs	1/31	*99%
Familial dysautonomia	1/31	99%
Canavan	1/41	98%
Mucolipidosis IV	1/127	95%

Niemann-Pick type A/B	1/90	97%
FANCC-related Fanconi anemia	1/89	>99%
Bloom syndrome	1/107	>99%
*with biochemical testing		

The Ashkenazi Jewish panel is useful for identifying carriers of these 8 conditions in an at-risk population. Because the diseases included in the panel are inherited in an autosomal recessive manner, the presence of a family history is not a prerequisite for testing consideration. The identification of disease-causing mutations allows for carrier testing of at-risk family members and prenatal diagnosis for pregnancies in which both parents are known carriers. Refer to Carrier Testing for Tay-Sachs Disease and Other GM2 Gangliosidosis Variants: Supplementing Traditional Biochemical Testing with Molecular Methods, Mayo Medical Laboratories Communique 2004 Jul;29(7) for more information regarding diagnostic strategy.

Of note, approximately 1 in 25 individuals of Ashkenazi Jewish ancestry are also carriers of cystic fibrosis (CF). Therefore, the American College of Medical Genetics also recommends that carrier screening for CF be offered to individuals of Ashkenazi Jewish ancestry who are pregnant or considering pregnancy. Carrier screening for CF is available by ordering CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel.

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

Cautions

This assay will not detect all of the mutations that cause these 8 diseases. Therefore, the absence of a detectable mutation does not rule out the possibility that an individual is a carrier of or affected with 1 or more of the listed diseases.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In rare cases, DNA alterations of undetermined significance may be identified.

Clinical Reference

Gross SJ, Pletcher BA, Monaghan KG: Carrier screening individuals of Ashkenazi Jewish descent. Genet Med 2008:10(1):54-56

Performance

Method Description

A laboratory-developed multiplex PCR-based assay is used to detect the following mutations: 84G->GG, IVS2(+1)G->A, N370S, delta55bp, V394L, D409H, L444P, and R496H mutations in the *GBA* gene (Gaucher disease); delta7.6kb, R247W, R249W, G269S IVS9(+1)G->A, 1278insTATC, and IVS12(+1)G->C mutations in the

HEXA gene (Tay-Sachs disease); 433(-2)A->G, E285A, Y231X (C->A & C->T), and A305E mutations in the *ASPA* gene (Canavan disease); R696P and IVS20(+6)T->C mutations in the *IKBKAP* gene (familial dysautonomia); 2281del6/ins7 mutation in the *BLM* gene (Bloom syndrome); 322delG and IVS4(+4)A->T mutations in the *FANCC* gene (Fanconi anemia); L302P, fsP330, R496L, and deltaR608 mutations in the *SMPD1* gene (Niemann-Pick disease types A and B); and delta6.4kb and IVS3(-2)A->G mutations in the *MCOLN1* gene (mucolipidosis type IV).(Fulton R, McDade R, Smith P, et al: Advanced multiplexed analysis with the FlowMetrix system. Clin Chem 1997;43:1749-1756; Ye F, Li MS, Taylor JD, et al: Fluorescent microsphere-based readout technology for multiplexed human single nucleotide polymorphism analysis and bacterial identification. Hum Mutat 2001 Apr;17[4]:305-316)

PDF Report

No

Day(s) Performed

Tuesday

Report Available

9 to 12 days

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81200-*ASPA aspartoacylase* (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)

81209-*BLM (Bloom syndrome, Rec! helicase-like)* (eg, Bloom syndrome) gene analysis, 2281 del6ins7 variant

81242-*FANCC (Fanconi anemia, complementation group C)* (eg, Fanconi anemia, type C) gene analysis, common variant (eg IVS4+4A->T)

81251-*GBA (glucosidase, beta acid)* (eg. Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)

81255-*HEXA (hexosaminidase A (alpha polypeptide)* (eg. Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G->C, G269S)

81260-*IKBKAP (*inhibitor of kappa light polypeptide gene enhance in B-cells, kinase complex-associated protein) (eg.

Familial dysautonomia) gene analysis common variants (eg, 2507_6T->C, R696P

81290-*MCOLN1 (mucolipin 1)* (eg. Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A->G, del6.4kb)

81330-*SMPD1 (sphingomyelin phosphodiesterase 1, acid sysosomal)* (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)

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83080 Hexosaminidase A and Tot (additional test)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
AJPO	Ashkenazi Jewish Panel Without CF	In Process

Result ID	Test Result Name	Result LOINC Value
53130	Result Summary	50397-9
53131	Result	82939-0
53132	Interpretation	69047-9
52425	Additional Information	48767-8
53133	Specimen	31208-2
53134	Source	31208-2
53135	Released By	18771-6