Ashkenazi Jewish Carrier Screening

MOL.TS.129.A
v2.0.2025

Ashkenazi Jewish carrier screening is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Ashkenazi Jewish genetic disorders gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Ashkenazi Jewish genetic disorders sequencing	81412
ASPA targeted mutation analysis	81200
BCKDHB targeted mutation analysis	81205
BLM targeted mutation analysis	81209
CFTR targeted mutation analysis	81220
FANCC targeted mutation analysis	81242

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Procedures addressed by this guideline	Procedure codes
G6PC targeted mutation analysis	81250
GBA targeted mutation analysis	81251
HEXA targeted mutation analysis	81255
IKBKAP targeted mutation analysis	81260
MCOLN1 targeted mutation analysis	81290
SMPD1 targeted mutation analysis	81330

Criteria

Requests for Ashkenazi Jewish carrier screening are reviewed using the following criteria.

Single Ashkenazi Jewish Genetic Diseases Carrier Screening Tests

Carrier screening is medically necessary for a single Ashkenazi Jewish disease if any of the following are met:

- The individual is of Ashkenazi Jewish ancestry, OR
- The individual has a family history of the condition for which testing is being requested, OR
- The individual's partner is a known carrier or affected with the condition for which testing is being requested

Ashkenazi Jewish Genetic Diseases Carrier Screening Panels

Carrier screening is medically necessary for all or any desired subset of the Ashkenazi Jewish genetic diseases eligible for coverage per the Coverage Guidance table when the following criteria are met:

- The individual is planning a pregnancy or currently pregnant, AND
- At least one partner of a couple is Ashkenazi Jewish (NOTE: Detection rates for testing are higher in people with Ashkenazi Jewish ancestry. If only one partner of a couple is Ashkenazi Jewish, testing should start in that person when possible.)

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Other Considerations

For information on the diagnostic testing of symptomatic individuals for the genetic conditions included in this guideline, please refer to the *Genetic Testing to Diagnose Non-Cancer Conditions* guideline or EviCore test-specific guidelines, as this testing is not addressed here.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

When testing is otherwise reimbursable, the following limitations apply:

- If an Ashkenazi Jewish carrier screening panel was previously performed and an updated, larger panel is being requested, only testing of previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
- If testing will be billed using procedure code 81412 to represent all tests performed for the assessment of carrier status based on Ashkenazi Jewish ancestry, no additional tests for this purpose will be reimbursed for the same date of service.
- If testing will be billed for separate genes because the panel code is not more appropriate (e.g., fewer than the 9 stated genes will be assessed or a different methodology is used), reimbursement for individual gene tests will be assessed based on the guidance provided in the Criteria section above and in the Table: *Coverage Guidance for Genes Included in Ashkenazi Jewish Carrier Screening Tests*.
- Carrier screening panels are reimbursable once per lifetime.
  - If an Ashkenazi Jewish carrier screening panel was previously billed, an additional carrier screening panel will not be reimbursable.
  - If a non-Ashkenazi Jewish carrier screening panel was previously billed, subsequent carrier screening of any type will not be reimbursable (e.g. individual genes, Ashkenazi Jewish carrier screening panels).

Table: Coverage Guidance for Genes Included in Ashkenazi Jewish Carrier Screening Tests

Condition, Gene, CPT Code, Required Claim Code

Condition	Gene	CPT	Required Claim Code
Bloom syndrome	BLM	81209	NONE
Canavan disease	ASPA	81200	NONE
Cystic fibrosis	CFTR	81220	NONE
Dihydrolipoamide dehydrogenase deficiency	DLD	81406	DLD
Familial dysautonomia	ELP1	81260	NONE
Familial hyperinsulinism	ABCC8	81401	ABCC8
Fanconi anemia, type C	FANCC	81242	NONE
Gaucher disease, type 1	GBA	81251	NONE
Glycogen storage disease, type 1A	G6PC	81250	NONE
Joubert syndrome, type 2	TMEM216	81479	TMEM216
Maple syrup urine disease, type 1b	BCKDHB	81205	NONE
Mucolipidposis, type IV	MCOLN1	81290	NONE
Nemaline myopathy, type 2	NEB	81400	NEB

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Condition	Gene	CPT	Required Claim Code
Niemann-Pick disease, type A	SMPD1	81330	NONE
Tay-Sachs disease	HEXA	81255	NONE
Usher syndrome, type 1F	PCDH15	81400	PCDH15
Usher syndrome, type 3	CLRN1	81400	CLRN1

Note:

Other tests may be eligible for coverage under the above criteria if the condition is associated with significant morbidity and mortality, the allele frequency is >1% in the Ashkenazi Jewish population, and the selected test method has >90% detection rate for disease-causing mutations.

What is Ashkenazi Jewish carrier screening?

Ashkenazi Jewish carrier screening is available for certain genetic conditions that are either more common or for which there are higher mutation detection rates in the Ashkenazi Jewish population. "Ashkenazi" refers to someone whose Jewish ancestors originally came from Central or Eastern Europe, such as Russia, Poland, Germany, Hungary, Lithuania. Most Jewish people in the US are of Ashkenazi descent. There are regional differences in the number and types of tests commonly offered. Individuals and providers may choose all or a subset of these conditions.[1-3]

Inheritance

The genetic diseases that are more common in the Ashkenazi Jewish population are typically inherited in an autosomal recessive manner. An affected individual must inherit a gene mutation from both parents.[1,2]

- Individuals who inherit only one mutation are called carriers. Carriers usually do not show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children.
- Two carriers of the same disease have a 25% chance, with each pregnancy, of having a child with the disorder.

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Prevalence

While these genetic diseases are individually rare, the overall chance for an individual of Ashkenazi Jewish descent to be a carrier for one of these genetic diseases is 1 in 4 to 1 in 5.[3] An individual can also be a carrier of more than one condition.

People from other ethnic backgrounds can be carriers of these conditions, but it is generally less common. The test is typically not as effective at identifying carrier status in individuals of non-Ashkenazi Jewish descent.

Test information

Ashkenazi Jewish carrier screening can be offered to couples or individuals of Ashkenazi Jewish descent when they are planning a pregnancy (preconceptional) or during a pregnancy (prenatal).[1-3]

One member of couple is Jewish

If only one member of the couple is Ashkenazi Jewish, carrier screening should start with the Ashkenazi Jewish partner. In general, both parents must be carriers to have an affected child, so reproductive partners of known carriers should also be offered testing even if not Jewish. In some cases, full gene sequencing would be most appropriate for testing of a non-Jewish partner.

Purpose of test

Carrier screening generally looks for a small number of gene mutations that are particularly common in the Ashkenazi Jewish population, although an increasing number of full gene sequencing panels are becoming available.

In addition, enzyme analysis is a particularly effective screening test for Tay-Sachs disease and can be preferred to mutation testing.

Detection rate

The carrier detection rate is greater than 95% in the Ashkenazi Jewish population for most diseases.[3]

The detection rate for these tests in the non-Ashkenazi population is unknown for most conditions, but generally low. Exceptions include cystic fibrosis and Tay-Sachs enzyme analysis, which each generally have good detection rates in non-Jewish populations.

A negative test result in one or both partners significantly lowers the chance of an affected child, but does not eliminate it.[2]

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Commonly tested conditions

The genes included in carrier screening panels vary widely between laboratories. The following table includes the most commonly tested conditions.

Ashkenazi Jewish genetic disease	Ashkenazi carrier frequency	What the test looks for	Chance of correctly finding an Ashkenazi Jewish carrier
Bloom syndrome[3]	1/107	1 mutation (2281del6ins7)	Greater than 99%
Canavan disease[3]	1/41	2 mutations (E285A, Y231X)	97.4%
Cystic fibrosis[2]	1/24	23 most common mutations in several ethnic groups	94%
Dihydrolipoamide dehydrogenase deficiency[4]	1/107	2 mutations (G229C and Y35X)	Greater than 95%
Familial dysautonomia[3]	1/31	2 mutations (2507+6TtoC, R696P)	Greater than 99%
Familial hyperinsulinism[4]	1/68	2 mutations (c.3989-9G>A and F1387del)	90%
Fanconi anemia group C[3]	1/89	1 mutation (IVS4+4AtoT)	Greater than 99%
Gaucher disease Type 1[3]	1/18	4 mutations (N370S, 84GG, L444P, IVS2+1GtoA)	Up to 94.6%
Glycogen storage disease type 1A (GSD1A)[5]	1/71	1 mutation (R83C)	93% to 100%

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Ashkenazi Jewish genetic disease	Ashkenazi carrier frequency	What the test looks for	Chance of correctly finding an Ashkenazi Jewish carrier
Joubert syndrome 2[6,7]	1/92	1 mutation (R12L)	99%
Maple syrup urine disease (MSUD)[8,9]	1/80	3 mutations (R183P, G278S, E372X)	About 99%
Mucolipidosis IV[3]	1/127	2 mutations (IVS3–2AtoG, Del6.4kb)	95%
Nemaline myopathy[4]	1/168	1 mutation (R2478_D2512del)	Greater than 95%
Niemann-Pick disease type A[3]	1/90	3 mutations (R496L, L302P, fsP330)	97%
Tay-Sachs disease[2,3]	1/31	Mutation analysis: 3 mutations (1278insTATC, 1421+1GtoC, G269S) OR	95%
		Hexosaminidase A enzyme analysis	About 98%
Usher syndrome III[4]	1/120	1 mutation (N48K)	Greater than 95%

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2008) guidelines outlined criteria for adding disorders to carrier screening in the Ashkenazi Jewish population:[3]

- the natural history must be well understood
- people affected with the disorder must have significant morbidity and/or mortality, and

- the test must have greater than 90% detection OR the allele frequency must be at least 1%.

Conditions that meet ACMG criteria

The following conditions meet these criteria:

- cystic fibrosis
- Canavan disease
- familial dysautonomia
- Tay-Sachs disease
- Fanconi anemia (group C)
- Niemann-Pick (type A)
- Bloom syndrome
- mucolipidosis IV
- Gaucher disease
- dilipoamide dehydrogenase deficiency[4]
- familial hyperinsulinism[4]
- glycogen storage disease type 1a[5]
- Joubert syndrome 2[6,7]
- maple syrup urine disease [8,9]
- nemaline myopathy,[4] and
- Usher syndrome type III.[4]

ACMG (2021) released an educational practice resource on carrier screening.[10] This consensus statement asserted that general population carrier screening should be ethnicity and family history agnostic. To accomplish this, screening all individuals in the prenatal/preconception period for autosomal recessive and X-linked conditions with a carrier frequency of ≥1/200 was suggested. ACMG generated a list of 113 genes meeting these criteria.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2017; reaffirmed 2023) Committee on Genetics issued an opinion that "ethnic-specific [e.g. Ashkenazi Jewish], panethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy and prenatal carrier screening."[11]

If providers choose to offer ethnic-specific screening to individuals of Ashkenazi Jewish ancestry, ACOG recommended that screening include Canavan disease, cystic fibrosis, familial dysautonomia, Tay-Sachs disease, Bloom syndrome, familial hyperinsulinism, Fanconi anemia, Gaucher disease, glycogen storage disease type I, Joubert syndrome, maple syrup urine disease, mucolipidosis type IV, Niemann-Pick disease, and Usher syndrome.[2]

Regardless of screening strategy chosen by the provider and regardless of the individual's ethnicity, ACOG recommended that all individuals who are considering pregnancy or are already pregnant be "...offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome, or women with a personal history of ovarian insufficiency."[11]

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2023) issued a practice guideline on carrier screening in support of an expanded panel approach that is ethnicity and family history agnostic. They recommended expanded carrier screening be made available for all individuals considering reproduction and all pregnant reproductive pairs. "The final decision to pursue carrier screening should be directed by shared decision-making, which takes into account specific features of patients as well as their preferences and values."[12]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for Ashkenazi Jewish carrier screening will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

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