Test Specific Guidelines

Ashkenazi Jewish Carrier Screening

MOL.TS.129.A
v1.0.2023

Introduction

Ashkenazi Jewish carrier screening is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

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
G6PC Targeted Mutation Analysis	81250
GBA Targeted Mutation Analysis	81251

Procedures addressed by this guideline	Procedure codes
HEXA Targeted Mutation Analysis	81255
IKBKAP Targeted Mutation Analysis	81260
MCOLN1 Targeted Mutation Analysis	81290
SMPD1 Targeted Mutation Analysis	81330

What Is Ashkenazi Jewish Carrier Screening?

Definition

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

These Jewish genetic diseases are 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 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.

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.[2,3] 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

Introduction

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. 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 particularly effective for Tay-Sachs disease and is generally 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 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]

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%

Ashkenazi Jewish genetic disease	Ashkenazi carrier frequency	What the test looks for	Chance of correctly finding an Ashkenazi Jewish carrier
Canavan disease[3]	1/41	2 mutations (E285A, Y231X)	97.4%
Cystic fibrosis[2]	1/29	23 most common mutations in several ethnic groups	97%
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 Phel1387del)	90%
Fanconi anemia group C[3]	1/89	1 mutation (IVS4+4AtoT)	Greater than 99%
Gaucher disease[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%
Joubert syndrome 2[6]	1/92	1 mutation (R12L)	99%
Maple syrup urine disease (MSUD)[7,8]	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%

Ashkenazi Jewish genetic disease	Ashkenazi carrier frequency	What the test looks for	Chance of correctly finding an Ashkenazi Jewish carrier
Tay-Sachs disease[3]	1/90	Mutation analysis: 3 mutations (1278insTATC, 1421+1GtoC, G269S) OR	92-94%
		Hexosaminidase A enzyme analysis	About 98%
Usher syndrome III[4]	1/120	1 mutation (N48K)	Greater than 95%

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Ashkenazi Jewish carrier screening.

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]
- maple syrup urine disease [7,8]
- nemaline myopathy,[4] and
- Usher syndrome type III.[4]

ACMG (2021) released an educational practice resource on carrier screening.[9] 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 2020) 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."[10]

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."[10]

Criteria

Introduction

Requests for Ashkenazi Jewish carrier screening are reviewed using these criteria.

Single Ashkenazi Jewish Genetic Diseases Carrier Screening Tests

Carrier screening may be considered 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 may be considered 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.)**

Billing and Reimbursement Considerations

If an Ashkenazi Jewish carrier screening panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, 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), individual gene test coverage will be assessed based on the guidance provided in the Coverage Guidance table.

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

Condition, Gene, CPT Code, Required Claim Code, Guideline ID

Condition	Gene	CPT	Required Claim Code	Guideline ID
Bloom syndrome	BLM	81209	NONE	MOL.TS.129
Canavan disease	ASPA	81200	NONE	MOL.TS.129
Cystic fibrosis	CFTR	81220	NONE	MOL.TS.129
Dihydrolipoamide dehydrogenase deficiency	DLD	81406	DLD	MOL.TS.129
Familial dysautonomia	ELP1	81260	NONE	MOL.TS.129
Familial hyperinsulinism	ABCC8	81401	ABCC8	MOL.TS.129
Fanconi anemia, type C	FANCC	81242	NONE	MOL.TS.129
Gaucher disease, type 1	GBA	81251	NONE	MOL.TS.129
Glycogen storage disease, type 1A	G6PC	81250	NONE	MOL.TS.129
Joubert syndrome, type 2	TMEM216	81479	TMEM216	MOL.TS.129
Maple syrup urine disease, type 1b	BCKDHB	81205	NONE	MOL.TS.129
Mucolipidposis, type IV	MCOLN1	81290	NONE	MOL.TS.129
Nemaline myopathy, type 2	NEB	81400	NEB	MOL.TS.129
Niemann-Pick disease, type A	SMPD1	81330	NONE	MOL.TS.129
Tay-Sachs disease	HEXA	81255	NONE	MOL.TS.129
Usher syndrome, type 1F	PCDH15	81400	PCDH15	MOL.TS.129

Condition	Gene	CPT	Required Claim Code	Guideline ID
Usher syndrome, type 3	CLRN1	81400	CLRN1	MOL.TS.129

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.**

References

Introduction

These references are cited in this guideline.

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