

# Ashkenazi Jewish Genetic Diseases

## Indications for Ordering

Carrier screening for 16 disorders in individuals of Ashkenazi Jewish descent who are planning a pregnancy or currently pregnant

## Test Description

Polymerase chain reaction and fluorescence monitoring

## Tests to Consider

### Primary tests

#### [Ashkenazi Jewish Diseases, 16 Genes 0051415](#)

- Preferred gene panel for carrier screening for individuals of Ashkenazi Jewish descent considering pregnancy or currently pregnant
- Detects 51 variants associated with 16 disorders common in Ashkenazi Jews

#### [Cystic Fibrosis \(CFTR\) 165 Pathogenic Variants 2013661](#)

- Carrier screening for expectant individuals and those planning a pregnancy AND diagnostic testing for individuals with symptoms of classic CF
  - Not included in prenatal screening panel for Ashkenazi Jews

In combination, the above two tests screen for all disorders specific to individuals of Ashkenazi Jewish ancestry recommended by the American College of Medical Genetics and Genomics (ACMG) and the American College of Obstetrics and Gynecology (ACOG).

### Related tests

Assess gene variant(s) associated with a specific disorder

- [ABCC8-Related Hyperinsulinism, 3 Variants 2013725](#)
- [Bloom Syndrome \(BLM\), 1 Variant 0051433](#)
- [Canavan Disease \(ASPA\), 4 Variants 0051453](#)
- [Dysautonomia, Familial \(IKBKAP\), 2 Variants 0051463](#)
- [Fanconi Anemia, Group C \(FANCC\), 2 Variants 0051468](#)
- [Gaucher Disease \(GBA\), 8 Variants 0051438](#)
- [Glycogen Storage Disease, Type 1A \(G6PC\), 9 Variants 2013740](#)
- [Joubert Syndrome Type 2 \(TMEM216\), 1 Variant 2013909](#)
- [Lipoamide Dehydrogenase Deficiency \(DLSD\), 2 Variants 2013735](#)
- [Maple Syrup Urine Disease, Type 1B \(BCKDHB\), 3 Variants 2013730](#)
- [Mucopolidiosis Type IV \(MCOLN1\), 2 Variants 0051448](#)
- [NEB-Related Nemaline Myopathy, 1 Variant 2013745](#)

- [Niemann-Pick Type A \(SMPD1\), 4 Variants 0051458](#)
- [Tay-Sachs Disease \(HEXA\), 7 Variants 0051428](#)
- [Usher Syndrome, Types 1F and 3 \(PCDH15 and CLRN1\), 2 Variants 2013750](#)

Prenatal or preconception carrier screening for spinal muscular atrophy (SMA)

- [Spinal Muscular Atrophy \(SMA\) Copy Number Analysis 2013436](#)
  - Recommended by ACOG for all women considering pregnancy or currently pregnant (ACOG Committee on Genetics, 2017)
  - Confirms suspicion of SMA
  - Carrier screen for reproductive partner of known SMA carrier
  - Family history of SMA

## Disease Overview

**Symptoms** – see Table 1

### Incidence and carrier frequency

- See Table 1 for incidence and carrier frequency in Ashkenazi Jews
- Largely unknown in non-Ashkenazi Jews

### Screening

- Routine preconception or prenatal carrier screening for genetic diseases common in Ashkenazi Jews is recommended by
  - ACOG (ACOG Committee on Genetics, 2017)
    - ABCC8-related hyperinsulinemia
    - Bloom syndrome
    - Canavan disease
    - Cystic fibrosis
    - Fanconi anemia group C
    - Familial dysautonomia
    - Gaucher disease
    - Glycogen storage disease type 1A
    - Joubert syndrome type 2
    - Maple syrup urine disease type 1B
    - Mucopolidiosis type IV
    - Niemann-Pick type A
    - Tay-Sachs disease
    - Usher syndrome (type 1F and type 3)
  - ACMG for nine of the disorders described in the ACOG guidelines (Gross, 2008)

- Screening for a specific disorder may be offered to non-Jewish individuals, including
  - Relatives who carry one or more variants included in the test
  - Reproductive partners who are carriers of one of the panel disorders, although detection rates for non-Jews is variable by disorder and largely unknown

## Genetics

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**Genes/variants** – see Table 2

**Inheritance** – autosomal recessive

## Test Interpretation

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### Sensitivity/specificity

- Clinical sensitivity/specificity – see Table 2
- Analytical sensitivity/specificity – 99%

### Results

- Positive
  - One pathogenic variant detected
    - Individual is a carrier of the associated disease
    - Screening for that disease should be offered to the individual's reproductive partner
    - Genetic counseling is recommended
- Negative
  - No targeted pathogenic variants identified
  - For residual carrier risk estimates, see Table 2

### Limitations

- Variants other than those tested on this panel will not be detected
- Diagnostic errors can occur due to rare sequence variations

## References

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**Table 1**

Disease ( <i>Gene</i> )	Disease Incidence in Ashkenazi Jews	Carrier Frequency in Ashkenazi Jews	Type of Disorder/Symptoms
ABCC8-related hyperinsulinism ( <i>ABCC8</i> )	1/10,800	1/52	<ul style="list-style-type: none"> <li>• Hypoglycemia that varies from mild to severe neonatal onset</li> <li>• With proper management, life span is normal</li> </ul>
Bloom syndrome ( <i>BLM</i> )	1/40,000	1/100	<ul style="list-style-type: none"> <li>• Pre- and postnatal growth deficiency</li> <li>• Sun sensitive skin lesions appear at 1-2 years of age</li> <li>• Benign and malignant tumors in childhood</li> <li>• Telangiectatic hypo- and hyperpigmented skin lesions</li> <li>• Male sterility</li> <li>• Life expectancy is decreased due to malignancy</li> </ul>
Canavan disease ( <i>ASPA</i> )	1/10,000	1/50	<ul style="list-style-type: none"> <li>• Macrocephaly</li> <li>• Loss of motor control beginning at 3-5 months of age</li> <li>• Failure to sit, stand, or ambulate</li> <li>• Survival usually until childhood or teenage years</li> </ul>
Familial dysautonomia ( <i>IKBKAP</i> )	1/3,600	1/32	<ul style="list-style-type: none"> <li>• Delayed motor milestones in infants and progressive deterioration of gait throughout life</li> <li>• Gastrointestinal dysfunction with emesis</li> <li>• Altered sensitivity to pain and temperature</li> <li>• Cardiovascular instability</li> <li>• Survival typically until 30s</li> </ul>
Fanconi anemia group C ( <i>FANCC</i> )	1/32,000	1/89	<ul style="list-style-type: none"> <li>• Progressive bone marrow failure during first decade of life</li> <li>• Increased risk of malignancy (hematological in ~20%, nonhematological in ~30%)</li> <li>• Physical malformations may include short stature, abnormal skin pigmentation or malformations of the eyes, ears, heart, forearms, thumbs, kidneys</li> <li>• Survival usually until childhood or teenage years</li> </ul>
Gaucher disease ( <i>GBA</i> )	1/900	1/15	<ul style="list-style-type: none"> <li>• Type 1 (most prevalent type among Ashkenazi Jews) <ul style="list-style-type: none"> <li>○ Bone disease</li> <li>○ Hepatosplenomegaly</li> <li>○ Anemia, thrombocytopenia</li> <li>○ Lung disease</li> <li>○ No primary central nervous system (CNS) disease</li> </ul> </li> <li>• Type 2 <ul style="list-style-type: none"> <li>○ CNS degeneration by age 2 years, with a rapidly progressive course; survival until age 4 years</li> </ul> </li> <li>• Type 3 <ul style="list-style-type: none"> <li>○ Slowly progressive CNS degeneration; survival until 20s</li> </ul> </li> </ul>
Glycogen storage disease type 1A ( <i>G6PC</i> )	1/20,000	1/71	<ul style="list-style-type: none"> <li>• Hepatomegaly</li> <li>• Growth delay/short stature</li> <li>• Hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia</li> <li>• Additional long-term complications include osteoporosis, delayed puberty, renal disease, systemic hypertension, hepatic adenomas with potential for malignant transformation</li> <li>• With treatment, individuals live into adulthood</li> </ul>
Joubert syndrome type 2 ( <i>TMEM216</i> )	1/34,000	1/92	<ul style="list-style-type: none"> <li>• “Molar tooth sign” cerebellar and brain stem malformation</li> <li>• Hypotonia</li> <li>• Developmental delay/intellectual disability</li> <li>• Individuals typically have a normal lifespan, but a minority may have a shortened lifespan depending on severity</li> </ul>
Lipoamide dehydrogenase deficiency ( <i>DLD</i> )	1/35,000	1/94	<ul style="list-style-type: none"> <li>• Early onset disease presents in infancy <ul style="list-style-type: none"> <li>○ Hypotonia, lethargy, and vomiting with progressive encephalopathy</li> <li>○ Survival usually until 1-2 years of life</li> </ul> </li> <li>• Primarily hepatic disease has variable onset from infancy to 30s <ul style="list-style-type: none"> <li>○ Liver injury/failure, usually preceded by nausea/vomiting</li> <li>○ Typically normal intellect with no neurological findings</li> <li>○ Life span varies depending on the severity of the condition</li> </ul> </li> </ul>

Disease ( <i>Gene</i> )	Disease Incidence in Ashkenazi Jews	Carrier Frequency in Ashkenazi Jews	Type of Disorder/Symptoms
Maple syrup urine disease type 1B ( <i>BCKDHB</i> )	1/50,000	1/113	<ul style="list-style-type: none"> <li>• Maple syrup odor in urine</li> <li>• Classically affected individuals present within the first few days of life with <ul style="list-style-type: none"> <li>○ Irritability</li> <li>○ Poor feeding and lethargy</li> <li>○ Intermittent apnea</li> </ul> </li> <li>• Progresses to coma and death within 7-10 days if untreated</li> </ul>
Mucopolidiosis type IV ( <i>MCOLN1</i> )	1/63,000	1/127	<ul style="list-style-type: none"> <li>• Severe psychomotor delay</li> <li>• Progressive visual impairment due to retinal degeneration and corneal clouding</li> <li>• Neurological state <ul style="list-style-type: none"> <li>○ Static until age 30 in most affected individuals</li> <li>○ Neurological degeneration in ~15%</li> </ul> </li> <li>• Variable life expectancy, most individuals live into adulthood</li> </ul>
<i>NEB</i> -related nemaline myopathy ( <i>NEB</i> )	1/47,000	1/108	<ul style="list-style-type: none"> <li>• Presents in the first year of life with <ul style="list-style-type: none"> <li>○ Muscle weakness of the face, neck, arms, and legs, which is static or very slowly progressive</li> <li>○ Hypotonia</li> <li>○ Feeding difficulties</li> </ul> </li> <li>• Individuals typically have a normal lifespan and have an active, independent life</li> </ul>
Niemann-Pick disease type A ( <i>SMPD1</i> )	1/32,000	1/90	<ul style="list-style-type: none"> <li>• Hepatosplenomegaly</li> <li>• Developmental delay and severe neurodegeneration</li> <li>• Progressive hypotonia and rigidity</li> <li>• Cherry-red spot on the macula of the retina</li> <li>• Survival until 3-5 years of age</li> </ul>
Tay-Sachs disease ( <i>HEXA</i> )	1/3,000	1/30	<ul style="list-style-type: none"> <li>• Progressive loss of motor skills beginning at 3–6 months of age</li> <li>• Progressive neurodegeneration resulting in blindness, seizures, and eventually total incapacitation</li> <li>• Survival until 4-6 years of age</li> </ul>
Usher syndrome type 1F ( <i>PCDH15</i> )	1/20,500	1/72	<ul style="list-style-type: none"> <li>• Congenital, bilateral, profound sensorineural hearing loss</li> <li>• Adolescent-onset retinitis pigmentosa</li> <li>• Loss of vestibular function</li> </ul>
Usher syndrome type 3 ( <i>CLRN1</i> )	1/82,000	1/143	<ul style="list-style-type: none"> <li>• Postlingual, progressive hearing loss</li> <li>• Late-onset progressive loss of vision due to retinitis pigmentosa</li> <li>• Variable loss of vestibular function</li> </ul>

**Table 2**

Disease ( <i>Gene</i> )	Variants Tested (HGVS Nomenclature)	Variants Tested (Legacy Nomenclature)	Clinical Sensitivity in Ashkenazi Jews	Clinical Sensitivity in Non-Ashkenazi Jews	Carrier Risk for Ashkenazi Jews After Negative Test
<i>ABCC8</i> -related hyperinsulinism ( <i>ABCC8</i> )	p.F1388del (c.4163_4165del) p.V187D (c.560T>A) c.3992-9G>A		97% (Glaser, 2011)	Unknown	1/1,700
Bloom syndrome ( <i>BLM</i> )	p.Y736Lfs (c.2207_2212delinsTAGATTC)	2281del6/ins7	97% (German, 2007)	~3%	1/3,300
Canavan disease ( <i>ASPA</i> )	c.433-2A>G p.Y231X (c.693C>A) p.E285A (c.854A>C) p.A305E (c.914C>A)		99% (Matalon, 2011)	55%	1/4,900
Familial dysautonomia ( <i>IKBKAP</i> )	p.R696P (c.2087G>C) c.2204+6T>C	IVS20+6T>C	99% (Gross, 2008)	Unknown	1/3,100
Fanconi anemia group C ( <i>FANCC</i> )	p.D231fs (c.67delG) c.456+4A>T	322delG IVS4+4A>T	99% (Gross, 2008)	Unknown	1/8,800

Disease ( <i>Gene</i> )	Variants Tested (HGVS Nomenclature)	Variants Tested (Legacy Nomenclature)	Clinical Sensitivity in Ashkenazi Jews	Clinical Sensitivity in Non-Ashkenazi Jews	Carrier Risk for Ashkenazi Jews After Negative Test
Gaucher disease ( <i>GBA</i> )	p.L29Afs (c.84dupG) c.115+1G>A p.N409S (c.1226A>G) c.1263_1317del55 p.V433L (c.1297G>T) p.D448H (c.1342G>C) p.L483P (c.1448T>C) p.R535H (c.1604G>A)	84G>GG IVS2+1G>A N370S del55bp V394L D409H L444P R496H	90% (Pastores, 2000)	55%	1/140
Glycogen storage disease type 1A ( <i>G6PC</i> )	p.Q27Rfs (c.79delC) p.Y128Tfs (c.379_380dupTA) p.R83H (c.248G>A) p.R83C (c.247C>T) p.G188R (c.562G>C) p.Q242X (c.724C>T) p.Q347X (c.1039C>T) p.G270V (c.809G>T) p.F327del (c.979_981delTTC)		99% (Ekstein, 2004)	Varies by ethnicity	1/7,000
Joubert syndrome type 2 ( <i>TMEM216</i> )	p.R73L (c.218G>T)		99% (Edvardson, 2010)	Unknown	1/9,100
Lipoamide dehydrogenase deficiency ( <i>DLD</i> )	p.Y35X (c.104dupA) p.G229C (c.685G>T)		99% (Shaag, 1999)	Unknown	1/9,300
Maple syrup urine disease type 1B ( <i>BCKDHB</i> )	p.R183P (c.548G>C) p.G278S (c.832G>A) p.E372X (c.1114G>T)		99% (Edelmann, 2001)	Unknown	1/11,000
Mucopolipidosis type IV ( <i>MCOLN1</i> )	c.406-2A>G g.511_6493del	IVS3-2A>G del6.4kb	95% (Schiffmann, 2005)	6-10%	1/2,500
<i>NEB</i> -related nemaline myopathy ( <i>NEB</i> )	exon 55 del (p.R2478_D2512del)		99% (Anderson, 2004)	Unknown	1/10,700
Niemann-Pick disease type A ( <i>SMPD1</i> )	p.L304P (c.911T>C) p.F333Sfs (c.996delC) p.R498L (c.1493G>T) p.R610del (c.1829_1831delGCC)	L302P fsP330 R496L R608del	90% (Wasserstein, 2006)	Varies by ethnicity	1/900
Tay-Sachs disease ( <i>HEXA</i> )	7.6 kb del p.G269S (c.805G>A) c.1073+1G>A p.Y427Ifs (c.1274_1277dupTATC) c.1421+1G>C Pseudodeficiency alleles: p.R247W (c.739C>T) p.R249W (c.745C>T)	IVS9+1G>A 1278dupTATC IVS12+1G>C	94% (Kaback, 1993)	59%	1/480
Usher syndrome type 1F ( <i>PCDH15</i> )	p.R245X (c.733C>T)		62% (Ben-Yosef, 2003)	Unknown	1/190
Usher syndrome type 3 ( <i>CLRN1</i> )	p.N48K (c.144T>G)		98% (Fields, 2002; Ness, 2003)	Unknown	1/7,000