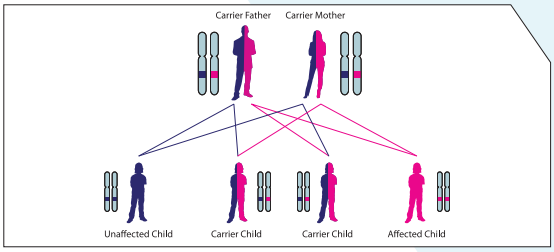
Expanded Carrier Screening

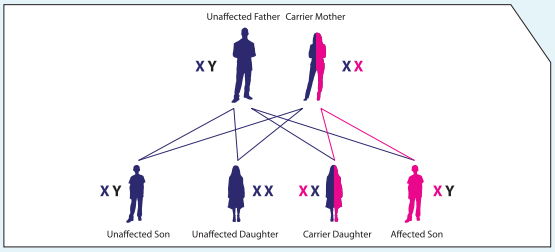
for the Ashkenazi Jewish Population

There are several genetic disease mutations that occur at increased frequencies in the Ashkenazi Jewish population. Our Expanded Ashkenazi Jewish Carrier Screening Panel covers 38 conditions that fall into this category. With the addition of these 18 disorders, Ashkenazi Jewish individuals have a 1 in 2 chance of being a carrier for at least one of these diseases. Because these disorders are inherited in an autosomal recessive or X-linked manner, your patient may be at risk for being a carrier for a genetic disorder without even knowing it.

How are these disorders inherited?

These disorders are inherited in one of two ways:





Autosomal recessive pattern

If each member of a couple is a carrier of one mutated gene, the risk of having future affected offspring is 25% with each pregnancy. Each pregnancy also carries a 50% chance of being an unaffected carrier and 25% chance of being and unaffected non-carrier. A person who is a carrier for an autosomal recessive condition generally does not display features of the disorder in question.

(Screening of both members of a couple can occur concurrently or sequentially; for couples where only one member is of Ashkenazi Jewish ancestry, screening should begin with the Ashkenazi Jewish member.)

X-linked pattern:

Fragile X syndrome is caused by an expansion of a CGG repeat in the 5' UTR of the *FMR1* gene. Female carriers have alleles that are in a premutation state with ≥55 CGG repeats or, rarely, in the full mutation state with ≥200 CGG repeats. If a female carrier transmits the premutation allele to a fetus, there is a risk of the allele expanding to a full mutation. Transmission of a full mutation causes fragile X syndrome in male fetuses and is the most common cause of intellectual disability in males. Females who inherit a full mutation allele may also be affected with intellectual disability.

(In general, male premutation carriers are not at risk for affected offspring and it is not recommended to perform carrier screening on males.)

Testing methods, sensitivity and limitations:

A blood sample is drawn and DNA is obtained from the white blood cells. Targeted mutation analysis is then performed to look for the presence of specific mutations. This testing is approximately 99% accurate. A negative test result for any given disease ***does not exclude*** an individual from being a carrier for that disease, but only ***reduces*** risk of being a carrier. The patient may still have a mutation that was not identified by this testing.

Turnaround time:

Results are reported to the referring physician within 7-10 days from the receipt of the specimen.

Specimen & Shipping requirements:

3 yellow-top (ACD-A or ACD-B) or 3 lavender-top (EDTA), 5-10 ml tubes of blood.

Mount Sinai

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Disease	Gene	Mutation(s) analyzed	Ashkenazi Jewish Carrier Frequency	Ashkenazi Jewish Molecular Diagnostic Rate	Residual carrier risk after NEGATIVE result
Abetalipoproteinemia	*MTTP*	p.G865*, p.S738*fs*	1 in 180	≥95%	1 in 3,600
Alport Syndrome, Autosomal Recessive	*COL4A3*	p.L14_L21del	1 in 188	≥95%	1 in 3,700
Arthrogryposis, Mental Retardation and Seizures	*SLC35A3*	p.S296G, p.Q172*	1 in 373	≥95%	1 in 7,400
Bardet-Biedl Syndrome	*BBS2*	p.D104A, p.R632P	1 in 107	≥95%	1 in 2,100
Bloom Syndrome	*BLM*	c.2207_2212delATCTGAinsTAGATTC	1 in 134	≥99%	1 in 13,300
Canavan Disease	*ASPA*	p.E285A, p.Y231*, p.A305E, c.433-2A>G	1 in 55	≥97%	1 in 1,800
Carnitine Palmitoyltransferase II Deficiency	*CPT2*	p.S113L, p.Q413*fs*, p.R124*, p.S38*fs*	1 in 51	≥95%	1 in 1,000
Congenital Amegakaryocytic Thrombocytopenia	*MPL*	c.79+2T>A	1 in 55	≥95%	1 in 1,100
Congenital Disorder of Glycosylation Ia	*PMM2*	p.P113L, p.F119L, p.R141H, p.V231M	1 in 57	≥90%[1]	1 in 600
Cystic Fibrosis	*CFTR*	p.E60*, p.R75*, p.G85E, c.262_263delTT, c.273+3A>C, c.274-1G>A, c.313delA, p.R117C, p.R117H, p.Y122*, c.489+1G>T, p.G178R, c.579+1G>T, p.L206W, c.803delA, p.F312del, c.948delT, p.G330*, p.R334W, p.R347P, p.R347H, p.R352Q, p.S364P, p.A455E, p.G480C, p.Q493*, p.I507del, p.F508del, p.V520F, c.1545_1546delTA, c.1585-1G>A, p.G542*, p.S549N, p.S549R/c.1647T>G, p.G551D, p.R553*, p.A559T, p.R560T, c.1680-1G>A, c.1766+1G>A, c.1766+5G>T, c.2051_2052delAAinsG, c.2052delA, c.2175_2176insA, p.G622D, c.1923_1931del9insA, c.2012delT, p.K710*, c.2657+5G>A, p.Q890*, c.2737_2738insG, c.2988G>A, c.2988+1G>A, c.3067_3072delATAGTG, p.R1066C, p.W1089*, p.Y1092*, p.M1101K, p.D1152H, p.R1162*, c.3528delC, p.R1158*, c.3659delC, p.S1196*, c.3717+12191C>T, c.3773_3774insT, p.W1282*, p.D1270N, p.S1255*, c.3744delA, p.N1303K	1 in 24	≥94%	1 in 400
Dyskeratosis Congenita, Autosomal Recessive	*RTEL1*	p.R1264H, p.M516I, p.R981W, p.R998*, p.G763V	1 in 203	≥95%	1 in 4,000
Ehlers-Danlos VIIC	*ADAMTS2*	p.Q225*, p.W795*	1 in 248	≥95%	1 in 4,900
Familial Dysautonomia	*IKBKAP*	c.2204+6T>C, p.R696P	1 in 31	≥99%	1 in 3,000
Familial Hyperinsulinism	*ABCC8*	c.3989-9G>A, p.F1387del	1 in 68	≥90%	1 in 700
Fanconi Anemia C	*FANCC*	c.456+4A->T, c.67delG	1 in 100	≥99%	1 in 9,900
Fragile X Syndrome	*FMR1*	CGG repeat	1 in 115	≥99%	1 in 11,400

[1]*Please note: there are no Ashkenazi Jewish patients with CDGIa described in the literature, presumably due to embryonic lethality of p.R141H homozygosity. Therefore, the exact carrier screening detection rate cannot be determined, but is approximated to be >90% as no compound heterozygous Ashkenazi Jewish patients have been described.*

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Disease	Gene	Mutation(s) analyzed	Ashkenazi Jewish Carrier Frequency	Ashkenazi Jewish Molecular Diagnostic Rate	Residual carrier risk after NEGATIVE result
Galactosemia	*GALT*	c.-1039_+789del5573ins129 , c.253-2A>G, p.S135L, p.Q188R, p.T138M, p.F171S, p.L195P, p.Y209C, p.K285N	1 in 172	≥88%	1 in 1,400
Gaucher Disease	*GBA*	p.N409S, p.L483P, c.84dupG, c.115+1G>A, c.1263_1317del, p.V433L, p.D448H, p.R535H	1 in 15	≥95%	1 in 300
Glycogen Storage Disease Ia	*G6PC*	p.R83C, p.Q347*	1 in 64	≥95%	1 in 1,300
Joubert Syndrome 2	*TMEM216*	p.R12L	1 in 110	≥95%	1 in 2,200
Lipoamide Dehydrogenase Deficiency (E3)	*DLD*	p.G229C, p.Y35*	1 in 107	≥95%	1 in 2,100
Maple Syrup Urine Disease Ib	*BCKDHB*	p.R183P, p.G278S, p.E372*	1 in 97	≥95%	1 in 1,900
Mucolipidosis IV	*MCOLN1*	c.406-2A>G, g.511_6943del	1 in 89	≥95%	1 in 1,800
Multiple Sulphatase Deficiency	*SUMF1*	p.S155P	1 in 320	≥95%	1 in 6,400
Nemaline Myopathy	*NEB*	p.R2478_D2512del, c.9619-2A>G	1 in 168	≥95%	1 in 3,300
Niemann-Pick Disease	*SMPD1*	Type A: p.L304P, c.996delC, p.R498L Type B: p.R610del	1 in 115	≥97%	1 in 3,800
3-Phosphoglycerate Dehydrogenase Deficiency	*PHGDH*	p.V490M	1 in 280	≥95%	1 in 5,600
Polycystic Kidney Disease, Autosomal Recessive	*PKHD1*	p.A1254*fs*, p.T36M, p.R496*, p.L1966*fs*, p.V3471G, p.D3230*fs*	1 in 107	≥90%	1 in 1,100
Retinitis Pigmentosa 59	*DHDDS*	p.K42E	1 in 118	≥95%	1 in 2,300
Smith-Lemli-Opitz Syndrome	*DHCR7*	c.964-1G>C, p.W151*, p.M1V, p.V326L, p.T93M, p.R352Q, p.R352W, p.R404C, p.S169L, p.R242C, p.R242H, p.F302L, p.G410S, p.E448K	1 in 36	≥75%	1 in 100
Spinal Muscular Atrophy	*SMN1*	Copy number and SNP g.27134T>G*analyses	1 in 41	≥94%	1 in 600
Tay-Sachs Disease	*HEXA*	c.1274_1277dupTATC, c.1421+1G>C, p.G269S, c.1073+1G>A, g.2644_10588del Pseudodeficiency Alleles: p.R247W, p.R249W	1 in 27	≥99%	1 in 1,300
		Hexosaminidase Activity biochemical testing			
Tyrosinemia I	*FAH*	p.P261L, c.554-1G>T, c.1062+5G>A, p.Q64H, p.W262*, p.E357*	1 in 150	≥95%	1 in 3,000
Usher IF	*PCDH15*	p.R245*	1 in 147	≥75%	1 in 600
Usher III	*CLRN1*	p.N48K	1 in 120	≥95%	1 in 2,400
Walker-Warburg	*FKTN*	c.1167-1168insA	1 in 120	≥95%	1 in 2,400
Wilson Disease	*ATP7B*	p.E1064A, p.H1069Q, p.R778L, p.M645R	1 in 70	≥88%	1 in 500
Zellweger Syndrome	*PEX2*	p.R119*	1 in 172	≥95%	1 in 3,400

- **Abetalipoproteinemia:** severe malabsorption of dietary fats and fat-soluble vitamins causing failure to thrive, diarrhea, blood abnormalities (acanthocytosis), and stool abnormalities (steatorrhea). Later in childhood symptoms include poor muscle coordination, ataxia, and retinitis pigmentosa.
- **Alport Syndrome, Autosomal Recessive:** progressive loss of kidney function (hematuria, proteinuria) resulting in end-stage renal disease, sensorineural hearing loss, and eye abnormalilties such as anterior lenticonus.
- **Arthrogryposis, Mental Retardation and Seizures:** arthrogryposis, mental retardation, autism spectrum disorder, epilepsy, microcephaly, and hypotonia.
- **Bardet-Biedl Syndrome:** features include retinitis pigmentosa, obesity polydactyly, intellectual disability/ developmental delay, renal problems, anosmia, genital abnormalities, and male infertility. Other affected organs include the heart, liver and digestive system. There is variable age of onset and severity of symptoms.
- **Bloom Syndrome:** poor growth, frequent infections, and possible learning disabilities. Increased predisposition for leukemia and cancers of the breast and colon.
- **Canavan Disease:** progressive disease of central nervous system with no cure. Symptoms include seizures, regression of milestones, severe mental retardation and death in childhood.
- **Carnitine Palmitoyltransferase II Deficiency:** characterized by recurrent episodes of myalgia and rhabdomyolysis causing myoglobinuria which may be triggered by exercise, stress, exposure to extreme temperatures, infections, or fasting. The first episode usually occurs during childhood or adolescence. This can damage the kidneys, in some cases leading to life-threatening kidney failure.
- **Congenital Amegakaryocytic Thrombocytopenia:** pancytopenia, decreased bone marrow activity, and very low platelet counts.
- **Congenital Disorder of Glycosylation Ia:** hypotonia, abnormal fat distribution, strabismus, developmental delay, and failure to thrive appear in infancy. Other symptoms include elevated liver function tests, seizures, and pericardial effusion that could lead to death under 1 year of life due to multiple organ failure. Affected individuals who survive infancy may have intellectual disability, lethargy, temporary paralysis, neuropathy, kyphoscoliosis, ataxia, contractures and retinitis pigmentosa.
- **Cystic Fibrosis:** thick mucus buildup in the lungs leading to breathing difficulty and infection, with no cure. Symptoms include poor digestion, male infertility and shortened life expectancy (into the 30s).
- **Dyskeratosis Congenita, Autosomal Recessive:** abnormally growing and poorly growing fingernails and toenails, pigmentary changes on neck and chest. Symptoms include bone marrow failure, aplastic anemia and increased risk for leukemia. Increased risk for cancers of the head, neck, anus, or genitals. Other features include pulmonary fibrosis, hair loss, osteoporosis, avascular necrosis of the joints, liver disease and short stature.
- **Ehlers-Danlos VIIC:** hypermobility, easy bruising, fragile skin, and blue sclera.
- **Familial Dysautonomia:** autonomic nervous system disorder (e.g. swallowing, sweating, pain sensitivity). Increased risk for pulmonary (e.g. pneumonia) and gastrointestinal complications.
- **Familial Hyperinsulinism:** inability to stop insulin production leading to seizures, poor muscle tone, poor feeding and breathing difficulty (newborns and children). Treatment options include glucose infusion, insulin release-reducing drugs, and/or surgical removal of portions of the pancreas. (Focal, or localized, disease is present in 1-2% of children who inherit a single paternal mutation).
- **Fanconi Anemia C:** bone problems (short stature, bone marrow failure, etc), predisposition to leukemia and possible learning disability/mental retardation.
- **Fragile X Syndrome:** X-linked condition - features include mental retardation, behavioral problems (autistic-like features, etc), and characteristic facial features in affected males. Affected females may also have milder clinical manifestations. Premutation carrier females are at increased risk for premature ovarian insufficiency; whereas permutation carrier males are at increased risk for Fragile X-associated tremor/ataxia syndrome.
- **Galactosemia:** feeding difficulties, lethargy, failure to thrive, jaundice, and bleeding within a few days after birth. Increased risk for sepsis and shock, developmental delay/intellectual disability, and cataracts. Managed by dietary restrictions.
- **Gaucher Disease:** enlargement of spleen and liver, blood abnormalities (anemia, easy bruising, impaired clotting, etc), and bone problems (joint pain, bone fractures, etc). Variable age of onset and severity of symptoms. Successful Enzyme Replacement Therapy exists, reducing or reversing symptoms.
- **Glycogen Storage Disease Ia:** biochemical abnormalities such as very low glucose level leading to delayed growth/development presenting in infancy. Symptoms include enlarged spleen, gastrointestinal problems, recurrent infection, and pancreatitis. Managed by dietary restrictions.
- **Joubert Syndrome 2:** neurological disorder with brain malformations leading to developmental delay, mental retardation, breathing difficult, ataxia, failure to thrive, retinal degeneration and renal dysfunction.
- **Lipoamide Dehydrogenase Deficiency (E3):** Variable age of onset and severity of symptoms including fatigue, episodes of decompensation, severed neurological decliner and sometimes death. Managed by dietary restrictions.
- **Maple Syrup Urine Disease Ib:** neurological impairment in infants including poor suck, irritability, lethargy and potential lapse into coma after ingesting dietary protein. Delay in diagnosis can cause impaired intellectual development. Managed by dietary restrictions.
- **Mucolipidosis IV:** severe neurodegenerative condition leading to abnormalities of the cornea and retina, inability to walk or speak.
- **Multiple Sulphatase Deficiency:** accumulation of sulfatides, sulfated glycosaminoglycans, sphingolipids, and steroid sulfates causing neurologic deterioration with mental retardation, skeletal anomalies, organomegaly, and ichthyosis
- **Nemaline Myopathy:** progressive disease causing muscle weakness, delayed motor milestones, and feeding/respiratory difficulty potentially leading to death in infancy.
- **Niemann-Pick Disease:** severe neurodegenerative condition leading to loss of brain function, enlargement of liver and spleen and shortened life expectancy (2-3 years).
- **3-Phosphoglycerate Dehydrogenase Deficiency:** microcephaly, psychomotor retardation, and seizures
- **Polycystic Kidney Disease, Autosomal Recessive:** cyst development in the kidneys causes kidney enlargement and can lead to kidney failure. Symptoms include cysts in the liver, hypertension, hematuria, recurrent urinary tract infections, kidney stones, and an increased risk for aneurysms. This condition is often lethal early in life.
- **Retinitis Pigmentosa 59:** childhood loss of night vision developing into peripheral blind spots and, later, leading to tunnel vision and blindness.
- **Smith-Lemli-Opitz Syndrome:** characteristic facial features, microcephaly, intellectual disability, and behavioral problems (e.g. autism). Abnormalities of the heart, lungs, kidneys, gastrointestinal tract, fingers/toes and genitalia are also common. Variable severity of symptoms.
- **Spinal Muscular Atrophy:** severe and progressive weakness of the voluntary muscles affecting breathing, swallowing, head/neck control, walking and crawling. Variable onset and severity, with shortened lifespan for those with onset in infancy.
- **Tay-Sachs Disease:** progressive disease of central nervous system leading to loss of coordination, seizures, difficulty swallowing, poor pulmonary function, blindness, paralysis, severe mental retardation and shortened life expectancy (3-5 years).
- **Tyrosinemia I:** tyrosine aminotransferase deficiency that can affect the eyes, skin, and mental development. Symptoms include photophobia, painful skin lesions on the palms and soles, and intellectual disability.
- **Usher IF:** profound hearing loss and retinitis pigmentosa.
- **Usher III:** postlingual onset of moderate to severe hearing loss and variable onset and severity of retinitis pigmentosa.
- **Walker-Warburg:** severe disease of the brain (seizures, developmental delay, mental retardation), muscles (weakness, feeding difficulty) and eyes (blindness). There is a shortened life expectancy (less than 3 years)
- **Wilson Disease:** copper accumulation in the liver (causing jaundice, fatigue, loss of appetite, and abdominal swelling), brain (causing nervous system and psychiatric problems), and eyes (causing Kayser-Fleischer rings and restricted ability to gaze upwards) with variable age of onset.
- **Zellweger Syndrome:** demyelination of white matter causing hypotonia, feeding problems, hearing loss, vision loss, and seizures. Other affected organs include the liver, heart, kidneys, and bones and there is a shortened life expectancy.

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