Who should be screened?

Carrier testing is recommended for individuals of Ashkenazi descent who are pregnant, planning a pregnancy, or serving as gamete donors to determine their risk of having a child with one of the autosomal recessive genetic disorders that occurs with increased frequency in the Ashkenazi Jewish population. If only one member of a couple is of Ashkenazi Jewish descent, carrier testing should be offered first to the Jewish individual.

What genetic disorders should be included in preconception/prenatal carrier screening for individuals of Ashkenazi Jewish descent?

The American College of Obstetricians and Gynecologists (ACOG) 2017 guidelines recommend offering carrier screening for the following four disorders: Canavan disease, cystic fibrosis, familial dysautonomia, and Tay-Sachs disease. In addition, the guidelines state that screening for 11 additional disorders should be considered: *ABCC8*-related hyperinsulinemia, Bloom syndrome, Fanconi anemia group C, Gaucher, glycogen storage disease type 1A, Joubert syndrome type 2, maple syrup urine disease type 1B, mucolipidosis type IV, Niemann-Pick type A and Usher syndrome (type 1F and type 3).

The American College of Medical Genetics (ACMG) 2008 guidelines recommend offering carrier screening for nine of the disorders mentioned in the ACOG guidelines.

ARUP tests for 17 disorders with increased carrier frequency in the Ashkenazi Jewish population—including all disorders recommended by ACOG and ACMG plus lipoamide dehydrogenase deficiency and *NEB*-related nemaline myopathy.

Why is carrier screening effective for individuals of Ashkenazi Jewish descent?

DNA-based carrier screening for genetic disorders occurring more frequently in Ashkenazi Jewish individuals is possible due to a relatively small number of common pathogenic variants in this population. Approximately one in four individuals of Ashkenazi Jewish descent is determined to be a carrier of any one of these disorders.

Why is screening using the Ashkenazi Jewish panels often ineffective in individuals of other ethnicities?

The variants on the Ashkenazi Jewish panel are unique to this population. Non-Ashkenazi Jewish individuals who are carriers of pathogenic variants would often go undetected using such a panel. Therefore, if a single member of a couple is Ashkenazi Jewish, that individual should be screened first. The non-Jewish member should only be tested for the disorder(s) of which his/her partner is a carrier. Testing of the non-Jewish individual may require gene sequencing depending on the panel's detection rate for the specific disorder in that ethnic group.

ARUP test information

Genetic screening offered by ARUP includes testing for seventeen disorders, including all disorders recommended by ACOG/ACMG, using the two test codes listed below.

- Ashkenazi Jewish Diseases, 16 Genes (ARUP test code 0051415)
- Cystic Fibrosis (*CFTR*) 165 Pathogenic Variants (ARUP test code 2013661)

References

1. ACOG committee opinion no. 691. Carrier screening for genetic conditions. *Obstet Gynecol* 2017;129(3):e41-e55.
2. Gross SJ, et al. ACMG practice guidelines: carrier screening in individuals of Ashkenazi Jewish descent. *Gen Med* 2008;10:54–6.

ARUP LABORATORIES

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Carrier Screening

For Individuals of Ashkenazi Jewish Descent

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Disease (*Gene*)	Characteristics	Carrier Rate in Ashkenazi Jewish	Number of Variants Tested	Detection in Ashkenazi Jewish
ABCC8-related hyperinsulinemia (*ABCC8*)	Chronic sinopulmonary disease, gastrointestinal malabsorption/pancreatic insufficiency, and male infertility. Life expectancy is approximately 35 years.	1/52	3	97%
Bloom syndrome (*BLM*)	Characterized by pre- and postnatal growth deficiency, sparse subcutaneous tissue, sun-sensitive telangiectatic hypo- and hyperpigmented skin lesions, chromosome instability causing benign and malignant tumors early in life, and male sterility.	1/100	1	97%
Canavan disease (*ASPA*)	Neurodegenerative brain disorder that results in macrocephaly and lack of head control by 3 to 5 months of age. This progresses to a failure to achieve sitting, ambulation, or speech, and eventually leads to death, typically in early childhood to teenage years.	1/50	4	99%
Cystic fibrosis (*CFTR*)*	Chronic sinopulmonary disease, gastrointestinal malabsorption/pancreatic insufficiency, and male infertility. Life expectancy is approximately 37 years.	1/24	165	96%
Familial dysautonomia (*IKBKAP*)	Debilitating disease resulting in gastrointestinal dysfunction, vomiting and autonomic crises, recurrent pneumonia, altered sensitivity to pain and temperature, scoliosis, and cardiovascular instability. Other characteristics include infantile hypotonia, deteriorating wide-based ataxic gait, and decreased life expectancy.	1/32	2	99%
Fanconi anemia group C (*FANCC*)	Presents with short stature, abnormal skin pigmentation, and multiple malformations that may affect eyes, ears, heart, oral cavity, thumbs, forearms, kidneys, or urinary tract. Other symptoms may include hearing loss, hypogonadism, developmental delay, progressive bone marrow failure, and malignancy.	1/89	2	99%
Gaucher disease (*GBA*)	Lysosomal storage disease with extreme symptom variability, ranging from perinatal lethality to asymptomatic individuals. Bone disease, hepatosplenomegaly, anemia, thrombocytopenia, lung disease, and central nervous system findings may occur. Life expectancy varies by disease subtype.	1/15	8	90%
Glycogen storage disease type 1A (*G6PC*)	Infants typically present at age 3 to 4 months with hepatomegaly, lactic acidosis, hyperuricemia, hyperlipidemia, and hypertriglyceridemia and/or hypoglycemic seizures. Other characteristics include growth delay leading to short stature, osteoporosis, delayed puberty, renal disease, and hepatic adenomas with potential for malignancy.	1/71	9	99%
Joubert syndrome type 2 (*TMEM216*)	Characterized by a “molar tooth sign” cerebellar and brain stem malformation, hypotonia, and developmental delay. Clinical manifestations and severity of the syndrome vary.	1/92	1	99%
Lipoamide dehydrogenase deficiency (*DLD*)	Variable presentation that ranges from early-onset neurologic disease to adult-onset disease that is primarily hepatic. Early-onset neurologic disease presents in infancy with hypotonia, lethargy, vomiting, and progressive encephalopathy, resulting in death within the first or second year of life. Adult-onset primarily hepatic disease has a variable onset from infancy to the fourth decade and presents with liver injury or failure, which is usually preceded by nausea and vomiting.	1/94	2	99%
Maple syrup urine disease type 1B (*BCKDHB*)	Most commonly presents in the first few days of life with irritability, poor feeding, lethargy, and intermittent apnea, and typically progresses to coma and death within 7 to 10 days if untreated.	1/113	3	99%
Mucolipidosis type IV (*MCOLN1*)	Early onset severe psychomotor delay and progressive visual impairment due to corneal clouding and retinal degeneration; while most affected individuals remain neurologically static until age 30, approximately 15% will display neurological degeneration.	1/127	2	95%
NEB-related nemaline myopathy (*NEB*)	Presents within the first year of life with hypotonia, feeding difficulties, and muscle weakness of the face, neck, arms, and legs; muscle weakness is static or progresses very slowly, but lifespan is not usually decreased.	1/108	1	99%
Niemann-Pick disease type A (*SMPD1*)	Lysosomal storage disorder characterized by hepatosplenomegaly, delayed physical and mental development, hypotonia, rigidity, intellectual disability, and death, typically by age 3.	1/90	4	90%
Tay-Sachs disease (*HEXA*)	Lysosomal storage disorder leading to neurological deterioration. In its severe form, it leads to loss of motor skills beginning at 3 to 6 months of age and progresses to blindness, seizures, total incapacitation, and eventual death, typically by 4 years of age.	1/30	7 (5 pathogenic variants, 2 pseudodeficiency alleles)	94%
Usher syndrome type 1F (*PCDH15*)	Congenital, bilateral, profound sensorineural hearing loss, adolescent-onset retinitis pigmentosa, and loss of vestibular function.	1/72	1	62%
Usher syndrome type 3 (*CLRN1*)	Post-lingual, progressive hearing loss, late-onset progressive vision loss due to retinitis pigmentosa, and variable loss of vestibular function.	1/143	1	98%

* Order ARUP test code 2013661