



PRECONCEPTION AND PRENATAL GENETIC SCREENING POCKET FACTS

During the preconception and prenatal period, a variety of screening and testing options are available for women and families. The screening options can take the form of screening for chromosomal disorders, screening for neural tube defects, or screening for single gene disorders.

This pocket guide will present “pocket facts” that assist with screening for single gene disorders that are generally available and widely utilized during the preconception and prenatal period. The disorders covered include: cystic fibrosis, fragile X, hemoglobinopathies, and conditions more common in the Eastern European Jewish population.

While this pocket guide does not offer the complete resource on these conditions, it offers reference tables to help with the testing process.

Selected online resources are listed here for additional information:

- www.genetests.org
- www.marchofdimes.com/gyponline
- www.nsgc.org/resourcelink.cfm

CYSTIC FIBROSIS

Cystic fibrosis (CF), an autosomal recessive disorder, is a chronic lung condition associated with gastrointestinal malabsorption due to faulty chloride ion transport. There are > 1000 mutations in the CF gene that can cause either classical or non-classical forms of CF. The American College of Medical Genetics (ACMG) recommends using the standard screening panel that includes 23 of the most common mutations found in a pan-ethnic United States population.¹ Carrier frequencies and detection rates vary across different ethnic groups.² Therefore, the patient’s ethnic background should be provided to the laboratory for accurate interpretation of test results.³ While screening negative for CF mutations will lower the risk for a couple, a negative result does not entirely eliminate the risk of having an affected fetus.²

CYSTIC FIBROSIS INCIDENCE CARRIER FREQUENCIES AND DETECTION RATES BY ETHNICITY²

Ethnicity	Disease incidence	Carrier frequency	Carrier detection rate	Prenatal detection rate	Approximate risk of affected fetus after negative test in one parent
Ashkenazi Jewish	1:2,300	1:24	94%	89%	1:83,000
Caucasian	1:2,500	1:25	88%	78%	1:21,000
Hispanic	1:13,500	1:58	72%	52%	1:18,000
African American	1:15,100	1:61	65%	42%	1:54,000
Asian American	1:35,100	1:94	49%	24%	1:75,000

Note: Detection rate and residual risk data based on the original ACMG, ACOG, NIH-recommended 25-mutation panel.⁴

HEMOGLOBINOPATHIES

Hemoglobinopathies are a diverse group of inherited blood disorders that result from variations in the structure and/or synthesis of hemoglobin. A complete blood count (CBC) in combination with a hemoglobin electrophoresis is the standard of care for hemoglobinopathy screening.

Prenatal diagnosis of α and β thalassemia is possible only if mutations have been previously identified in both parents.

Prenatal diagnosis of the single mutation causing sickle cell disease is widely available.¹

Risk for carrying a hemoglobin variant based on ethnicity:¹

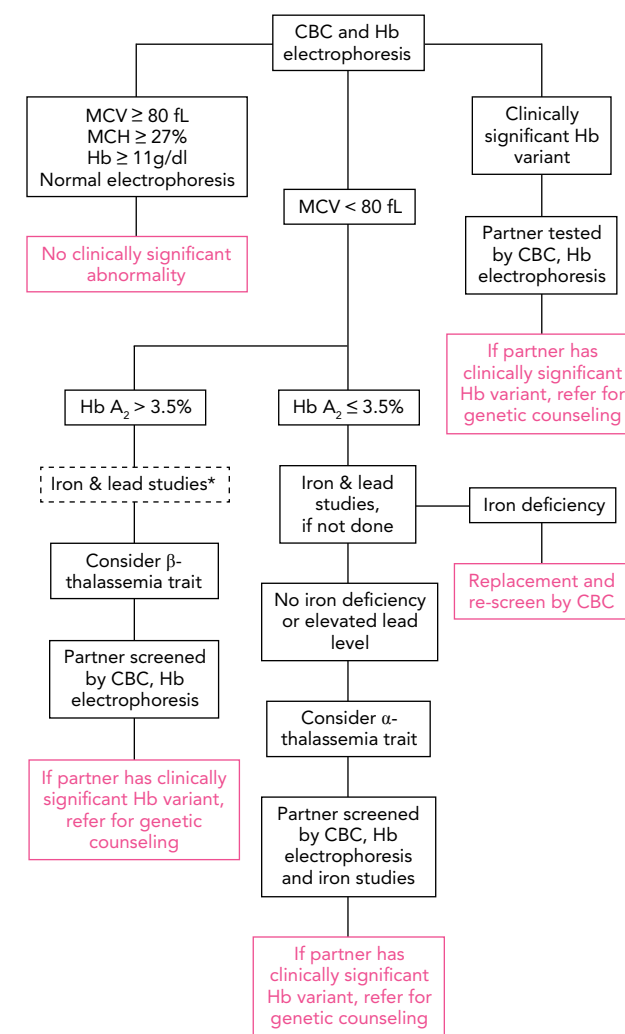
High risk: those with African, Southeast Asian ancestry, and Mediterranean ancestry.

Low risk: those with northern European, Japanese, Native American, Inuit (Eskimo), and Korean ancestry.

However, ethnicity is not always a good predictor of risk because individuals from at-risk groups may have children with a partner outside their ethnic group.¹

Table from Langfelder-Schwind et al. Cystic Fibrosis Prenatal Screening in Genetic Counseling: Practice Recommendations. J Genet Couns 2005; 14(1):1-15, with kind permission from Springer Science and Business Media.

BASIC ALGORITHM^{1,2}



*Iron or lead studies may be considered regardless of Hb A₂ level for possible β -thalassemia since Hb A₂ is not always reliable in the presence of iron deficiency or other circumstances.

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HEMOGLOBINOPATHIES

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CONDITIONS MORE COMMON IN THE EASTERN EUROPEAN JEWISH POPULATION

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Note: All URLs were accessed on October 30, 2006.

FRAGILE X SYNDROME

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CONDITIONS MORE COMMON IN THE EASTERN EUROPEAN JEWISH (EEJ) POPULATION

The American College of Obstetricians and Gynecologists (ACOG) recommends offering carrier screening for Tay-Sachs disease, cystic fibrosis, Canavan disease and familial dysautonomia to individuals of EEJ descent (Ashkenazi Non-Sephardic).¹⁻⁴ (See Table 1A). The American College of Medical Genetics has made similar carrier screening recommendations for cystic fibrosis (CF), Tay-Sachs and Canavan disease.^{1,5} ACOG has stated “individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening” for mucopolidosis IV, Niemann-Pick disease Type A, Fanconi anemia group C, Bloom Syndrome and Gaucher disease. (See Table 1B.) Note: Since individuals from at-risk groups may marry or have children with a partner outside their ethnic group, ethnicity is not always a good predictor of risk.

Tay-Sachs Disease Severe progressive neurodegenerative condition, usually fatal by 5 years. (See Table 1A for specific sensitivity.)

Cystic fibrosis Sensitivity of testing is higher in the EEJ population. (See CF section in this guide.)

Canavan Disease Severe neurodegenerative condition; usually is fatal by 3 to 5 years of age.

Niemann-Pick Disease (Type A) Associated with failure to thrive, hepatosplenomegaly, and progressive mental and physical deterioration; usually is fatal by 4 years of age.

Fanconi Anemia (Group C) Variable condition recognized in early childhood with severe anemia, failure to thrive and developmental delay. Up to one-fourth of patients will develop leukemia or other cancers. There are occasional heart, limb or kidney malformations.

Bloom Syndrome Characterized by prenatal growth restriction and butterfly rash in the mid-face region. Occasionally associated with mental deficiency. Significantly increased risk for various malignancies.

Gaucher Disease Variable condition presenting in childhood or adulthood in the majority of affected EEJ individuals. Characterized by hepatosplenomegaly, brittle bones and restricted movement of the joints.

Familial Dysautonomia Neurological condition characterized by decreased pain and temperature sensation, absence of overflow tearing, pernicious vomiting, spine curvature and blood pressure lability.

TABLE 1A. CONDITIONS RECOMMENDED BY ACOG FOR CARRIER SCREENING AMONG EASTERN EUROPEAN JEWISH POPULATIONS.

Disease	Disease incidence in Ashkenazi Jewish populations	Testing method	Ashkenazi Jewish carrier frequency	Non-Ashkenazi Jewish carrier frequency	Ashkenazi Jewish carrier detection rate	Non-Ashkenazi Jewish carrier detection rate
Tay-Sachs ^{1,6}	1/3,600 before population based carrier screening.	DNA analysis for Jewish individuals. Hex A enzyme serum and/or leukocyte activity in low-risk populations.*	1/30	General population risk = 1/300. Higher in individuals of Celtic, French, Cajun and Pennsylvania Dutch backgrounds.	94% for the six most common mutations by DNA. 98% by Hex A enzyme activity.	59% for the six most common mutations by DNA.
Cystic Fibrosis ⁷	1/2,300	DNA	1/24	See CF table	89% for the most common mutations.	See CF table
Canavan Disease ⁸	1/6,400 - 1/13,456	DNA	1/40-58	Unknown	98% for the four most common mutations.	40%-60%
Familial Dysautonomia ⁹	1/3,700	DNA	1/36	< 1/150	> 99% for the two most common mutations.	Unknown

*Hex A enzyme analysis on pregnant women and those taking oral contraceptives **must** be done on leukocytes.

TABLE 1B. CONDITIONS IN WHICH ACOG RECOMMENDS INDIVIDUALS OF EASTERN EUROPEAN JEWISH DESCENT INQUIRE ABOUT THE AVAILABILITY OF CARRIER SCREENING.

Disease	Disease incidence in Ashkenazi Jewish populations	Testing method	Ashkenazi Jewish carrier frequency	Non-Ashkenazi Jewish carrier frequency	Ashkenazi Jewish carrier detection rate	Non-Ashkenazi Jewish carrier detection rate
Niemann-Pick (Type A) ¹⁰⁻¹²	1/40,000	DNA	1/70	Unknown	92% for the three most common mutations	Unknown
Fanconi Anemia (Group C) ^{13,14}	1/100,000 in general population, Group C = ~15% of cases	DNA	1/89	1/300 for all groups	85% for the two most common mutations	Unknown
Bloom Syndrome ^{15,16}	< 300 cases reported	DNA	1/100	Unknown	97%-98% for the single mutation	Unknown
Gaucher Disease ^{17,18}	1/1000	DNA	1/10	Unknown	90% for the four most common mutations	50%-60%
Mucopolidosis Type IV ^{19,20}	Unknown	DNA	1/100-1/127	Unknown	95% for the two most common mutations	6-10%

FRAGILE X SYNDROME

Fragile X syndrome, the most common form of inherited mental retardation, is a condition caused by the presence of a variable length, triplet repeat CGG nucleotide expansion within the fragile X gene, *FMR1*. It is inherited in an X-linked fashion. Almost all males and approximately half of females with the full mutation have some degree of mental retardation, with males being more severely affected.¹ Premutation carriers can have additional consequences such as premature ovarian failure among women and fragile X-associated tremor/ataxia syndrome (FXTAS). The stability of the CGG repeat number is important when counseling for fragile X syndrome and is influenced by the gender of the carrier, the size of the repeat and the presence of AGG nucleotide interruptions within the repeat.^{2,3} The following table describes classifications based on ranges of CGG repeat numbers.

Repeat Number ⁴	Classification
~5 to ~44	Stable
~45 to ~54	Intermediate/Gray zone
~55 to ~230	Premutation
> 230	Full mutation

Expansion into full mutation only happens through transmission from a mother carrying a premutation.³ When interpreting repeat numbers in the gray zone, family and clinical history needs to be taken into account, since not all repeats will expand. In these cases, the risk of expansion to a full mutation occurs in later generations, once an individual is found to have a premutation.² Molecular DNA analysis

AUTOSOMAL RECESSIVE INHERITANCE*

- If both members of a couple are carriers of a specific condition, each of their offspring has a 1-in-4 (25%) chance of having the condition.
- Carriers have no physical symptoms.

*All conditions described in this pocket guide, with the exception of fragile X, are autosomal recessive.

ACKNOWLEDGMENTS

Modified from Genetic Screening Pocket Facts originally developed in 2001 by the Comprehensive Genetic Disease Program at the NYS Institute

(PCR and Southern blot) is the method of choice for determining CGG repeat number and methylation status.

Number of Maternal Premutation CGG Repeats ³	% Expanded to Full Mutation
55-59*	3.7%
60-69	5.3%
70-79	31.1%
80-89	57.8%
90-99	80.1%
≥ 100	98.4%

*Note: To date, no female with fewer than 59 repeats has had a child with a full mutation.

General population screening for fragile X syndrome is not recommended at this time. Populations who should be offered testing:⁵

- Any child or adult with a developmental disability of unknown etiology.
- Any individual who has a diagnosis on the autism spectrum.
- Individuals with a family history of unexplained mental retardation or developmental delay.
- Individuals with a family history of fragile X syndrome.
- Fetuses of carrier mothers.
- Women experiencing fertility problems associated with high follicle-stimulating hormone (FSH) levels.
- Men and women experiencing late onset intention tremor/ataxia of unknown origin.

for Basic Research in Developmental Disabilities, Staten Island, New York 10314 with funding from the March of Dimes.

For more information, contact the March of Dimes via e-mail at: askus@marchofdimes.com

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Preconception and Prenatal Genetic Screening Pocket Facts, #09-2120-06 12/06

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