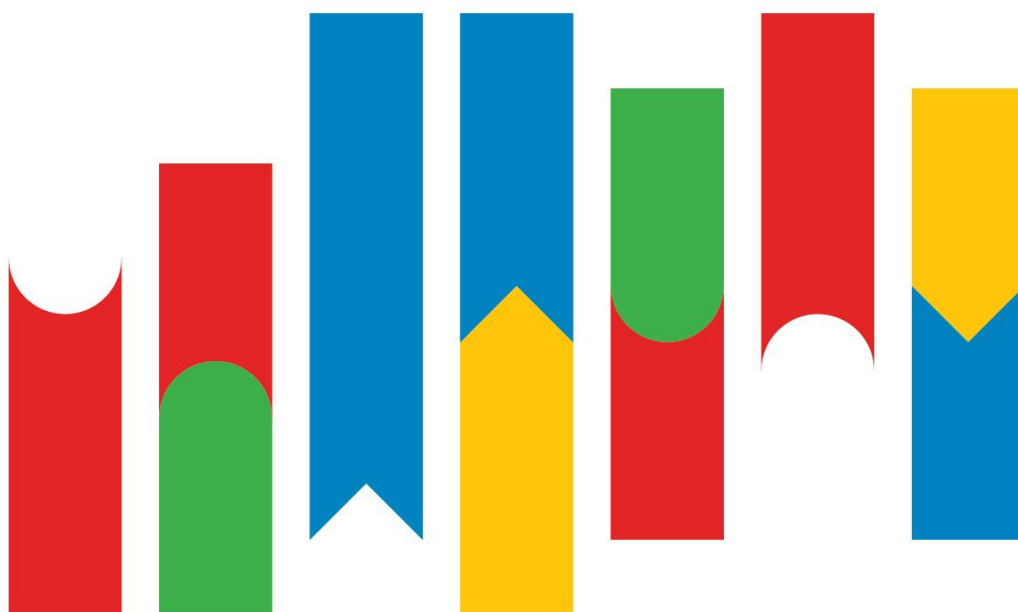


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Technical Bulletin



DNA life

3-Methylcrotonyl-CoA carboxylase deficiency

Report Type: Carrier Status

About: 3-methylcrotonyl-coA carboxylase (MCC) deficiency is an inherited organic acid disorder that can lead to brain damage in infants and young children. Symptoms may also include poor appetite, nausea, vomiting, extreme sleepiness, irritability, low muscle tone, and muscle weakness. If not treated, breathing problems, seizures, liver failure, coma and sometimes even death can occur. With prompt and lifelong treatment, children with MCC deficiency can often live normal lives. The appearance of clinical symptoms in MCC deficiency is variable, and some children with MCC deficiency never have symptoms. Even as adults, some people with MCC deficiency never have symptoms and are only identified when a sibling is diagnosed.¹

Genetics: MCC deficiency is caused by mutations in either the MCCC1 or the MCCC2 genes which encode the alpha and beta protein subunits, respectively, of an enzyme called 3-methylcrotonyl-coA carboxylase that is necessary for breaking down the amino acid leucine.^{2,3,4} Because of the defect, toxic levels of 3-hydroxy-isovaleric acid and 3-methylcrotonyl-glycine accumulate in the body and cause brain damage.^{2,3}

Most mutations in the tested genes are private, meaning they are only carried in individual families or small populations.³

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified 3-methylcrotonyl-coA deficiency as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test includes nine mutations in the MCCC1 and MCCC2 genes.

MCCC1 [A289V, L437P, D532H, R385S]; MCCC2 [E99Q, S173L, R193C, V339M, I437V]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
MCCC1	German and Turkish	4%	1 in 146	1 in 151

^aPercentage of affected patients carrying mutations detected by this test.³

^bCarrier risk before testing.³

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with 3-methylcrotonyl-coA carboxylase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
271.8 Other specified disorders of carbohydrate transport and metabolism Applies to: • Essential benign pentosuria • Fucosidosis • Glycolic aciduria • Hyperoxaluria (primary) • Mannosidosis • Oxalosis • Xylosuria • Xylulosuria	V82.71 Screening for genetic disease carrier status

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Abacavir hypersensitivity

(DC:TB-0224.001 06DEC2012)

Report Type: Pharmacogenetics

About: Abacavir, which is used to treat HIV infection, is well tolerated by most people, but some individuals become hypersensitive with symptoms that include fever, skin rash, fatigue, gastrointestinal problems and respiratory problems. Hypersensitivity can be severe and, in rare cases, fatal.

Genetics: The mechanism of abacavir hypersensitivity is not known, but clinical symptoms suggest an immunological reaction influenced by genetic factors. Human leukocyte antigen-B (HLA-B) genetic variants have been associated with immunological response. Many studies have demonstrated an increased risk for abacavir hypersensitivity in patients with a variant HLA-B allele, HLA-B*5701.^{1,2,3,4} Genetic testing for this allele can indicate whether an individual may be hypersensitive to abacavir.

Genetic testing for HLA-B*5701 prior to abacavir therapy has been shown to reduce the incidence of abacavir hypersensitivity.⁵ In a 2008 *New England Journal of Medicine* study, screening HIV-1 infected subjects for the presence of HLA-B*5701 resulted in a 60% reduction in the incidence of clinically-suspected hypersensitivity compared to standard of care with no genetic screening. Suspected abacavir hypersensitivity reactions were reported in 7.8% (66/847) of subjects who received no HLA-B*5701 screening prior to abacavir treatment. In contrast, of patients who received abacavir only if they were negative for HLA-B*5701, only 3.4% (27/803) ($p < 0.0001$) had suspected abacavir hypersensitivity reactions. These results predicted that 61% of HLA-B*5701 positive subjects would develop abacavir hypersensitivity during treatment with abacavir as compared to 4.5% of HLA-B*5701 negative subjects. Several other studies have replicated the clinical utility of screening for the presence of HLA-B*5701 prior to abacavir therapy.^{6,7,8}

Recommendations: FDA's boxed warning on the Ziagen label states that patients with the HLA-B*5701 allele are at high risk for experiencing hypersensitivity reactions. The label also contains a recommendation for screening for the HLA-B*5701 allele before the initiation of abacavir treatment, regardless of whether or not the patient has tolerated abacavir in the past.⁹

The NIH Clinical Pharmacogenetics Implementation Consortium Guidelines strongly recommend HLA-B*5701 screening before abacavir is administered and do not recommend its use in HLA-B*5701-positive individuals. Moreover, the NIH also notes that patients testing negative for HLA-B*5701 who are administered abacavir should also be carefully monitored for hypersensitivity because they still have a low (3%) risk of developing a hypersensitivity reaction.¹⁰ These recommendations are consistent with those of the U.S. Department of Health and Human Services and the European Medicines Agency.¹⁰

Possible Outcomes: Hypersensitive, Typical Risk

Markers or Alleles Tested: HLA-B [HLA-B*5701]

The test includes rs2395029, which is a marker for the HLA-B*5701 allele in Caucasians and Hispanics.^{11,12,13,14} The linkage between rs2395029 and HLA-B*5701 has not been investigated in African or Asian populations (see Limitations and Warnings).

Specificity and sensitivity of the test: The presence of HLA-B*5701 has a positive predictive value of approximately 47% to 61% for either immunologically confirmed (IM) or clinically diagnosed (CL) abacavir hypersensitivity. Thus, 47% to 61% of patients who have the HLA-B*5701 allele would be predicted to develop a hypersensitive reaction to abacavir. The negative predictive value of the test is 96% to 100%. Thus, almost all patients who do not have the HLA-B*5701 allele will not develop a hypersensitive reaction to abacavir.^{5,10,15}

Measurement	Method of Diagnosis	Percentage of Patients
Sensitivity - % of people with hypersensitivity who will get a positive test result	IM*	100%
Sensitivity - % of people with hypersensitivity who will get a positive test result	CL*	46% - 50%
Specificity - % of people without hypersensitivity who will get a negative test result	IM/CL	97%
Positive Predictive Value - % of people with a positive test result who will become hypersensitive	IM/CL	47% - 61%
Negative Predictive Value - % of people with a negative test result who will not become hypersensitive	IM/CL	96% - 100%

*IM, immunologically confirmed by initial clinical evaluation, followed by a positive result on an abacavir skin patch test; CL, clinically diagnosed by reported symptoms.

Ethnic Distribution of Tested Alleles: Abacavir hypersensitivity is observed in about 8% of individuals of Western European ancestry^{5,6} but is much less common in East Asian populations.^{16,17,18} Correspondingly, the prevalence of HLA-B*5701 is about 6% to 7% in Western Europe and U.S. Caucasians but less than 1% in East Asian (Korean, Chinese, Japanese, Taiwanese) and African populations. The prevalence of the risk allele is higher in South and Southeast Asian populations; the frequency is about 5% to 20% in Asian Indian populations and about 4% among Thais.¹⁰

Limitations and Warnings: The marker tested for HLA-B*5701 applies to patients of Caucasian or Hispanic ethnicity and may not apply to other ethnic populations. Approximately 6% of patients that receive a positive test result may not be HLA-B*5701-positive and, thus, may not be at increased risk of a hypersensitivity reaction to abacavir.^{10,12,13} If clinically indicated, patients of non-Hispanic or non-Caucasian ethnicity could be advised to undergo HLA sequencing to assess their risk of abacavir hypersensitivity. Patients testing negative for HLA-B*5701 may develop abacavir hypersensitivity.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.27 Other drug allergy	N/A
Applies to:	
• Allergic reaction NEC (due) to correct medical substance properly administered • Drug allergy NOS • Drug hypersensitivity NOS • Hypersensitivity (due) to correct medical substance properly administered	

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Acrodermatitis enteropathica

Report Type: Carrier Status

About: Acrodermatitis enteropathica (AE) is a very rare inherited zinc deficiency disease that occurs in early infancy if the child is fed cow's milk shortly after weaning from breastfeeding. The disease is characterized by periorificial (around the natural orifices) and acral (in the limbs) dermatitis, alopecia (loss of hair), and diarrhea. Generalized zinc deficiency causes immune system impairment, infections and failure to thrive. If not treated, multiple organ failure can cause death. However, zinc supplementation can reverse all symptoms.¹

Genetics: AE is caused by mutations in the SLC39A4 gene, which encodes a transmembrane protein called the zinc transporter ZIP4.² ZIP4 is highly expressed in the duodenum and jejunum for zinc absorption and in the kidney for zinc reabsorption. Mutations in SLC39A4 significantly decrease the zinc uptake activity of the ZIP4 protein, causing severe zinc deficiency, growth retardation, immune system dysfunction, dermatitis, diarrhea and alopecia.

The test includes two common mutations in the SLC39A4 gene found in Tunisian families. 1223_1227delCCGGG was found in six unrelated families^{2,3,4} and L48X was found in three unrelated families.⁴

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes two mutations in the SLC39A4 gene.

SLC39A4 [1223_1227delCCGGG, L48X]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
SLC39A4	Tunisian	68%	1 in 500	1 in 1,560

^aPercentage of affected patients carrying mutations detected by this test.²

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of in 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.⁵ The actual carrier rate and the post-test residual risk are likely to be lower.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with acrodermatitis enteropathica, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
686.8 Other specified local infections of skin and subcutaneous tissue Applies to: • Bacterid (pustular) • Dermatitis vegetans • Ecthyma • Perlèche	V82.71 Screening for genetic disease carrier status

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Age-related macular degeneration

Report Type: Health Conditions

About: Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries.¹ This progressive neurodegenerative disease is characterized by the loss of photoreceptors in the macula and presence of drusen. Risk factors for AMD include age and cigarette smoking, and research indicates that genetic factors are also associated with the disease.^{2,3}

Genetics: Based on twin studies, it is estimated that 46% to 71% of the variation in the overall severity of age-related macular degeneration is genetically determined.⁴

The complement system plays a crucial role in the body's defense against harmful bacteria or pathogens, and dysfunction of the complement cascade may lead to significant damage to macular cells, resulting in atrophy and degeneration.⁵ The test includes variants in three genes that encode proteins of the complement system: A307A (rs1061147) in the CFH gene, IVS10 (rs547154) in the C2 gene, and P314L (rs1047286) in the C3 gene. These variants are associated with increased risk for AMD.^{1,5,6} The A69S variant of ARMS2, which is a mitochondrial protein, is also associated with increased risk for AMD.^{7,8}

The CFH gene encodes complement factor H, which is a key regulator of the complement system. A defect in CFH may lead to uncontrolled activation of the complement system, resulting in more inflammation and damage to the cells in the retina.⁹ Complement component C2 is a protease that is involved in the activation of the classical complement pathway.⁹ Complement component C3 plays an important role in the activation of both classical and alternative complement pathways.^{5,10}

Recommendations: Screening for impaired visual acuity should be performed in older adults as recommended by the U.S. Preventative Services Task Force.¹¹

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
C3	rs1047286	T	1.50	Caucasian	20.3%	Validated	19168221
ARMS2	rs10490924	T	2.20	Asian	44.0%	Validated	18436811
ARMS2	rs10490924	T	2.69	Caucasian	19.9%	Validated	16174643
CFH	rs1061147	A	2.34	Caucasian	37.2%	Validated	15870199
C2	rs547154	T	0.44	Caucasian	6.2%	Validated	16518403

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
362.50 Macular degeneration (senile), unspecified	N/A

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Alpha-1 antitrypsin deficiency

Report Type: Carrier Status

About: Alpha-1 antitrypsin deficiency (AATD) is one of the most common, potentially fatal, single-gene diseases in the world.¹ The disease can cause emphysema and chronic obstructive pulmonary disease (COPD). Individuals with AATD may remain healthy throughout their lives, but AATD leaves an individual at great risk for developing potentially fatal lung and liver disease.^{2,3}

Genetics: AATD is caused by mutations in the SERPINA1 gene, which encodes the protease inhibitor alpha-1 antitrypsin protein (AAT). AAT inactivates the enzyme neutrophil elastase (NE), which normally aids in the digestion of bacteria and cellular debris. If left unchecked, NE damages the alveoli of the lung, leading to emphysema and COPD.³

More than 100 SERPINA1 mutations have been identified.³ While some are harmless, others cause a moderate to severe deficiency of AAT in the blood. There are three main alleles of the SERPINA1 gene: M (normal), Z (disease-causing) and S (sometimes disease-causing).³ The S allele is the most common variant, found in 1 in 30 people in North America and 1 in 18 in Southern Europe.¹ The Z allele is present in 1 in 109 people in North America and 1 in 65 people in Northern Europe.¹

The Z allele encodes an altered AAT protein that accumulates in the liver, resulting in damage to lung alveoli and liver cells.⁴ Ninety-five percent of individuals with AATD are homozygous for the Z allele (ZZ genotype) and have reduced AAT plasma levels.³ The ZZ genotype is also associated with emphysema in adults and with liver disease in children and adults. The onset of lung disease in smokers with AATD is between 40 and 50 years old, whereas the onset is delayed to age 60 in non-smokers, who often can have a normal life span.³

Patients with the MZ phenotype who smoke display impaired lung function, and ZS heterozygotes have an increased risk of lung or liver disease. MS and SS individuals do not appear to be at an increased risk for lung or liver disease.^{3,4,5}

AATD has been identified in virtually all populations and ethnic groups but is most common in individuals of Northern European (Scandinavian and British) and Iberian (Spanish and Portuguese) descent. It is estimated that one in 2,500 U. S. Caucasians has AATD.¹ Though individuals with AATD may remain healthy throughout their lives, they are at great risk for developing potentially fatal lung and liver disease.⁶ AATD is not a rare disease but has been infrequently diagnosed.⁶

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes two mutations in the SERPINA1 gene.
SERPINA1 [S allele, Z allele]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
SERPINA1	North America	95%	1 in 12	1 in 221
SERPINA1	Northern Europe	95%	1 in 15	1 in 281
SERPINA1	Southern Europe	95%	1 in 7	1 in 121
SERPINA1	Middle East and North Africa	95%	1 in 16	1 in 301
SERPINA1	Africa	95%	1 in 12	1 in 221
SERPINA1	Far East Asia	95%	1 in 570	1 in 11,381
SERPINA1	Southeast Asia	95%	1 in 84	1 in 1,661

^aPercentage of affected patients carrying mutations detected by this test.³

^bCarrier risk before testing.¹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other very rare mutations associated with alpha-1 antitrypsin deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
273.4 Alpha-1-antitrypsin deficiency	V82.71 Screening for genetic disease carrier status
Applies to:	
• AAT deficiency	

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Alzheimer's disease, late onset

Report Type: Health Conditions

About: Late-onset Alzheimer's disease (AD) accounts for approximately 95% of AD cases in the U.S.¹ This neurodegenerative disease is characterized histologically by the presence of amyloid beta plaques and neurofibrillary tangles in cortical white matter, and clinically by memory loss.² The strongest risk factor for AD is age. The risk of AD increases with every decade starting at about 60 years of age, so that more than 40% of people 85 or older are affected with AD. The second strongest risk factor is family history of the disease. Other risk factors for AD may include elevated cholesterol levels, coronary artery disease and abnormal glucose regulation. Research indicates that genetic factors, such as variants in the APOE gene, are also associated with onset of AD.³

Genetics: Although the genes and mutations that contribute to developing late-onset AD are not completely understood or identified, the epsilon-4 variant of the apolipoprotein E gene (APOE) has been associated with both, the lifetime risk for, and the age-of-onset of AD.^{4,5} APOE has been confirmed as a risk factor in many studies comprised of individuals ranging in ages between 40 to 90 years.⁶ The APOE gene encodes a protein that was originally identified as a cholesterol transport molecule, and yet its role in the development of AD is not well understood.

There are three common APOE alleles which have been studied with respect to their effects on AD risk. The APOE epsilon-2 allele is the least common, and is found in approximately 7% of unaffected individuals and in only 4% of people affected with AD, indicating that this allele may be partially protective against development the disease. APOE epsilon-3 is the most common allele and is found in nearly 80% of people not affected with AD. It is not believed to have protective or risk properties, but rather is thought to play a neutral role.⁷

APOE epsilon-4 is the risk conferring allele, found in approximately 14% of people not affected with AD, but in nearly 40% of all people affected with AD. An individual with one allele of APOE epsilon-4 has an increased likelihood of developing AD, and having two alleles increases risk further. In addition, epsilon-4 is associated with a tendency to develop AD at an earlier age than for those individuals who do not have the epsilon-4 allele.⁸ However, it is important to note that many people who are homozygous for epsilon-4 do not develop AD and are free of dementia at a late age, suggesting that AD is caused by multiple factors: some genetic, some environmental and some due to the interaction between genes and environment.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested: The test includes two markers (rs429358, rs7412) that are used to determine a patient's APOE-epsilon 4 status.

rs429358 ^a genotype	rs7412 ^a genotype	APOE diplotype ^b	Caucasian ^c	African descent ^c	Asian ^c	Hispanic ^c	AD Risk ^d
T/T	T/T	e2/e2	0.9%	0.9%	0.1%	0%	Average risk

T/T	C/T	e2/e3	12.0%	9%	8.5%	5.6%	Average risk
T/T	C/C	e3/e3	60.6%	55.9%	73.9%	72.2%	Average risk
C/T	C/T	e2/e4	2.1%	0%	1.2%	0%	Above average risk
C/T	C/C	e3/e4	22.4%	30.6%	15.7%	20%	Above average risk
C/C	C/C	e4/e4	2.0%	3.6%	0.7%	2.2%	Increased risk

^aThe APOE alleles are defined⁹ by two SNPs: rs429358 (C/T) and rs7412 (C/T). Thus, epsilon-2 is rs429358-T, rs7412-T; epsilon-3 is rs429358-T, rs7412-C; epsilon-4 is rs429358-C, rs7412-C. The genotype shows the SNP status for both chromosomes.

^bAPOE alleles: epsilon-2 (e2), epsilon-3 (e3), epsilon-4 (e4). The diplotype shows the allele status for both chromosomes.

^cDiplotype frequency in a control (unaffected) population.¹⁰

^dRisk of late-onset Alzheimer's disease.⁶

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
331.0 Alzheimer's disease	N/A

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Aminoglycoside antibiotics-induced hearing loss

(DC:TB-0225.001 06DEC2012)

Report Type: Pharmacogenetics

About: For more than 60 years, aminoglycoside antibiotics such as streptomycin, gentamicin, neomycin, paromomycin, kanamycin, spectinomycin, amikacin, netilmicin and tobramycin have been widely used. They continue to be used, especially in developing countries, for the treatment of severe bacterial infections. However, aminoglycoside use also carries the risk of both nephrotoxicity and ototoxicity.¹ Certain genetic variants further increase the risk of aminoglycoside-induced ototoxicity.

Genetics: The most frequent cause of inherited aminoglycoside-induced ototoxicity is the 1555A>G mutation in the mitochondrial MT-RNR1 gene.² Mitochondria, which are organelles that provide energy for the cell, have DNA molecules (mtDNA) that are distinct from the chromosomal DNA in the nucleus of the cell. The MT-RNR1 gene encodes an RNA component of the mitochondrial ribosome called 12S rRNA.³ The mechanism by which the 1555A>G mutation leads to the death of hair cells in the inner ear after administration of aminoglycoside antibiotics is not completely understood, but may involve decreased mitochondrial protein synthesis, decreased energy production and increased reactive oxygen species formation.¹

Individuals with the 1555A>G mutation are at risk because even a single course (a standard multi-dose regimen prescribed by a physician) of treatments with aminoglycoside antibiotics will cause severe hearing loss. In every known case, individuals always suffer significant and irreversible hearing loss within a few days to weeks after aminoglycoside treatment.² Since mitochondrial genes are maternally inherited, as all the cytoplasm, which includes mitochondria, comes from the egg, every child of a female carrier of the mutation is likely to inherit the 1555A>G mutation, while the children of male mutation carriers will not.²

Additionally, individuals carrying the 1555A>G mutation are at risk for late-onset sensorineural hearing loss even without exposure to aminoglycoside antibiotics. Approximately 40% and 70% of 1555A>G carriers will develop hearing loss by age 30 and 65, respectively.^{2,4,5}

Each cell contains thousands of mtDNA molecules because there are multiple copies of the mtDNA molecule in each of the hundreds of mitochondria that are found in the cell.⁴ The 1555A>G mutation is always homoplasmic, meaning that all copies of the mtDNA in the cell will carry the mutation.^{2,4,5}

Mode of Inheritance: Maternal²

Possible Outcomes: Typical Risk, Do Not Prescribe

Markers or Alleles Tested: MT-RNR1 [1555A>G]

Recommendations: Patients with the 1555A>G mutation should avoid treatment with aminoglycoside antibiotics, and alternative antibiotics should be prescribed when necessary. However, these patients may still be at risk of hearing loss even without exposure to aminoglycoside antibiotics. These patients should also avoid noise exposure, and regular audiometric assessment may be indicated.²

Female patients with the 1555A>G mutation who have or are planning to have children should inform their pediatrician so that aminoglycoside antibiotics can be avoided. Patients with the 1555A>G mutation should be counseled that the mutation is transmitted maternally and that other family members may also be at risk of aminoglycoside-induced hearing loss.²

Ethnic distribution of tested alleles: The 1555A>G mutation is found in all ethnic groups, is carried by approximately 1 in 500 people in Western countries and is found in 20-30% of deaf individuals from Spain and Asia.^{2,6,7}

Limitations and Warnings: Hearing loss is always a possible side effect of aminoglycoside use, even in the absence of the 1555A>G mutation.^{1,2,4,8}

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
976.6 Poisoning by anti-infectives and other drugs and preparations for ear, nose, and throat	N/A

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Amyotrophic lateral sclerosis (familial)

Report Type: Carrier Status

About: Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease, is a progressive, neurodegenerative disease that affects motor neurons in the brainstem and spinal cord. ALS patients gradually lose their strength, their ability to walk, and the use of their hands and arms. Eventually, ALS patients die from respiratory failure. The median age of onset is 55 years, and death usually occurs within one to five years after onset.^{1,2}

Genetics: Most cases of ALS occur in individuals with no family history of ALS (sporadic ALS). However, 10% of ALS cases can be attributed to an inherited genetic defect (familial ALS). Single mutations responsible for familial ALS have been found in at least six genes.^{1,2} The mechanisms by which mutations in this diverse group of genes lead to ALS are not well understood, but the mutations ultimately lead to death of motor neurons, which is the hallmark of ALS.^{3,4}

Mutations in the ALS2 gene cause type 2 familial ALS. Type 2 familial ALS usually begins in early childhood or adolescence and slowly worsens for 10-15 years. The ALS2 gene codes for the alsin protein, which may interact with factors that regulate vesicle transport and microtubule assembly. The test includes the 1867delCT mutation in the ALS2 gene, also known as L623FS.⁵

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: NA

Mutations Tested: The test includes one mutation in the ALS2 gene.

ALS2 [1867delCT]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with amyotrophic lateral sclerosis, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

335.20 Amyotrophic lateral sclerosis	V82.71 Screening for genetic disease carrier status
Applies to:	
• Motor neuron disease (bulbar) (mixed type)	

References

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Amyotrophic lateral sclerosis (sporadic)

Report Type: Health Conditions

About: The incidence of sporadic amyotrophic lateral sclerosis (ALS) is 1.89 per 100,000/year in North America and Europe. This progressive neurodegenerative disease is characterized by motor neuron degeneration in the primary motor cortex, brainstem, and spinal cord, which causes muscular paralysis and atrophy.¹ Research indicates that genetic factors are associated with the disease.^{2,3}

Genetics: Most people who develop ALS do not have a family history of the disease. These cases are classified as sporadic ALS. However, about 10% of ALS patients have another affected family member and are classified as familial ALS (FALS). The clinical features of sporadic ALS and FALS are very similar. At least 11 genes associated with risk for familial ALS have been identified, but less progress has been made in uncovering the genetic causes of sporadic ALS.^{4,5} More than 38 candidate genes have been examined in at least 76 studies, but the results have been inconclusive or could not be replicated.⁶ Genome-wide association studies have identified three genes with possible association to sporadic ALS. Unfortunately, it has also been difficult to replicate these results.

One gene, DPP6, is included on the test because it showed an association with sporadic ALS in two studies, though it should be noted that there was an overlap of data between the studies.^{2,3} The marker rs10260404 in the DPP6 gene was associated with ALS in a study with cases and controls from the Netherlands, the U.S., Sweden and Belgium.³ This association was replicated in a second study of individuals from Ireland together with previously published data from the U.S. and the Netherlands cohorts.² However, one study with populations from Ireland, the U.S., the Netherlands and Poland⁷ and another study with populations from the U.S., Italy and Germany⁸ failed to find an association. Because of the conflicting evidence, the association of rs10260404 with ALS should remain tentative until more confirming evidence is found in independent studies with larger sets of patients.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
DPP6	rs10260404	C	1.20	Caucasian	43.8%	Preliminary	18084291

^aGene or locus containing the tested marker

^bMarkers tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
335.20 Amyotrophic lateral sclerosis	V82.71 Screening for genetic disease carrier status
Applies to:	
• Motor neuron disease (bulbar) (mixed type)	

References

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ApoE, type III hyperlipoproteinemia and CVD risk

Report Type: Health Conditions

About: Cardiovascular disease refers to a set of conditions that affect the heart and blood vessels. It is the leading cause of death worldwide.¹ Risk factors for cardiovascular disease include smoking, being overweight, hypertension and high cholesterol and triglyceride levels.² Risk of cardiovascular disease is also significantly increased in patients with type III hyperlipoproteinemia (HLP), a condition diagnosed primarily by a biochemical test for the presence of triglyceride-rich particles in plasma called β -VLDL.³ Type III HLP is also characterized by increased total cholesterol, LDL cholesterol, and triglyceride levels⁴ and an elevated VLDL cholesterol to triglyceride ratio.⁵ Through this elevation of blood lipids, type III HLP predisposes individuals to severe atherosclerosis and increased risk of cardiovascular disease⁴. This sustained cholesterol elevation also leads to development of xanthomas in some patients.⁶ Genetic factors are significant contributors to the development of type III HLP-related cardiovascular disease.

Genetics: The apolipoprotein E (APOE) gene encodes a ligand for the LDL receptor that is needed for lipoprotein clearance. The gene has three common alleles, ϵ 2, ϵ 3 and ϵ 4, that encode the E2, E3 and E4 isoforms of the protein, respectively. The APOE isoforms differ in their ability to bind lipoprotein receptors, with the E2 isoform binding with less than 2% of the strength of E3 or E4, which bind with approximately equal affinity.⁷ Type III HLP is observed primarily in patients who are homozygous for ϵ 2; more than 90% of affected patients are homozygous for ϵ 2.⁸ However, only 5% of patients with the homozygous genotype develop the disease.^{4,7} It is thought, therefore, that at least one additional pathogenic genetic and/or environmental factor, such as diabetes, obesity, low estrogen level, or hypothyroidism, might be necessary for the disease to develop⁴. Indeed, clinical symptoms of type III HLP tend to present in men in the fourth decade of life and in women after menopause.^{9,10}

Recommendations: For patients with an outcome of “Increased Risk”, consider earlier or increased frequency of screening for blood cholesterol levels, as suggested by the National Cholesterol Education Program (NCEP) Expert Panel and other groups.

Possible Outcomes: Increased Risk, Typical Risk

Markers Tested

Genotyping of APOE diplotype was performed in 86,067 healthy participants of mixed ethnicity (primarily from North America, Europe, and Asia),¹¹ as presented in the table below:

Gene ^a	Diplotype ^b	Population Frequency ^c	PMID ^d
APOE	e2/e2	0.007	17878422
APOE	e2/e3	0.116	17878422
APOE	e2/e4	0.022	17878422

APOE	e3/e3	0.623	17878422
APOE	e3/e4	0.213	17878422
APOE	e4/e4	0.019	17878422

^aGene containing the tested marker.

^bDiplotype tested.

^cEthnicity of the population in the corresponding study.

^dPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
429.2 Cardiovascular disease, unspecified • Arteriosclerotic cardiovascular disease [ASCVD] • Cardiovascular arteriosclerosis • Cardiovascular: ◦ degeneration (with mention of arteriosclerosis) ◦ disease (with mention of arteriosclerosis) ◦ sclerosis (with mention of arteriosclerosis)	N/A

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Argininosuccinate lyase deficiency

Report Type: Carrier Status

About: Argininosuccinate lyase deficiency (ASLD) is an inherited disease that can cause the accumulation of potentially fatal levels of ammonia in the blood of newborn infants.^{1,2,3} In the more common and serious neonatal form of ASLD, infants that appear normal at birth start accumulating ammonia and other toxic metabolites shortly thereafter. The affected infant may appear irritable, feed poorly, become lethargic, vomit, show poor muscle tone, suffer seizures and lose consciousness. If not treated promptly, the accumulation of toxic metabolites like ammonia can cause irreversible brain damage, seizures, coma and ultimately death. A milder form of ASLD can develop late in infancy or early childhood.^{4,5,6}

Genetics: Argininosuccinate lyase deficiency (ASLD) is caused by mutations in the ASL gene, which encodes an enzyme in the urea cycle called argininosuccinate lyase.^{1,2,3} Argininosuccinate lyase is responsible for splitting argininosuccinate into arginine and fumarate. Disease-causing mutations in the ASL gene reduce or eliminate the activity of argininosuccinate lyase, which blocks the urea cycle and leads to the accumulation of toxic levels of ammonia produced by the breakdown of protein.^{5,7}

The test includes the most common recurrent mutations in the ASL gene. ASLD has been reported in Caucasian and Arab populations. The Q354X mutation is very common in patients with ASLD in Saudi Arabia.⁷

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified argininosuccinate lyase deficiency as one of 29 diseases for which newborn screening should be mandated.⁸

Mutations Tested: The test includes seven mutations in the ASL gene.

ASL [D87G, R193Q, Q354X, R385C, Q116X, V178M, IVS5+1G>A]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
ASL	panethnic	50%	<1 in 500	1 in 999

^aPercentage of affected patients carrying mutations detected by this test.¹

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of in 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.⁹ The actual carrier rate and the post-test residual risk are likely to be lower.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with ASLD, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.6 Disorders of urea cycle metabolism Applies to: • Argininosuccinic aciduria • Citrullinemia • Disorders of metabolism of ornithine, citrulline, argininosuccinic acid, arginine, and ammonia • Hyperammonemia • Hyperornithinemia	V82.71 Screening for genetic disease carrier status

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Asthma

Report Type: Health Conditions

About: Asthma affected 9% of children below the age of 18 in 2007. This chronic lung condition is characterized by airway hyperresponsiveness and bronchoconstriction, which causes wheezing and difficulty breathing. Risk factors for asthma include atopy and family history.¹ Research indicates that genetic factors, such as variants in the ORMDL3 gene, are also associated with the disease.²

Genetics: The genetics of asthma are not well understood, and only one gene, ORMDL3, has a clear association with the condition. The rs7216389 marker is located near ORMDL3, a gene of unknown function. A number of studies have shown an association between the marker and susceptibility to asthma, including a large research program looking at asthmatics from Germany and Great Britain.² ORMDL3 has also been linked to asthma in studies looking at African American, Chinese and Hispanic populations.^{3,4,5} However, these projects were relatively small and further research is needed to confirm the link between ORMDL3 and susceptibility to asthma in these ethnic groups. The ORMDL3 gene has also been associated with exacerbated symptoms in patients with asthma; however, this observation also requires further validation.

The interleukin 1 receptor related gene 1 (IL1RL1) is a member of the interleukin receptor family of cytokine receptors and has been associated with asthma in early research reports.⁶

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
ORMDL3	rs7216389	T	1.50	Caucasian	48.7%	Validated	18395550
ORMDL3	rs7216389	T	1.62	Hispanic	56.0%	Validated	19133921
IL1RL1	rs1420101	A	1.16	Caucasian	35.0%	Preliminary	19198610

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in

genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
493.1 Extrinsic asthma Applies to: - Asthma: - allergic with stated cause - atopic - childhood - hay - platinum - Hay fever with asthma	N/A

References

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- Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature*. 2007;448:470-3.
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Atrial fibrillation

Report Type: Health Conditions

About: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. This heart condition is the leading cause of arrhythmia-related hospitalizations and can contribute to stroke. Risk factors for AF include age, diabetes, hypertension and heart failure. Research indicates that genetic factors are also associated with AF.^{1,2}

Genetics: The rs2200733 marker is associated with an increased risk of AF in many populations.^{3,4} How rs2200733 affects heart rhythm is unknown and may be mediated through genes in the surrounding area. The closest known gene is PITX2, which is important in controlling asymmetry of the developing heart.⁵ The next closest gene is ENPEP, which encodes an aminopeptidase responsible for the breakdown of angiotensin II in the vascular endothelium. However, mutations in these genes have not yet been shown to cause AF.

The T allele of rs2200733 was found to be associated with increased risk for atrial fibrillation in a large genome-wide association study conducted in Iceland.³ These results were replicated in the same study in a second and larger Icelandic population, as well as in two more groups of individuals of European ancestry from Sweden and the US. Collectively, these results showed that a T allele at rs2200733 increases the risk of AF. The association appears stronger for earlier onset AF in both U.S. and Icelandic groups; individuals younger than 60 years had the highest relative risk. Additionally, each T allele carried a risk of diagnosis 2.28 years earlier. A large follow-up study from four cohorts of individuals of European descent was conducted, and in all four populations, rs2200733 was strongly associated with AF.⁴ This study also showed an interaction with age of onset for the marker; younger individuals (less than 60 years old) had higher risk in three of the four populations studied. This marker was also studied in a Han Chinese population from Hong Kong. Although results were similar, the sample size for this population was too small to achieve statistical significance.³

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
PITX2	rs2200733	T	1.42	Asian	47.6%	Validated	17603472
PITX2	rs2200733	T	1.72	Caucasian	11.5%	Validated	17603472

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
427.31 Atrial fibrillation	N/A

References

1. Damani SB, Topol EJ. Molecular genetics of atrial fibrillation. *Genome medicine*. 2009;1:54.
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Autoimmune polyglandular syndrome, type I

Report Type: Carrier Status

About: Autoimmune polyglandular syndrome 1 (APS1), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is an autoimmune disease that affects the parathyroid and adrenal glands and causes ectodermal defects. APS1 is diagnosed when patients present with at least two out of the three main clinical symptoms: mucocutaneous candidiasis (thrush), hypoparathyroidism and adrenocortical insufficiency (Addison's disease). Patients also often develop additional endocrine and ectodermal symptoms well into the fifth decade of life that can include type 1 diabetes, hypothyroidism, hepatitis, ovarian or testicular failure, malabsorption, nail bed pitting, alopecia and vitiligo.¹

Genetics: APS1 is caused by mutations in the AIRE gene,² which encodes a transcription factor important for testing immune system cells for "self" recognition.³ Disease-causing mutations in the AIRE gene reduce or eliminate the body's ability to turn on the expression of "self" genes, allowing some immune cells that recognize 'self' to circulate and destroy specific organs, mainly in the endocrine system.

APECED is a rare disease in most populations, but the incidence of APECED in Finland, Sardinia and Iranian Jews is 1 in 25,000, 1 in 14,400 and 1 in 9,000, respectively.⁴

The test includes more than forty mutations in the AIRE gene, including the two most common mutations (R257X and 967-979del13) that cause APS1. These two mutations have a worldwide distribution and represent the major variants in European and U.S. populations. We also test for two mutations that are common among Sardinians and Iranian Jews (R139X and Y85C, respectively) where the incidence of APECED is particularly high.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes 44 mutations in the AIRE gene.

AIRE [C311fsX376 (1058delT), L397fsX478, A502fsX519, 64-69del6, IVS5-5delCTC (G218fsX284), S135fsX147 (c.402delC), 967-979del13, L417fsX478, P370fsX370, L323fsX372, M388fsX422, C434fsX479, H415fsX422, V80L, Y85C, C311Y, T16M, L29P, W78R, G228W, P252L, Q358X, P539L, R15C, F77S, M1L, R303P, L97P, C446G, E298K, K83E, R257X, Y90C, R139X, R203X, X546C, L28P, L93R, IVS11+1G>A (GT>AT, X476), IVS8+5G>T, IVS7+1G>A, IVS3-2A>T, IVS3+2T>C, C449fsX502 (1471delCinsTT)]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
AIRE	Finnish	71%	1 in 80	1 in 273

AIRE	Iranian Jews	100%	1 in 48	0
AIRE	Norwegian	48%	1 in 150	1 in 288
AIRE	Slovenian	67%	1 in 104	1 in 313
AIRE	Polish	71%	1 in 250	1 in 860

^aPercentage of affected patients carrying mutations detected by this test.

^bCarrier risk before testing.^{5,6,7,8,9,10}

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with type 1 autoimmune polyglandular syndrome, it is possible to carry a mutation that is not on our test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
258.1 Multiple endocrine neoplasia [MEN] type I Applies to: • Wermer's syndrome	V82.71 Screening for genetic disease carrier status

References

1. Jankovic M, Nussenzweig A, Nussenzweig MC. Antigen receptor diversification and chromosome translocations. *Nature immunology*. 2007;8:801-8.
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Bartter syndrome, type 4a

Report Type: Carrier Status

About: Bartter syndrome type 4A is a rare disease that is characterized by severe renal salt excretion, hypokalemic alkalosis (reduced blood potassium and elevated blood pH) and elevated calcium in the urine. The syndrome is associated with sensorineural deafness and progression to chronic renal failure, which is an uncommon complication for other types of Bartter Syndrome. Affected individuals have a triangular face, protruding ears and large eyes. Affected fetuses are at risk for polyhydramnios (excess amniotic fluid), premature birth and excessive urination after birth.¹

Genetics: Bartter syndrome type 4A is caused by mutations in the BSND (Bartter syndrome, infantile, with sensorineural deafness) gene that encodes barttin, which is a subunit of renal and inner ear chloride channels. Because these channels are important for chloride reabsorption in the kidney and for potassium recycling in the inner ear, defects in the BSND gene can lead to kidney failure and sensorineural deafness, a type of hearing loss caused by a failure to relay signals from the ear to the brain.¹

The test includes the G47R mutation in the BSND gene that was found to cause infantile Bartter syndrome with sensorineural deafness in Japanese patients.^{1,2}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: NA

Mutations Tested: The test includes one mutation in the BSND gene.

BSND [G47R]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with Bartter syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
255.13 Bartter's syndrome	V82.71 Screening for genetic disease carrier status

References

1. Kitanaka S, Sato U, Maruyama K, Igarashi T. A compound heterozygous mutation in the BSND gene detected in Bartter syndrome type IV. *Pediatric nephrology (Berlin, Germany)*. 2006;21:190-3.
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Beta-blockers

(DC:TB-0233.002 07MAY2013)

Report Type: Pharmacogenetics

About: Beta-blockers (carvedilol, metoprolol, etc.) are used as a standard therapy for heart failure.¹ This class of drugs antagonizes beta-adrenergic receptors and down-regulates the effects of catecholamine hormones (epinephrine and norepinephrine). Genetic variants that affect beta-adrenergic signaling may influence outcomes in heart failure patients treated with beta-blockers.

Genetics: G-protein-coupled receptor kinases (GRKs) desensitize signaling of beta-adrenergic receptors. A gain-of-function variant in GRK5 (Gln41Leu) is associated with survival benefits in heart failure patients.^{1,2} The Gln41Leu mutation is thought to provide a “natural” beta block, producing a more rapid desensitization of the beta-adrenergic receptor. In patients without the Gln41Leu mutation, beta-blockers provided patients with a typical survival benefit. In patients with the Gln41Leu mutation, beta-blockers were unlikely to provide additional survival benefit to heart failure patients. However, it is important to note that in heart failure patients who are not treated with beta-blockers, individuals with Gln41Leu had increased survival compared to those without.¹ The Gln41Leu mutation is more common in individuals of African ancestry, which may explain why African-Americans have a lower chance of responding to beta-blockers compared to other groups. This genetic effect is found in African-American patients;¹ it is not known if the tested mutation has the same effect in patients of non-African ancestry.

Recommendations: NA

Possible Outcomes: Reduced Therapeutic Benefit, Typical Therapeutic Benefit

Markers or Alleles Tested: GRK5 [rs17098707]

Ethnic Distribution of Tested Alleles: The minor allele (Leu41) frequency is 1.7% in Caucasians and 23.1% in African-Americans.²

Limitations and Warnings: The results of this test are based on a study of heart failure patients. Thus, they may not apply to patients being treated with beta-blockers for other conditions.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to: Unspecified adverse effect of medicinal substance NEC properly administered	

References

1. Liggett SB, Cresci S, Kelly RJ, et al. A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure. *Nature medicine*. 2008;14:510-7.
2. Cresci S, Kelly RJ, Cappola TP, et al. Clinical and genetic modifiers of long-term survival in heart failure. *Journal of the American College of Cardiology*. 2009;54:432-44.

Beta-blockers, LVEF response

(DC:TB-0208.002 07MAY2013)

Report Type: Pharmacogenetics

About: Beta-blockers (carvedilol, metoprolol, etc.) are used as a standard therapy for heart failure.¹ This class of drugs antagonizes beta-adrenergic receptors and down-regulates the effects of catecholamine hormones (epinephrine and norepinephrine). Genetic variants that affect beta-adrenergic signaling may influence outcomes in heart failure patients treated with beta-blockers.

Genetics: In heart failure patients, the benefits of treatment with beta-blockers for left ventricular ejection fraction (LVEF) are associated with variants in the ADRB1 gene, which encodes the beta(1)-adrenergic receptor.² A meta-analysis of three pharmacogenetic studies in heart failure patients found that individuals who are homozygous for the Arg389 allele have a greater increase in LVEF in response to beta-blockers (carvedilol, metoprolol or bisoprolol) compared to individuals who carry the Gly389 allele.² This genetic effect was also reported in a study involving patients who underwent 1.5 years of carvedilol treatment.³

In a number of small studies, the Arg389 allele has been studied in relation to other phenotypes, including exercise heart rate, response to rate-control therapy in atrial fibrillation, changes in heart rate and blood pressure in patients with essential hypertension and LV hypertrophy, and transplant-free survival in heart failure patients.^{4,5,6,7} However, it is still controversial whether Arg389 modifies the outcomes of beta-blocker therapy. Some studies showed no association, while others reported significant associations but do not always agree on the direction of the genetic effect.

Recommendations: NA

Possible Outcomes: Enhanced Benefit, Beneficial

Markers or Alleles Tested: ADRB1 [rs1801253]

Ethnic Distribution of Tested Alleles:

Ethnicity	Arg389 allele (C allele) frequency ⁸
Caucasian	~70%
East Asians	75-85%
Africans	~60%

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test,

nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to: Unspecified adverse effect of medicinal substance NEC properly administered	

References

1. Liggett SB, Cresci S, Kelly RJ, et al. A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure. *Nature medicine*. 2008;14:510-7.
2. Muthumala A, Drenos F, Elliott PM, Humphries SE. Role of beta adrenergic receptor polymorphisms in heart failure: systematic review and meta-analysis. *European journal of heart failure*. 2008;10:3-13.
3. Chen L, Meyers D, Javorsky G, et al. Arg389Gly-beta1-adrenergic receptors determine improvement in left ventricular systolic function in nonischemic cardiomyopathy patients with heart failure after chronic treatment with carvedilol. *Pharmacogenetics and genomics*. 2007;17:941-9.
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Beta-ketothiolase deficiency

Report Type: Carrier Status

About: Beta-ketothiolase deficiency is an inherited organic acid disorder with symptoms that include intermittent ketoacidotic episodes of vomiting, dehydration, difficulty breathing, extreme fatigue and, occasionally, seizures. Symptoms appear between the ages of 6 to 24 months. There are no clinical symptoms between episodes, which can be induced by infections, fasting or intake of protein-rich foods. Beta-ketothiolase deficiency is very rare and as of 2010, only about 90 beta-ketothiolase deficient patients were reported worldwide.¹

Genetics: Beta-ketothiolase deficiency is caused by mutations in the ACAT1 gene, which encodes mitochondrial acetyl-CoA acetyltransferase. This enzyme plays a key role in breaking down proteins and fats from food by converting ketone, a byproduct of fats, and isoleucine, a building block of proteins, into smaller molecules that can be used to produce energy. Mutations in the ACAT1 gene, which decrease or eliminate the activity of the encoded enzyme, prevent the normal breakdown of proteins and fats, resulting in the accumulation of toxic ketones in the blood (ketoacidosis) and causing organ damage, especially to the brain. More than 70 different mutations have been identified, but only a few occur in more than two independent families.¹

The test includes mutations in the ACAT1 gene that cause beta-ketothiolase deficiency. The most common mutation, R208X, was detected in eight Vietnamese and two unrelated Dutch patients and was not found in 400 healthy Vietnamese controls..¹

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified beta-ketothiolase deficiency as one of 29 diseases for which newborn screening should be mandated.²

Mutations Tested: The test includes eight mutations in the ACAT1 gene.

ACAT1 [T297M, IVS11+2T>C, Q272X, IVS8+1G>T, G152A, G183R, R208X, 149delC]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
ACAT1	Vietnamese	88%	1 in 500	1 in 3,993

^aPercentage of affected patients carrying mutations detected by this test.¹

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.³ The actual carrier rate and the post-test residual

risk are likely to be lower.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with beta-ketothiolase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.2 Other disturbances of aromatic amino-acid metabolism Applies to: • Albinism • Alkaptonuria • Alkaptonuric ochronosis • Disturbances of metabolism of tyrosine and tryptophan • Homogentisic acid defects • Hydroxykynureninuria • Hypertyrosinemia • Indicanuria • Kynureninase defects • Oasthouse urine disease • Ochronosis • Tyrosinosis • Tyrosinuria • Waardenburg syndrome	V82.71 Screening for genetic disease carrier status

References

1. Fukao T, Nguyen HT, Nguyen NT, et al. A common mutation, R208X, identified in Vietnamese patients with mitochondrial acetoacetyl-CoA thiolase (T2) deficiency. *Molecular genetics and metabolism*. 2010;100:37-41.
2. Newborn screening: toward a uniform screening panel and system. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2006;8 Suppl 1:1S-252S.
3. Orphanet web site. <http://www.orpha.net/>. Accessed July 10, 2012.

Beta-thalassemia

Report Type: Carrier Status

About: Beta-thalassemia is an inherited blood disorder that abolishes or causes a decrease in production of beta hemoglobin. In the most severe form of the disease, known as thalassemia major or Cooley's anemia, the patient requires lifelong blood transfusions to survive. Such patients may live 40 years or longer, but the most common cause of death is heart failure. In the less severe form of beta-thalassemia, known as thalassemia intermedia, the patient has significant anemia but does not require blood transfusions.¹

Genetics: Beta-thalassemia is caused by mutations in the HBB gene, which encodes the beta subunit of hemoglobin.^{1,2} HBB mutations that decrease production of the beta subunit of hemoglobin are classified as beta-plus thalassemia, whereas HBB mutations that abolish production of the beta subunit of hemoglobin are classified as beta-zero thalassemia.³ Over 200 HBB mutations that cause beta-thalassemia have been identified. However, only a limited number of mutations are common in each at-risk population.²

Other mutations in the HBB gene give rise to abnormal hemoglobins with other disease characteristics, including sickle cell hemoglobin (HbS), hemoglobin C (HbC) and hemoglobin E (HbE).³

Beta-thalassemia is found in people of Mediterranean, Middle Eastern, African, South Asian (Indian, Pakistani, etc.), Southeast Asian and Chinese descent. The highest carrier frequencies are found in Cyprus (14%) and Sardinia (10.3%).² In certain areas of India and Asia, the incidence of beta-thalassemia is 1 in 2000 births.⁴ The high prevalence of the beta-thalassemia mutations in areas of the world where malaria is endemic suggests that mutations associated with beta-thalassemia may confer some protection against malaria.⁵

Mode of Inheritance: Autosomal Recessive²

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Obstetricians and Gynecologists (ACOG) recommends offering carrier screening for hemoglobinopathies to people of African, Southeast Asian and Mediterranean ancestry.⁶ The American College of Medical Genetics identified beta-thalassemia as one of 29 diseases for which newborn screening should be mandated.⁷

Mutations Tested: The test includes 21 mutations in the HBB gene.

HBB [cd8-AA, cd8/9+G, 41/42-TTCT, cd44-C, cd39C>T, IVS1+110G>A, IVS1+1G>A, IVS1+6T>C, IVS2+1G>A, 17A>T, Hb Malay, cd24T>A, -29A>G, -87C>G, -28A>G, -88C>T, IVS2+745C>G, IVS2+849A>G, IVS2+654C>T, IVS2+849A>C, IVS1+5G>T]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
HBB	Mediterranean	91%	1 in 7	1 in 68
HBB	Middle East	91%	1 in 49	1 in 534
HBB	Thai	91%	1 in 11	1 in 112
HBB	Chinese	91%	1 in 100	1 in 1,101
HBB	West African	75%	1 in 11	1 in 41

^aPercentage of affected patients carrying mutations detected by this test.^{1,2}

^bCarrier risk before testing.^{2,8,9,10,11}

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with beta-thalassemia, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
282.44 Beta thalassemia Applies to: • Beta thalassemia major • Cooley's anemia • Homozygous beta thalassemia • Severe beta thalassemia • Thalassemia intermedia • Thalassemia major	V78.3 Screening for other hemoglobinopathies

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Biotinidase deficiency

Report Type: Carrier Status

About: Biotinidase deficiency is an inherited disorder that is caused by a defect in how the body processes biotin. Children with profound biotinidase deficiency usually show symptoms at about three months of age, but the disease may remain undetected until the age of 10. The most common symptoms are seizures, low muscle tone, vision and hearing problems, delayed development and various skin problems (skin rash, hair loss and yeast infections). The disease is treatable with life-long, high doses of biotin. Early diagnosis is important, because the hearing loss, vision loss and delayed development cannot be reversed by biotin supplementation. Some children with a milder form of the disorder called partial biotinidase deficiency may not show signs of the disorder until after a prolonged infection.¹

Genetics: Biotinidase deficiency is caused by mutations in the BTD gene, which encodes biotinidase, an enzyme that separates biotin from food protein and makes biotin available for use in metabolic reactions.^{1,2}

Over 40 mutations in the BTD gene associated with biotinidase deficiency have been identified. The test includes some of the most common mutations found in the United States. The C33FfsX36, Q456H and R538C mutations and the double mutation D444H:A171T are all associated with profound biotinidase deficiency, which usually causes symptoms in children around three months of age.³ The C33FfsX36 mutation, also known as 98_104delGCGGCTGinsTCC, is a 7-base pair deletion combined with a 3-base pair insertion.³ The A171T mutation is always found together with D444H as a double mutation.⁴ However, D444H, by itself, is associated with partial biotinidase deficiency, which may not be diagnosed until after a prolonged infection.⁵

The worldwide incidence, as determined by newborn screening, of profound biotinidase deficiency is 1 in 137,401 persons, of partial biotinidase deficiency is 1 in 109,921 and of the combined incidence of profound and partial biotinidase deficiency is 1 in 61,067.⁶

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified biotinidase deficiency as one of 29 diseases for which newborn screening should be mandated.⁷

Mutations Tested: The test includes five mutations in the BTD gene.

BTD [Q456H, R538C, A171T, c.1330G>C (p.Asp444His, D444H), C33FfsX36]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c

BTD	General	60%	1 in 120	1 in 299

^aPercentage of affected patients carrying mutations detected by this test^{2,4}

^bCarrier risk before testing²

^cCarrier risk after a “not a carrier” test result

Limitations and Warnings: Since there are other mutations associated with biotinidase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.6 Other deficiencies of circulating enzymes	V82.71 Screening for genetic disease carrier status
Applies to:	
• Hereditary angioedema	

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Bloom syndrome

Report Type: Carrier Status

About: Bloom syndrome is a rare, inherited disease. Affected individuals have an elfin appearance with a small, slender body, long narrow face, small lower jaw, prominent nose and ears, and a high-pitched voice. A red patch may develop on the face after exposure to sunlight. Individuals with Bloom syndrome are more susceptible to infections of the middle ear and lung, can develop diabetes at an earlier age, and are at risk for a broad range of cancers occurring at an earlier age. Cancer is the most common cause of death in patients with Bloom syndrome.^{1,2}

Genetics: Bloom syndrome is caused by mutations in the BLM gene, which encodes a member of the RecQ DNA helicase family.² These proteins are important for DNA replication, DNA repair and genetic recombination. A mutation in the genes that encode this family of proteins can explain the widespread and diagnostic chromosome breakage observed in cells taken from Bloom syndrome patients as well as the frequent occurrence of cancer that is characteristic of the disease.^{2,3}

Bloom syndrome is found mostly in people of Ashkenazi Jewish descent, although it occurs in all ethnic groups. The incidence of Bloom syndrome is 1 in 48,000 in people of Ashkenazi Jewish descent, who comprise about one-third of individuals with Bloom syndrome. One mutation, blm(Ash), is responsible for most instances of Bloom syndrome in Ashkenazi Jews.⁴ This mutation is a combination of a 7-base pair insertion and a 6-base pair deletion at position 2281 of the BLM cDNA.^{4,5}

Mode of Inheritance: Autosomal Recessive^{2,5,6}

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics (ACMG) recommends offering carrier screening for Bloom syndrome to individuals with Ashkenazi Jewish ancestry.⁷

Mutations Tested: The test includes 9 mutations in the BLM gene. ACMG recommends screening in Ashkenazi Jews for one mutation, which is underlined below.⁷

BLM [R836fsX, S186X, Q975fsX, W803fsX, W428X, W567X, Q645X, R899X, blmAsh]

Ethnic Prevalence and Frequency of Mutations Tested⁸

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
BLM	Ashkenazi Jew	99%	1 in 107	1 in 10,601

^aPercentage of affected patients carrying mutations detected by this test

^bCarrier risk before testing

^cCarrier risk after a “not a carrier” test result

Limitations and Warnings: Since there are other rare mutations associated with Bloom syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
757.39 Other specified anomalies of skin	V82.71 Screening for genetic disease carrier status
Applies to:	
• Accessory skin tags, congenital • Congenital scar • Epidermolysis bullosa • Keratoderma (congenital)	

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Breast cancer

Report Type: Health Conditions

About: Breast cancer affects approximately 12% of women in the U.S. and is the second leading cause of cancer-related deaths. Symptoms may include a lump in the breast, discharge from the nipple or a change in breast shape or size. Risk factors for breast cancer include family history of the disease, reproductive history, age, and body mass index. Research indicates that genetic factors are also associated with the disease.¹

Genetics: Genes associated with increased breast cancer risk can be classified into three groups: high penetrance genes, intermediate penetrance genes and low penetrance susceptibility alleles.² Mutations in high penetrance genes confer greater than 10-fold increase in risk for breast cancer, and mutations in intermediate penetrance genes confer a 2- to 4-fold increase in risk. Low penetrance susceptibility alleles each confer a 1- to 1.5-fold increase in risk. Five to ten percent of breast cancers are caused by mutations in high penetrance genes, such as BRCA1 and BRCA2. For the majority of breast cancers (90-95%), the genetic contribution consists of intermediate penetrance mutations and low penetrance susceptibility alleles.^{2,3} While there are many known markers, they may only account for 30% of the total genetic risk for breast cancer.²

The test includes mutations in intermediate penetrance genes and several low penetrance susceptibility alleles.

Checkpoint kinase 2 (CHEK2) and Partner and localizer of BRCA2 (PALB2) are intermediate penetrance genes that interact with BRCA1 and BRCA2, respectively, to repair DNA damage and are associated with increased breast cancer risk.² The alleles tested are two of the more common intermediate risk alleles in these genes. Most mutations in CHEK2 are very rare, but the CHEK2 1100delC mutation is found in approximately 1% of Caucasians, particularly those of Northern and Eastern European descent.^{2,4} This allele occurs less frequently in African-American and Hispanic women and is extremely rare or absent in other ethnic groups.⁵ Women with the 1100delC allele have approximately twice the risk of developing breast cancer compared to women who do not have the allele.⁶ Additionally, women who have the allele and at least two first-degree relatives (mother, sister, or daughter) with a history of the disease have about four times the risk for breast cancer compared to women who do not have the allele. Finally, there appears to be a trend for the CHEK2 1100delC allele to be associated with earlier onset of the disease.⁶

Like CHEK2, most alleles of PALB2 are very rare, but the PALB2 1592delT allele was shown to be present in approximately 1% of breast cancer patients in a study of Caucasian women in Finland.⁷ In this study, carriers of the PALB2 1592delT allele are estimated to have about four times the risk for breast cancer compared to women who do not have the allele. So far, this allele has not been detected in other countries or ethnic groups and may be specific to Finnish women.²

More than ten low-risk alleles for breast cancer are included on the test. Each of these susceptibility alleles confers a small risk for breast cancer. Women are likely to have more than one of these common risk alleles, which when combined, could lead to a higher risk for breast cancer.² In one study, a woman with 14 risk alleles is predicted to have a 6-fold increase in her risk for breast cancer compared to women who do not carry any of those particular risk alleles.⁸ The association of breast cancer risk with these markers is based on high-quality and reproducible data, but the disease mechanisms

underlying these associations are not well established. Moreover, many of these markers may not be tagging the actual causative mutation that is directly involved in breast cancer development and progression. Details on two of the low-risk alleles are below.

At least five high-quality studies have demonstrated an association between breast cancer and the G allele of the rs1219648 marker in the FGFR2 (fibroblast growth factor receptor 2) gene, which encodes a protein that promotes cell growth. The largest study involved Caucasian women,⁹ but the G allele has also been associated with an increased risk for breast cancer in Jewish (Ashkenazi and Sephardic) and Chinese populations.^{10,11}

Unlike most of the low-risk alleles, which were identified in Caucasians, the A allele of rs2046210 near the estrogen receptor 1 gene (ESR1) was first identified to be associated with breast cancer in a study of Chinese women.¹¹ This association was replicated in Caucasian women in the same publication. The ESR1 gene encodes a protein that mediates estrogen signaling in the breast.

Recommendations: Routine screening for breast cancer is recommended by the U.S Preventative Services Task Force for women aged 50 to 74 years.¹²

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
CHEK2	CHEK2*1100delC	del	2.34	Caucasian	0.7%	Validated	15122511
CASP8	rs1045485	C	0.89	Caucasian	12.5%	Validated	17293864
MSRP30	rs10941679	G	1.19	Caucasian	24.2%	Validated	18438407
FGFR2	rs1219648	G	1.20	Asian	38.7%	Validated	19219042
FGFR2	rs1219648	G	1.23	Caucasian	46.5%	Validated	18438407
Intergenic_8q24	rs13281615	G	1.21	Caucasian	45.8%	Validated	18577746
Intergenic_2q35	rs13387042	A	1.11	Caucasian	56.2%	Validated	17529974
ESR1	rs2046210	A	1.36	Asian	35.1%	Validated	19219042
ESR1	rs2046210	A	1.11	Caucasian	28.8%	Validated	19219042
FGFR2	rs2981578	G	1.20	African	83.0%	Validated	19223389
TNRC9	rs3803662	T	1.12	Asian	68.5%	Validated	19219042
TNRC9	rs3803662	T	1.27	Caucasian	24.8%	Validated	17529974
PALB2	1592delT	del	3.94	Caucasian	0.2%	Preliminary	17287723
MMP7	rs12184413	T	1.00	Asian	27.0%	Preliminary	18648013
intergenic_2q35	rs13387042	A	1.21	Hispanic	38.0%	Preliminary	17529974

LSP1	rs3817198	T	1.06	Caucasian	67.3%	Preliminary	17529967
AKAP9	rs6964587	T	1.08	Caucasian	38.8%	Preliminary	18334708
MAP3K1	rs889312	C	1.13	Caucasian	30.8%	Preliminary	17529967

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
239.3 Neoplasm of unspecified nature of breast	V76.10 Breast screening, unspecified

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Caffeine metabolism

Report Type: Pharmacogenetics

About: Caffeine is the most widely consumed stimulant in the world. It acts as an adenosine receptor antagonist and thus modulates cAMP activity. The drug is metabolized to an inactive product by the liver enzyme cytochrome P450 1A2.¹

Genetics: Cytochrome P450 1A2 is encoded by the CYP1A2 gene. Variants of CYP1A2 can affect enzyme activity and, thus, a patient's ability to metabolize caffeine. The A allele of the rs762551 marker in the CYP1A2 gene (CYP1A2*1F)† increases the activity of the enzyme, resulting in significantly enhanced caffeine metabolism.^{1,2} Individuals homozygous for the A allele are classified as “fast” caffeine metabolizers, whereas individuals with a C allele (CYP1A2*1A) are classified as “slow” caffeine metabolizers.³ However, increased caffeine metabolism by A allele homozygotes was observed in smokers but not in non-smokers, suggesting that in the absence of an inducer like smoking, A allele homozygotes may not be significantly different than C carriers.²

Coffee intake has been observed to be associated with increased risk for myocardial infarction in “slow” caffeine-metabolizing individuals with a C allele at rs762551 in the CYP1A2 gene.³ In a study assessing the relationship between coffee drinking habits and myocardial infarction, researchers found that young (less than 59 years) individuals with the “slow” CYP1A2 genotype have an increased risk for heart attack if they are heavy coffee drinkers. Risk was greater for individuals who drank more than four cups of coffee per day than for individuals who drank two to three cups per day. The risk was not gender-specific and was not affected by smoking status.³ Caffeine is the only major compound found in filtered coffee that is known to be metabolized by the cytochrome P450 1A2 (CYP1A2) enzyme, suggesting that caffeine is the component of coffee that increases the risk of heart attack.

†The CYP1A2 allele designation is based upon the recommendations of the International Human CYP Allele Nomenclature Committee⁴ and is reflected in this report.

Recommendations: NA

Possible outcomes: Slow Metabolizer, Fast Metabolizer

Markers or Alleles Tested: CYP1A2 [rs762551]

Ethnic Distribution of Tested Alleles: The C allele frequency at rs762551 was reported to be approximately 29% to 33% in Caucasians, 30% to 39% in Asians and 40% to 51% in Africans.⁵

Limitations and Warnings: An important consideration regarding A homozygotes (“fast” caffeine metabolizers) is that some studies have found that they do not differ from the C homozygotes (“slow” caffeine metabolizers) in the absence of a CYP1A2 inducer like tobacco or omeprazole.^{2,6} Therefore, it is possible that “fast” caffeine metabolizers who are non-smokers, or not taking an inducer of CYP1A2, might have similar caffeine-associated, heart attack risk as the “slow” caffeine metabolizer.

Moreover, the A allele of rs762551 is also found in other haplotypes besides CYP1A2*1F (CYP1A2 Allele Nomenclature table).⁷ Importantly, the frequency of the A allele of is not significantly different between Asians (63%, Koreans) and Caucasians (71%, Swedes), but the frequency of CYP1A2*1F haplotype was found to be significantly lower in Asians (0.4 to 7.7%) compared to Caucasians (57%).^{5,8} In Caucasians, the A allele is mostly found in the CYP1A2*1F haplotype, while in Asians, it is mostly found in other haplotypes that contain additional mutations. In Asians, the CYP1A2*1F haplotype cannot be identified by testing for rs762551 alone and there is a lack of association of the A allele of rs762551 with increased enzyme activity or inducibility.⁸ Therefore, this test is not recommended for Asians.

The CYP1A2 enzyme can metabolize a variety of compounds in addition to caffeine, such as the arthritis drug leflunomide. C homozygous individuals had a 9.7-fold higher risk for overall leflunomide-induced toxicity than did heterozygotes.⁹ Some of the known CYP1A2 substrates, inhibitors and inducers are listed below in a table reproduced from Cytochrome P450 drug interaction table.¹⁰

In addition to genetics, a patient's ability to metabolize caffeine may also depend on nongenetic factors. Smoking, diet, oral contraceptives, and a variety of other drugs affect CYP1A2 activity.⁵

Known CYP1A2 Substrates	Known CYP1A2 Inhibitors	Known CYP1A2 Inducers
amitriptyline caffeine clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine N-DeMe mexillettine naproxen olanzapine ondansetron phenacetin acetaminophen→NAPQI propranolol riluzole ropivacaine tacrine theophylline tizanidine verapamil (R)warfarin zileuton zolmitriptan	fluvoxamine ciprofloxacin cimetidine amiodarone fluoroquinolones furafylline interferon methoxsalen mibefradil	broccoli brussell sprouts char-grilled meat insulin methylcholanthrene modafinil nafcillin beta-naphthoflavone omeprazole tobacco

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
N/A	V77.99 Screening for other and unspecified endocrine, nutritional, metabolic, and immunity disorders

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Canavan disease

Report Type: Carrier Status

About: Canavan disease is an inherited, fatal disease that is characterized by a progressive deterioration of the white matter of the brain. The first symptoms appear when the infant is three to nine months old and may include hypotonia, macrocephaly, abnormal posture and intellectual disability. Most strikingly, children with Canavan disease cannot crawl, walk, sit or talk. They may suffer seizures, have trouble swallowing, and become paralyzed, mentally retarded or blind. Most children with Canavan disease die before age four, but some children may survive into their teens and twenties.¹

Genetics: Canavan disease is caused by mutations in the ASPA gene, which encodes the enzyme aspartoacylase that breaks down a molecule called N-acetyl aspartic acid (NAA). NAA is important for the growth and maintenance of myelin, and loss of myelin leads to the progressive death of neurons in the brain.¹

The test includes a dozen mutations in the ASPA gene. A305E accounts for 40% to 60% of the disease-causing alleles in non-Jewish populations. Y231X accounts for 14% of mutations detected in Ashkenazi Jews.¹

Canavan disease affects all ethnic groups but is more common in people of Ashkenazi Jewish descent. The carrier rate of Canavan disease in Ashkenazi Jews is 1 in 41.² In individuals not of Ashkenazi Jewish descent, the carrier rate is unknown and assumed to be much lower.¹

Mode of Inheritance: Autosomal Recessive^{1,3,4}

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) recommends offering prenatal and preconception Canavan disease carrier screening to individuals with Ashkenazi Jewish ancestry.^{5,6}

Mutations Tested: The test includes 12 mutations in the ASPA gene. ACMG recommends screening in Ashkenazi Jews for two mutations, which are underlined below.²

ASPA [245insA, 827delGT, E285A, Y231X, A305E, G274R, F295S, P280S, Y109X, M195R, C218X, 433-2A>G]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c	Incidence ^d
ASPA	Ashkenazi Jew	97%	1 in 41	1 in 1,539	1 in 6,700

^aPercentage of affected patients carrying mutations detected by this test.²

^bCarrier risk before testing.²

^cCarrier risk after a “not a carrier” test result.

^dNumber of Canavan disease patients born in one year in the U.S.

Limitations and Warnings: Since there are other mutations associated with Canavan disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
330.1 Leukodystrophy Applies to: • Krabbe's disease • Leukodystrophy: ◦ NOS ◦ globoid cell ◦ metachromatic ◦ sudanophilic • Pelizaeus-Merzbacher disease • Sulfatide lipidosis	V82.71 Screening for genetic disease carrier status

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Carbamazepine hypersensitivity

(DC:TB-0227.001 06DEC2012)

Report Type: Pharmacogenetics

About: Carbamazepine is FDA-approved for treatment of epilepsy, mania/bipolar disorder and neuropathic pain. The most serious side effects associated with carbamazepine therapy are dangerous hypersensitivity reactions, also known as Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).¹ SJS and TEN are serious blistering reactions of the skin and mucous membranes that can be permanently disabling or fatal.

Genetics: In 2007, FDA issued an alert that carbamazepine-associated SJS and TEN are significantly more common in patients with the HLA-B*1502 allele.^{2,3} A corresponding boxed warning was added to the label for carbamazepine drugs (see Recommendations below). The HLA-B*1502 allele occurs almost exclusively in the Asian population, consistent with the increased incidence of SJS/TEN in some Asian countries compared to countries with mainly Caucasian populations. In 2004, a small study in Han Chinese patients was the first to describe an association between HLA-B*1502 and carbamazepine-induced SJS;⁴ a follow-up study indicated HLA-B*1502 was not associated with other carbamazepine-induced adverse reactions, namely maculo-papular exanthema or drug hypersensitivity syndrome.⁵ The association of HLA-B*1502 and carbamazepine-induced SJS/TEN has been replicated in studies from Taiwan,⁵ Hong Kong,⁶ Malaysia⁷ and Thailand.⁸ A recent study from Taiwan showed clinical utility of prescreening patients for HLA-B*1502 before prescribing carbamazepine.⁹ The avoidance of carbamazepine in HLA-B*1502 positive patients was associated with a decrease in incidence of carbamazepine induced SJS/TEN.

The HLA-B*1502 allele has also been shown to be associated with increased risk of SJS/TEN for antiepileptic drugs that are related to carbamazepine, such as phenytoin and oxcarbazepine.^{8,10,11,12}

Recommendations: FDA's boxed warning on Carbatrol, Epitol, Equetro and Tegretol drug labels recommends HLA-B*1502 screening for patients of Asian ancestry prior to carbamazepine therapy; patients who test positive for the HLA-B*1502 allele should not be treated with carbamazepine unless the benefits clearly outweigh the risks (prescribing info). FDA's alert on carbamazepine hypersensitivity notes that patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of ever developing these events from carbamazepine, even if the patient is positive for the HLA-B*1502 allele. FDA further states that patients who test positive for HLA-B*1502 may also be at increased risk of SJS/TEN from other antiepileptic drugs that have been associated with SJS/TEN.² Healthcare professionals who prescribe carbamazepine products should be aware of the difficulty in ascertaining ethnic ancestry, as well as the possibility of mixed ancestry.

Possible Outcomes: Hypersensitive, Typical, Unknown

Markers or Alleles Tested: HLA-B [HLA-B*1502]

This test includes rs3909184 and rs2844682, which together tag the HLA-B*1502 allele in Han Chinese.¹³ Patients with one or two HLA-B*1502 alleles are assigned a “Hypersensitive” result. Patients with no HLA-B*1502 alleles are assigned a “Typical” result.

For patients with a particular genotype (rs3909184 (G/C), rs2844682 (C/T)), the HLA-B*1502 status cannot be determined, and thus these patients are assigned an “Unknown” result. These patients may require further evaluation.

Ethnic Distribution of Tested Alleles: The HLA-B*1502 allele is more prevalent in individuals of Asian ancestry.³ The HLA-B*1502 allele has been observed in about 10% to 15% of patients in parts of China, Thailand, Malaysia, Indonesia, the Philippines and Taiwan. The frequency of this allele in South Asian individuals, such as Indians, is about 2% to 4%, but the frequency may be higher in some groups. The frequency of HLA-B*1502 is much lower (less than 1%) in Japan and Korea.¹⁴ The HLA-B*1502 allele is also less frequently found (less than 1%) in those of African, European, Hispanic or Native American descent.³

Limitations and Warnings: The markers tested for HLA-B*1502 are most applicable to patients of Han Chinese descent.¹³ If clinically indicated, patients of other Asian ethnicities could be advised to undergo HLA sequencing to assess their risk of carbamazepine hypersensitivity. Other HLA alleles have been shown to be associated with carbamazepine hypersensitivity in people of Caucasian and Japanese descent, in whom HLA-B*1502 is largely absent.¹⁵ Many HLA-B*1502-positive Asian patients treated with carbamazepine will not develop SJS/TEN. Conversely, these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. Therefore, healthcare professionals are advised to watch for symptoms in all patients.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.27 Other drug allergy	N/A
Applies to:	
- Allergic reaction NEC (due) to correct medical substance properly administered - Drug allergy NOS - Drug hypersensitivity NOS - Hypersensitivity (due) to correct medical substance properly administered	

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Carnitine deficiency, primary systemic

Report Type: Carrier Status

About: Carnitine deficiency, primary systemic (CDSP) is a lethal disorder that is characterized by progressive weakness, cardiomyopathy and encephalopathy due to fasting low blood sugar. Affected individuals are usually normal at birth and healthy for several years but develop heart disease and heart failure in late infancy or early childhood. L-carnitine therapy from birth prevents the symptoms. Identification of disease-causing mutations is important because the disorder is progressive and lethal and may be one of the causes of sudden infant deaths.¹

Genetics: CDSP is caused by mutations in the SLC22A5 gene, which encodes organic cation transporter 2 that helps certain cells in the body take up carnitine.² Carnitine is a natural substance found in food and is necessary for the conversion of fat to energy. Mutations in the SLC22A5 gene prevent the cell from taking up carnitine and result in an acute metabolic disorder early in life with fasting low blood sugar, heart muscle disease and sudden death.³

The test includes 10 recurrent mutations in the SLC22A5 gene. R254X is common in Chinese patients and about 1 in every 125 people carries this mutation in Southern China.⁴

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified carnitine deficiency as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test includes ten mutations in the SLC22A5 gene.

SLC22A5 [T468R, R254X, T440M, T219fsX284, W283C, R169W, Y211C, N32S, P46S, Y4X]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
SLC22A5	Taiwanese	35%	1 in 100	1 in 153

^aPercentage of affected patients carrying mutations detected by this test.⁶

^bCarrier risk before testing.⁷

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with primary systemic carnitine deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.82 Carnitine deficiency due to inborn errors of metabolism	V82.71 Screening for genetic disease carrier status

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Cerebrotendinous xanthomatosis

Report Type: Carrier Status

About: Cerebrotendinous xanthomatosis (CTX) is a rare, inherited lipid storage disease that is characterized by chronic diarrhea during infancy, development of cataracts in the late childhood, formation of tendon fat deposits (xanthomas) in young adults and progressive neurologic dysfunction in the adults. Laboratory tests find high plasma and tissue cholestanol concentrations but normal-to-low plasma cholesterol concentration. Individuals with CTX also have an increased risk for developing cardiovascular disease.¹

Genetics: Cerebrotendinous xanthomatosis (CTX) is a lipid storage disorder caused by mutations in the CYP27A1 gene that encodes a mitochondria enzyme called sterol 26-hydroxylase. The CYP27A1 enzyme plays an important role in maintaining normal cholesterol levels in the body by breaking down excess cholesterol to form bile acids. Individuals with mutations in sterol 26-hydroxylase accumulate cholesterol and its derivative cholestanol in many tissues, including the lens of the eye, nerve cells, muscle tendons and the brain.¹

The test includes 29 mutations in the CYP27A1 gene. Some mutations occur at high frequencies in certain ethnic groups: A216P in Italians,² T339M in Sephardic Jews,³ R395C in Caucasians¹ and R474W in Japanese.¹

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes 29 mutations in the CYP27A1 gene

CYP27A1 [G472A, R474W, P441S, Q461X, IVS7+1G>A, IVS7+5G>T, R405Q, E408X, P401R, R405W, IVS6+1G>A, IVS6-1G>T, D354G, P384L, K284X, T339M, R270X, IVS4+1G>A, R231X, W260X, E195X, A216P, IVS2+1G>A, Q159X, R137W, G145G, R127W, R127Q, R395C]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
CYP27A1	North African Jews	31%	1 in 5	1 in 7
CYP27A1	Dutch	86%	1 in 111	1 in 787

^aPercentage of affected patients carrying mutations detected by this test.^{3,4}

^bCarrier risk before testing.⁵

^cCarrier risk after a "not a carrier" test result.

Limitations and Warnings: Since there are other mutations associated with cerebrotendinous xanthomatosis, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.7 Lipidoses Applies to: - Chemically induced lipidosis - Disease: - Anderson's - Fabry's - Gaucher's - I cell [mucopolipidosis I] - lipoid storage NOS - Niemann-Pick - pseudo-Hurler's or mucopolipidosis III - triglyceride storage, Type I or II - Wolman's or triglyceride storage, Type III - Mucopolipidosis II - Primary familial xanthomatosis	V82.71 Screening for genetic disease carrier status

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Citrullinemia, type I

Report Type: Carrier Status

About: Citrullinemia is an inherited disorder that can cause the accumulation of potentially fatal levels of ammonia in the blood of newborn infants. In the classical type I form of citrullinemia (CTLN1), affected infants may appear normal at birth but then may become irritable and lethargic, feed poorly, vomit, show poor muscle tone, suffer seizures, and lose consciousness. If not treated promptly, the accumulation of toxic metabolites like ammonia and glutamine can cause irreversible brain damage, seizures, coma and ultimately death. A milder form of CTLN1 can develop in children or adults, and women may also experience a form of CTLN1 during pregnancy or after birth.¹

Genetics: CTLN1 is caused by mutations in the ASS1 gene, which encodes a key enzyme in the urea cycle called argininosuccinate synthase. This enzyme is responsible for the condensation of citrulline and aspartate to argininosuccinic acid. Disease-causing mutations in the ASS1 gene reduce or eliminate the activity of argininosuccinate synthase. This blocks the urea cycle and leads to the accumulation of toxic levels of ammonia produced by the breakdown of protein.^{1,2}

The test includes the three most common mutations in the ASS1 gene that cause CTLN1: IVS6-2A>G, R304W, and G390R. These three mutations have a worldwide distribution, including the U.S., Canada, Bolivia, Spain, Austria, Israel, Turkey, Korea and Japan.^{2,3,4}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified citrullinemia as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test includes 15 mutations in the ASS1 gene.

ASS1 [Q380X, K310Q, V345G, V269M, R307C, Y190D, E191K, R86H, R95S, R272C, 952delG, S180N, R304W, IVS6-2A>G, G390R]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
ASS1	panethnic	46%	1 in 119	1 in 220

^aPercentage of affected patients carrying mutations detected by this test.⁴

^bCarrier risk before testing.¹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with citrullinemia type 1, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.6 Disorders of urea cycle metabolism Applies to: • Argininosuccinic aciduria • Citrullinemia • Disorders of metabolism of ornithine, citrulline, argininosuccinic acid, arginine, and ammonia • Hyperammonemia • Hyperornithinemia	V82.71 Screening for genetic disease carrier status

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Clopidogrel metabolism

(DC:TB-0237.001 06DEC2012)

Report Type: Pharmacogenetics

About: Clopidogrel (Plavix) is an oral anti-platelet agent used to inhibit blood clots in patients with coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Clopidogrel is a prodrug that must be metabolized to an active form to be effective. The CYP2C19 enzyme, a member of the cytochrome P450 superfamily, metabolizes clopidogrel to the active metabolite via a two-step reaction. Multiple cytochrome P450 enzymes contribute to the metabolism of clopidogrel, but CYP2C19 acts in both steps of the reaction, accounting for 45% of the first oxidation step and for 20% of the second step.¹

Genetics: Variants of the CYP2C19 gene that lead to reduced enzyme function have been shown to be associated with reduced metabolism of clopidogrel to its active form in many ethnic populations.^{2,3,4,5,6} Individuals can be classified based on their CYP2C19 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (higher than normal enzyme activity), Extensive Metabolizer (normal enzyme activity), Intermediate Metabolizer (intermediate enzyme activity) and Poor Metabolizer (low or no enzyme activity).⁷

In 2010, FDA added a boxed warning to the Plavix label indicating that clopidogrel can be less effective in CYP2C19 poor metabolizers and that genetic tests can help define a therapeutic strategy. In 2011, the NIH Clinical Pharmacogenetics Implementation Consortium issued guidelines describing clinical actions that can be implemented based on metabolizer status (see "Recommendations" below).⁷

The evidence is strongest for patients who are being treated with clopidogrel and receive percutaneous coronary intervention (PCI). Poor or intermediate metabolizers who receive PCI are at significantly increased risk of stent thrombosis, which can result in myocardial infarction and death.^{8,9,10} For other indications, many studies have shown that poor metabolizers (2% to 15% of patients) and intermediate metabolizers (18% to 45% of patients) may be at risk for adverse cardiac events, such as myocardial infarction and stroke, when treated with clopidogrel;^{7,11} however, recent studies dispute this claim.^{9,12,13}

Recommendations: FDA's boxed warning on the Plavix label recommends that alternative treatments should be considered for patients identified as CYP2C19 poor metabolizers.¹⁴ The NIH Clinical Pharmacogenetics Implementation Consortium Guidelines recommend that prasugrel or another alternative be considered for intermediate and poor metabolizers.⁷ The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group also recommends alternative therapies, such as prasugrel.¹⁵

Concurrent use of clopidogrel with CYP2C19 inhibitors may affect clopidogrel response, particularly in extensive and ultra-rapid metabolizers. In these individuals, concurrent use of clopidogrel with CYP2C19 inhibitors (see "Known CYP2C19 Inhibitors" table below) may result in a poor metabolizer phenotype; as such, these individuals may have increased risk for cardiac adverse events when being treated with clopidogrel.¹⁴

Concurrent use of clopidogrel with omeprazole or esomeprazole should be avoided.¹⁴ Concurrent use of clopidogrel with other CYP2C19 substrates (see "Known CYP2C19 Substrates" table below) may affect clopidogrel response.¹⁶

A patient's CYP2C19 metabolizer status may result in unexpected responses to other drugs, such as benzodiazepines, phenytoin, barbiturates and others¹⁷ (see "Known CYP2C19 Substrates" table below).

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers or Alleles Tested: CYP2C19 [CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*8, CYP2C19*17]

Ethnic Distribution of Tested Alleles

The CYP2C19 panel detects alleles that have a combined frequency of over 99% in major ethnic groups.⁷

CYP2C19	Allele	Caucasian	African	East Asian	Middle Eastern	Enzyme activity
Wild-type	*1	63%	68%	60%	87%	Normal
rs4244285	*2	15%	15%	29%	12%	None
rs4986893	*3	0.42%	0.52%	8.9%	1.1%	None
rs28399504	*4	0.25%	0.093%	0.049%	ND ^a	None
rs56337013	*5	0.0073%	ND	0.062%	ND	Reduced
rs72552267	*6	0.017%	0%	0%	ND	None
rs41291556	*8	0.35%	0%	0%	ND	Reduced
rs12248560	*17	21%	16%	2.7%	ND	Increased

^aNot Determined

Predicted CYP2C19 Metabolizer Status⁷

CYP2C19 Diplotype	Predicted Metabolizer Status
*2-*8/*2-*8	Poor Metabolizer
*1/*2-*8, *17/*2-*8	Intermediate Metabolizer
*1/*1	Extensive Metabolizer
*1/*17, *17/*17	Ultrarapid Metabolizer

Limitations and Warnings: Many rare CYP2C19 variants have been identified, but are not part of this test. It is possible, but unlikely, that the patient may have a variant that is not included in this test.

In addition to the genetic variants included in this test, other genetic and nongenetic factors can influence the effective dose of clopidogrel, including variants in other genes, age, sex, nutrition, lifestyle, other medications and route of administration.¹⁶

CYP2C19 genotype and metabolizer status may also affect responses to other drugs¹⁷.

Known CYP2C19 Inhibitors and Substrates Tables

Known CYP2C19 Substrates ¹⁸	Known CYP2C19 Inhibitors ¹⁸
Proton-pump Inhibitors lansoprazole omeprazole pantoprazole rabeprazole	Proton-pump Inhibitors lansoprazole omeprazole pantoprazole rabeprazole
Anti-epileptics diazepam phenytoin S-mephenytoin phenobarbitone	Other chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oxcarbazepine probenicid ticlopidine topiramate
Other amitriptyline carisoprodol citalopram chloramphenicol clomipramine clopidogrel cyclophosphamide hexobarbital imipramine N-deME indomethacin R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin	

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Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to:	
Unspecified adverse effect of medicinal substance NEC properly administered	

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Colorectal cancer

Report Type: Health Conditions

About: Among cancers, colorectal cancer has the second highest incidence for women and third highest incidence for men in the world.¹ Symptoms may include bloody stool, changes in bowel habits and stomach discomfort.² Risk factors for colorectal cancer include age, obesity and physical activity.³ Research indicates that genetic factors are also associated with the disease.⁴

Genetics: Mutations in high penetrance genes have been shown to lead to hereditary syndromes that predispose patients to colorectal cancer, such as familial adenomatous polyposis or Lynch syndrome (also called hereditary non-polyposis colorectal cancer). However, these high risk mutations only account for 3% to 5% of all colorectal cancers.⁴ The remaining genetic risk is hypothesized to be due to multiple common, low-risk susceptibility alleles, each contributing a small amount of risk. The test includes 10 low risk susceptibility alleles for colorectal cancer. Some of these markers are described below.

CRAC1 mutations cause hereditary mixed polyposis syndrome (HMPS), a disease that has only been found in Ashkenazi Jews and which predisposes to the development of colorectal cancer. The rs4779584 marker, which is not a causative mutation for HMPS, was shown to be associated with sporadic colorectal cancer in Caucasians. This association was confirmed in the same publication in a large Caucasian population.⁵

BMP4 encodes a protein that is important for cell growth and early initiation of colorectal cancer. The protein binds to BMP receptor 1A, and mutations in the BMPR1A gene cause a rare hereditary disease called juvenile polyposis syndrome.⁶ The rs4444235 marker, which is near BMP4, was shown to be associated with colorectal cancer in a large study of Caucasians.⁷

CDH1 and RHPN2 encode proteins that are important cell-cell adhesion molecules.⁸ Reduction of cell-cell adhesion is an early event in any cancer and is required for metastasis. The rs9929218 marker in the CDH1 gene and the rs10411210 marker near RHPN2 were shown to be associated with colorectal cancer in a large study of Caucasians.⁷

Variants in the 8q24 region are also associated with breast cancer and prostate cancer. There are no known genes in this region and it is not known how 8q24 variation results in increased cancer risk. However, the G allele of rs6983267 has been shown to be associated with development of colorectal adenomas.⁹ This colorectal cancer marker was identified simultaneously by academic groups in the U.S., Canada and the United Kingdom.^{9,10,11} The data were replicated in at least seven additional publications. The G allele has also shown association with colorectal cancer in a Japanese-American population.¹⁰ Interestingly, the G allele is more common than the A allele in African-American and Hispanic populations, although the association with colorectal cancer in these groups has only been demonstrated in small studies.¹¹

Recommendations: The U.S Preventative Services Task Force recommends screening for colorectal cancer in adults, beginning at age 50 years and continuing until age 75 years.¹²

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
RHPN2	rs10411210	T	0.87	Caucasian	8.4%	Validated	19011631
Intergenic_10p14	rs10795668	A	0.87	Caucasian	32.3%	Validated	18372905
EIF3H	rs16892766	C	1.27	Caucasian	10.6%	Validated	18372905
LOC120376	rs3802842	C	1.18	Caucasian	23.5%	Validated	18753146
BMP4	rs4444235	T	1.13	Caucasian	55.8%	Validated	19011631
CRAC1	rs4779584	T	1.23	Caucasian	16.8%	Validated	18084292
SMAD7	rs4939827	T	1.20	Caucasian	47.3%	Validated	18372901
Intergenic_8q24	rs6983267	G	1.19	Asian	38.7%	Validated	17618282
Intergenic_8q24	rs6983267	G	1.27	Caucasian	48.7%	Validated	17618284
Intergenic_20p12	rs961253	A	1.14	Caucasian	40.3%	Validated	19011631
CDH1	rs9929218	A	0.92	Caucasian	29.5%	Validated	19011631

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

211.3 Benign neoplasm of colon	V76.51 Special screening for malignant neoplasms of colon
Applies to:	
• Appendix • Cecum • Ileocecal valve • Large intestine NOS	

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Coronary artery disease

Report Type: Health Conditions

About: Coronary artery disease (CAD), also known as coronary heart disease, is the leading cause of death in the U.S. This disease is a major consequence of atherosclerosis and can lead to chest pain and heart attack.¹ Risk factors for CAD are numerous, but family history is a major one. Research indicates that multiple genetic factors are associated with the CAD.²

Genetics: CAD is a complex genetic disorder. It is estimated that the genetic risk of atherosclerosis involves variants in hundreds of genes with a variety of functions in regulating blood pressure, lipid and cholesterol metabolism, pro-inflammatory processes and cell adhesion and migration.²

The test includes a variant at the 9p21 locus, a well-known genetic risk factor for CAD.³ The association of 9p21 variants with early-onset CAD was first identified and replicated in a large genome-wide association study in the U.K. in 2007.⁴ In this study, the C allele at the rs1333049 marker in the 9p21.3 region was associated with CAD in Caucasians. A later study of early-onset CAD replicated the risk for rs1333049 in Caucasians,⁵ and yet another study that included patients from nine European study groups confirmed the association.⁶ Genetic variants in the 9p21 region have also been associated with increased risk for many phenotypes related to CAD, including coronary atherosclerosis, CAD severity and progression, risk of intracranial or abdominal aortic aneurysms, as well as stroke.³ Interestingly, the increased CAD risk conferred by 9p21 has been shown to be mitigated by a diet rich in fresh fruit and vegetables.⁷

It is not known what role 9p21 plays in cardiac function. The closest sites of interest to rs1333049 are a non-coding RNA of unknown function (ANRIL), which may regulate nearby genes, and CDKN2A and CDKN2B, which regulate the cell cycle.⁸ Susceptibility at this site does not associate with other risk factors, so the effect is thought to be independent. The same region has also been associated with type 2 diabetes,⁹ suggesting that there may be a shared mechanism involved in susceptibility for the diseases.

The U.K. study, among other studies, also identified additional markers included in the test. Of these, the MTHFD1L (methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like) gene (rs6922269) encodes a protein that affects serum levels of homocysteine, which is a known risk factor for cardiovascular disease.⁴

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
Intergenic_9p21	rs1333049	C	1.30	Asian	51.2%	Validated	18264662

Intergenic_9p21	rs1333049	C	1.29	Caucasian	45.6%	Validated	18362232
HNF1A	rs2259816	A	1.08	Caucasian	38.1%	Validated	19198612
Intergenic_1q41	rs3008621	G	1.10	Caucasian	87.8%	Validated	19164808
Intergenic_10q11	rs501120	T	1.11	Caucasian	83.3%	Validated	19164808
MTHFD1L	rs6922269	A	1.17	Caucasian	26.1%	Validated	17554300
MRAS	rs9818870	T	1.15	Caucasian	16.8%	Validated	19198612
SMAD3	rs17228212	C	1.19	Caucasian	33.9%	Preliminary	17634449
Intergenic_8p22	rs17411031	G	0.86	Caucasian	27.4%	Preliminary	17634449
Intergenic_2q36	rs2943634	C	1.22	Caucasian	65.5%	Preliminary	17634449
Intergenic_5q21	rs383830	A	1.60	Caucasian	79.2%	Preliminary	17554300
SEZ6L	rs688034	T	1.27	Caucasian	33.2%	Preliminary	17554300
CDH13	rs8055236	G	1.91	Caucasian	80.5%	Preliminary	17554300

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
414.1 Coronary atherosclerosis	N/A
Applies to:	
- Arteriosclerotic heart disease [ASHD] - Atherosclerotic heart disease	

• Coronary (artery): ◦ arteriosclerosis ◦ arteritis or endarteritis ◦ atheroma ◦ sclerosis ◦ stricture	

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Crigler-Najjar syndrome

Report Type: Carrier Status

About: Crigler-Najjar syndrome (CNS) is a serious inherited disease that results in the accumulation of toxic levels of bilirubin in the blood. While almost half of infants develop jaundice due to elevated bilirubin levels, those with CNS do not respond to classical treatments and have severe persistent jaundice.¹ CNS is classified into two types based on responsiveness to phenobarbital treatment, which induces UGT1A1 enzyme activity.² Type 1 CNS is more severe, and patients accumulate large deposits of bilirubin in their organs, including the brain, which can cause brain damage (kernicterus or bilirubin encephalopathy) within the first weeks to years of life and can be fatal. Type 2 patients typically have lower levels of bilirubin so brain damage is rarely observed, and many type 2 patients survive into adulthood without complications.¹

Genetics: CNS is caused by mutations in the UGT1A1 gene, which encodes uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1,³ which is involved in removal of bilirubin from the body. Bilirubin is normally removed from the blood by cells in the liver, where it is made water-soluble by UGT1A1 so that it can be excreted in the bile.⁴ Mutations in the UGT1A1 gene reduce or eliminate the activity of the enzyme, resulting in an accumulation of bilirubin in the blood stream. The buildup of bilirubin in the blood and organs results in severe jaundice and can cause organ damage and, in severe cases, lead to death.

Most of the known UGT1A1 mutations are extremely rare, found in one or two individuals or a family with CNS. However, at least two recurrent (founder) mutations have been identified; the test includes a founder mutation found in Tunisia (Q357R)⁵ and a founder mutation found in France (A401P).⁶

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes 61 mutations in the UGT1A1 gene.

UGT1A1 [L233R, A478D, I370V, E463A, Q185P, R403C, M204V, V160E, P34Q, W40R, G493R, IVS4+1G>T, L443P, 1186delG, N400D, H376R, I294T, 973delG, 397_402delCAACAA, L175Q, Q331R, L131P, K437X, 801delC, Q357X, A368T, A292V, C280X, W335X, S375F, 652insT, Q283X, S488F, K428E, W483X, 1223insG, IVS4-1G>A, P387R, 1220delA, 1043delA, IVS3-2A>G, Q331X, R341X, N279Y, IVS1+1G>C, 517delC, C177R, H39D, Y74X, R209W, Y192X, Y486D, V225G, Q357R, G377V, S381R, F170del, R336W, 878_890del, A401P, Q239fsX256]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c

UGT1A1	Caucasian	39%	1 in 500	1 in 819

^aPercentage of affected patients carrying mutations detected by this test.⁶

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.⁷ The actual carrier rate and the post-test residual risk are likely to be lower.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with Crigler-Najjar syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.4 Disorders of bilirubin excretion Applies to: • Hyperbilirubinemia: ◦ congenital ◦ constitutional • Syndrome: ◦ Crigler-Najjar ◦ Dubin-Johnson ◦ Gilbert's ◦ Rotor's	V82.71 Screening for genetic disease carrier status

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Cystic fibrosis

Report Type: Carrier Status

About: Cystic fibrosis (CF) is the most common genetic disease in Caucasians and affects over 70,000 people worldwide.^{1,2,3} The main diagnostic indicator of CF is that patients secrete an excess of sodium and chloride ions in their sweat. The most well-known symptoms include thick mucus in the lungs that leads to chronic and persistent respiratory infections and may lead to respiratory failure. Pancreatic insufficiency with malabsorption occurs in many individuals with CF. The symptoms of the disease vary widely among individuals depending on what types of mutations are found in the gene, as well as other genetic and environmental factors.⁴

Genetics: CF is caused by defects in the CFTR gene, which encodes an ion channel protein that is responsible for the transport of electrolytes across cell membranes.^{1,4} Although over 1,900 variants in the CFTR gene are now known,⁵ the most recurrent mutation, known as deltaF508, comprises up to 70% of CF cases found in some populations and is by far the most common CFTR mutation in the world. Only a few mutations occur at greater than 1% frequency, so that a panel of the 23 most common mutations is sufficient to account for a majority of CFTR mutations that cause classic CF in the general population (see table below).^{1,6,7} The vast majority of CF mutations are very rare.

There is a wide spectrum of clinical phenotypes associated with CFTR protein dysfunction,⁸ including (1) classic CF; (2) disorders that do not meet the definition of classic CF (e.g., congenital bilateral absence of the vas deferens (CBAVD), recurrent idiopathic pancreatitis); and (3) disorders that are associated with CFTR mutations, but do not follow a Mendelian pattern of inheritance (e.g., allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, idiopathic bronchiectasis).^{9,10}

Mode of Inheritance: Autosomal Recessive¹

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: In 2001, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) recommended offering prenatal and preconception CF carrier screening to all non-Hispanic white and Ashkenazi Jewish women of reproductive age using a pan-ethnic 25 mutation panel. In 2004, this recommendation was expanded to include all women of reproductive age, regardless of ethnicity, using a revised 23-mutation panel.^{1,11} The ACMG also identified CF as one of 29 diseases for which newborn screening should be mandated.¹²

If a patient has an R117H mutation, additional haplotype analysis is recommended to determine if the patient has the 5T allele.⁶ If the R117H and 5T mutations are on the same chromosome, the patient's offspring may be at risk for classic CF. If the R117H and 5T mutations are on different chromosomes, the patient's male offspring may be at risk for CBAVD. Refer to GeneReviews and the ACMG guidelines^{6,11} for a detailed discussion on the wide spectrum of phenotypes associated with the R117H and 5T mutations.

Emerging New Technologies: FDA has approved a drug for treatment of patients with two copies of the G551D mutation. Drugs for patients with other mutations are also being developed.¹³

Mutations Tested: The test includes 82 CF mutations in the CFTR gene. The 23 mutations recommended by ACMG/ACOG are underlined below.¹¹

CFTR [1078delT, 1677delTA, 1717-1G>A, 1812-1G>A, 1898+1G>A, 1949del84, 2043delG, 2055del9>A, 2105del13ins5, 2108delA, 2184delA, 2307insA, 2789+5G>A, 2869insG, 3120+1G>A, 3120G>A, 3171delC, 3272-26A>G, 3659delC, 3667ins4, 3791delC, 3849+10kbC>T, 3876delA, 3905insT, 394delTT, 405+1G>A, 405+3A>C, 444delA, 574delA, 621+1G>T, 663delT, 711+1G>T, 712-1G>T, 846delT, 935delA, 936delTA, A455E, A561E, C524X, D1152H, deltaF311, deltaF508, deltaI507, G1349D, G178R, G330X, G542X, G551D, G622D, G85E, K710X, L206W, L558S, M1101K, N1303K, P205S, P574H, P750L, Q1100P, Q1238X, Q359K/T360K, Q493X, R1158X, R1162X, R117H, R334W, R347P, R352Q, R553X, R560T, R709X, S1196X, S1251N, S364P, S549N, S549R (A>C), S549R (T>G), V232D, V520F/I, W1089X, W1204X, W1282X]

Ethnic Prevalence and Frequency of Mutations Tested^{7,14}

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c	Incidence ^d
CFTR	Ashkenazi Jew	94%	1 in 24	1 in 384	1 in 2,270
CFTR	Non-Hispanic Caucasian	88%	1 in 25	1 in 206	1 in 2,500
CFTR	African American	64%	1 in 61	1 in 171	1 in 15,100
CFTR	Hispanic Caucasian	72%	1 in 58	1 in 203	1 in 13,500
CFTR	Asian American	49%	1 in 94	1 in 183	1 in 35,100

^aPercentage of affected patients carrying the 23 mutations in the ACMG/ACOG recommended panel;⁷ the actual test detection rate may be higher.

^bCarrier risk before testing.

^cCarrier risk after a “not a carrier” test result.

^dNumber of CF patients born in one year in the U.S.

Limitations and Warnings: Since there are many very rare mutations associated with CF, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing

laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.1 Cystic fibrosis without mention of meconium ileus	V77.6 Screening for cystic fibrosis
Applies to: • Cystic fibrosis NOS	Applies to: • Screening for mucoviscidosis

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Diabetes, permanent neonatal

Report Type: Carrier Status

About: Neonatal diabetes (ND) is a rare form of diabetes that leads to low birth weight and the appearance of other symptoms, including hyperglycemia, excretion of glucose in the urine, dehydration and failure to thrive, within the first six months of life. In severe cases, infants may develop ketoacidosis, which can lead to coma. Once diagnosed, the condition can be corrected by administering insulin.¹

Genetics: ND is caused by mutations in several different genes that reduce or eliminate the production of insulin in the pancreas. ND can be temporary or permanent. In about half of the cases, insulin production resumes within 18 months, although the diabetes may return later in life; this is referred to as transient neonatal diabetes (TND). If the insulin deficiency is permanent, the condition is called permanent neonatal diabetes (PND). Mutations in several different genes can give rise to the two conditions, although sometimes different mutations in the same gene can give rise to either TND or PND. When first diagnosed, ND cannot be classified as transient or permanent by clinical symptoms alone; genetic testing can provide more definitive information as certain mutations are associated with the transient or the permanent form of ND.^{1,2}

Mutations in the PCNJ11, ABCC8, INS and GCK genes account for 30%, 19%, 20% and 4%, respectively, of reported PND cases.¹ These genes function in glucose homeostasis. INS encodes insulin and the other three genes encode proteins in pancreatic beta cells that are involved in regulating the secretion of insulin.

The test includes mutations in ABCC8 and GCK, the most common genes involved in autosomal recessive permanent neonatal diabetes. Most cases of PND are due to spontaneous mutations, but some mutations do recur in unrelated families.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes five mutations in two genes.

ABCC8 [E382K, P45L, N72S]; GCK [R397L, IVS8+2T>G]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with permanent neonatal diabetes, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing

laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
775.1 Neonatal diabetes mellitus	V77.1 Screening for diabetes mellitus
Applies to: Diabetes mellitus syndrome in newborn infant	

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Diabetes, type 1

Report Type: Health Conditions

About: Type 1 Diabetes (T1D) is a chronic disease that is characterized by the autoimmune destruction of pancreatic beta cells.¹ Symptoms include thirst, frequent urination, hunger, fatigue, weight loss, itchy skin and blurry eyesight, among others.² Individuals with T1D are unable to produce sufficient insulin to control blood glucose levels and as a result, require insulin. T1D is caused primarily by genetic factors that control the immune system and interact with environmental triggers.¹

Genetics: The majority of the genetic susceptibility to T1D lies in the Human Leukocyte Antigen complex (HLA) on chromosome 6.^{3,4} It is estimated that the HLA region accounts for about 40% of the observed familial clustering of T1D, while the currently known non-HLA genes account for about 7% to 8%.^{5,6}

The HLA Class II genes encode molecules that present “non-self”-derived proteins to T-cells. This group includes HLA-DRB1, HLA-DQA1 and HLA-DQB1, which represent the primary determinants of T1D risk. Risk is calculated based on the presence or absence of alleles in markers rs2187668 (A) and rs7454108 (C), which together tag the highest T1D risk genotype combination in Caucasians (HLA-DRB1*0301-DQA1*0501-DQB1*0201/HLA-DRB1*04-DQA1*0301-DQB1*0302).^{7,8} In addition, there are alleles at HLA Class I and Class III genes that have been implicated in T1D risk, but these have not been as well characterized.⁹

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
ERBB3	rs11171739	C	1.34	Caucasian	40.7%	Validated	17554300
IL2RA	rs12251307	C	1.33	Caucasian	89.8%	Validated	18978792
CLEC16A	rs12708716	A	1.89	Asian	76.2%	Validated	19178520
CLEC16A	rs12708716	A	1.23	Caucasian	68.1%	Validated	17554260
PTPN2	rs1893217	C	1.30	Caucasian	11.5%	Validated	17554260
IFIH1	rs1990760	T	1.18	Caucasian	62.5%	Validated	17554260
Intergenic_4q27	rs2069763	T	1.13	Caucasian	32.9%	Validated	19073967
HLA	rs2187668	A	3.64	Caucasian	8.0%	Validated	18252895
PTPN22	rs2476601	A	1.96	Caucasian	11.7%	Validated	17554260

CTLA4	rs3087243	G	1.18	Caucasian	54.0%	Validated	17554260
SH2B3	rs3184504	T	1.35	Caucasian	44.5%	Validated	19073967
INS	rs3741208	T	1.25	Caucasian	35.7%	Validated	17554260
HLA	rs7454108	C	7.23	Caucasian	18.1%	Validated	18252895
PTPN22	rs2488457	G	1.41	Asian	67.3%	Preliminary	16470599
IL2RA	rs3118470	C	1.18	Asian	54.8%	Preliminary	19106270

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
250.01 Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled	V77.1

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Diabetes, type 2

Report Type: Health Conditions

About: Type 2 diabetes (T2D) accounts for approximately 90% of individuals with diabetes. It is estimated that over 6% of individuals in the world between the ages of 20 and 79 have the condition.¹ This chronic disease is characterized by high blood glucose levels that are caused by a defect in the insulin signaling pathway.² Risk factors for T2D include family history and obesity, and research indicates that multiple genetic factors are also associated with the disease.¹

Genetics: T2D arises from a combination of genetic and environmental factors.¹ The heritability of T2D is well-established by familial studies, yet environmental and lifestyle factors must also play a role in the development of T2D because the prevalence of T2D has increased dramatically in the last 50 years, a period of time too brief to be explained by changes in gene frequencies. Most of the genetic variants associated with an increased risk for T2D impact the development or function of pancreatic beta-cells, which produce, store and secrete the hormone insulin.³ In addition, genetic factors associated with fat mass and increased risk for obesity also contribute to the development of T2D.¹

Genes in the T2D test that affect pancreatic beta-cells include CDKAL1,⁴ CDKN2B,⁵ HHEX,^{6,7,8} HNF1B,⁹ JAZF1,¹⁰ KCNJ11,^{11,12} KCNQ1,¹³ NOTCH2,¹⁴ SLC30A8,^{6,7,15,16} TCF7L2^{17,18,19} and WFS1.²⁰

The T2D test also includes genes associated with fat mass and obesity risk, such as FTO,²¹ IGF2BP2,^{22,23} PPARG,^{24,25} ADIPOQ²⁶ and ESR1.^{27,28}

The most consistent evidence for the association of genetic markers with T2D has come from large-scale T2D genetic studies in European populations.

Individuals of African American ancestry are twice as likely to develop Type 2 Diabetes (T2D) as those of Caucasian ancestry, particularly African American women. African American populations have been studied for most of the Caucasian T2D-associated gene markers. Due to differences in allele frequencies in the two ethnic population and the smaller number of African Americans studied, only a few of the Caucasian markers have been found to be associated with T2D in Africans.

Recently, many studies initially conducted in Caucasian populations have been replicated in Japanese populations, and an overlap in disease variants has been discovered. In addition, the shared variants appear to confer a higher disease risk in Japanese versus Caucasians. This may be due to the fact that the Japanese (in Japan) are a leaner and more homogenous population in comparison. A large proportion of Asian type 2 diabetics are non-obese, and studies have shown that non-obese T2D patients progress to insulin dependence faster. Non-obese T2D Europeans or Japanese-Americans have a higher prevalence of TCF7L2 and PPARG risk alleles, respectively, compared to individuals who do not have T2D.^{29,30,31} Furthermore, it has been shown that although they are not obese, the fat distribution of non-obese type 2 diabetics tends to be abdominal. The gene variants repeatedly showing the highest odds ratios associated with T2D in Japanese are TCF7L2, CDKAL1, CDKN2B and KCNQ1. As with other populations, recently replicated studies in Chinese populations show an overlap in disease variants compared to those discovered in Caucasian populations.³²

Recommendations: The U.S. Preventative Services Task Force recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mmHg.³³

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
WFS1	rs10010131	G	1.12	Caucasian	67.7%	Validated	18040659
CDKN2B	rs10811661	T	1.27	Asian	57.7%	Validated	18477659
CDKN2B	rs10811661	T	1.20	Caucasian	80.1%	Validated	17463246
MTNR1B	rs10830963	G	1.16	Asian	41.7%	Validated	19241057
MTNR1B	rs10830963	G	1.09	Caucasian	30.0%	Validated	19060907
NOTCH2	rs10923931	T	1.13	Caucasian	9.3%	Validated	18372903
CDKAL1	rs10946398	C	1.16	Caucasian	33.6%	Validated	17463249
HHEX	rs1111875	G	1.27	Asian	31.5%	Validated	18477659
HHEX	rs1111875	G	1.15	Caucasian	58.4%	Validated	17463246
SLC30A8	rs13266634	C	1.17	Asian	53.0%	Validated	18469204
SLC30A8	rs13266634	C	1.12	Caucasian	76.1%	Validated	17463249
IGF2BP2	rs1470579	C	1.18	Asian	26.2%	Validated	18477659
IGF2BP2	rs1470579	C	1.19	Caucasian	29.6%	Validated	17463246
PPARG	rs1801282	C	1.75	Asian	95.2%	Validated	11289058
PPARG	rs1801282	C	1.23	Caucasian	90.3%	Validated	17463249
KCNQ1	rs2237892	C	1.43	Asian	65.5%	Validated	18711367
KCNQ1	rs2237892	C	1.29	Caucasian	92.5%	Validated	18711367
KCNJ11	rs5219	T	1.25	Asian	35.5%	Validated	18162508
KCNJ11	rs5219	T	1.15	Caucasian	36.0%	Validated	17463246
HNF1B	rs7501939	T	1.15	Caucasian	43.4%	Validated	17603484
CDKAL1	rs7754840	C	1.27	Asian	42.3%	Validated	18766326
TCF7L2	rs7903146	T	1.51	African	33.7%	Validated	17601994
TCF7L2	rs7903146	T	1.59	Asian	2.4%	Validated	19012045
TCF7L2	rs7903146	T	1.38	Caucasian	27.9%	Validated	17463246
FTO	rs8050136	A	1.27	Caucasian	46.0%	Validated	17463249

JAZF1	rs864745	T	1.10	Caucasian	48.7%	Validated	18372903
ESR1	rs1569788	C	1.25	African	52.9%	Preliminary	18305958
ADIPOQ	rs182052	A	1.24	African	38.7%	Preliminary	19056609
ESR1	rs3020314	C	1.23	Caucasian	25.7%	Preliminary	18854778
Intergenic_6q24	rs4897081	A	1.28	African	51.0%	Preliminary	18560894

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
250.02 Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled	V77.1 Screen-diabetes mellitus

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Dihydropyrimidine dehydrogenase deficiency

Report Type: Carrier Status

About: Dihydropyrimidine dehydrogenase (DPD) deficiency is a serious inherited disorder that leads to the accumulation of pyrimidines in the body. The most common symptoms include convulsive disorders, mental retardation and delays in motor development. Less frequently, patients have dysmorphic features, including small heads, eye abnormalities and growth retardation.¹ Symptoms of complete deficiency are typically observed first in infancy or early childhood. In families where siblings have the same DPYD gene mutation, sometimes only one sibling will develop symptoms.¹

Genetics: DPD deficiency is caused by mutations in the DPYD gene, which encodes an enzyme that is involved in the breakdown of pyrimidines.² Pyrimidine levels are strictly regulated because they have many roles in the body, including regulation of nervous system function.³ Pathogenic mutations in the DPYD gene reduce or eliminate the activity of the DPD enzyme, resulting in an accumulation of pyrimidines that leads to clinical symptoms.¹

Individuals who are homozygous for DPYD mutations are often asymptomatic but are at risk for severe adverse events when treated with 5-fluorouracil (5-FU), a chemotherapeutic agent, or its prodrugs, capecitabine or tegafur.⁴ DPD is required for the breakdown and clearance of 5-FU. In patients with DPD deficiency, administration of 5-FU or its prodrugs can result in toxic accumulation of 5-FU and has been associated with severe complications, even death, in response to treatment. It is estimated that 4% to 7% of the U.S. population have a DPD deficiency, which can be asymptomatic and not detected until they are treated with 5-FU or its prodrugs.⁴

The test includes 11 mutations in the DPYD gene, including the most common variant, IVS14+1G>A (also known as DPYD*2A). In one study from Northern Europe, this mutation accounted for more than half of the mutations in patients from 17 families with severe deficiency.¹ This mutation has also been associated with mild deficiency.⁴

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes eleven mutations in the DPYD gene.

DPYD [V335L, R235W, R886H, M182K, P86L, I560S, IVS11+1G>T, E386X, H978R, IVS14+1G>A, A777S]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
DPYD	Caucasian	52%	1 in 56	1 in 115

^aPercentage of affected patients carrying mutations detected by this test.^{1,5}

^bCarrier risk before testing.⁵

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with dihydropyrimidine dehydrogenase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.6 Other deficiencies of circulating enzymes	V82.71 Screening for genetic disease carrier status
Applies to:	
• Hereditary angioedema	

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Dubin-Johnson syndrome

Report Type: Carrier Status

About: Dubin-Johnson syndrome (DJS), also known as hyperbilirubinemia type II, is a rare, inherited disorder. Most individuals with DJS have no symptoms, but as teenagers, patients may develop jaundice caused by chronic or intermittent conjugated hyperbilirubinemia.¹ Individuals with DJS have a normal lifespan.

Genetics: DJS is caused by mutations in the ABCC2 gene,^{2,3} which encodes canalicular multispecific organic anion transporter 1. This protein is found in liver cells and excretes waste substances into bile, including bilirubin. When the ABCC2 protein product is inactivated by mutation, liver cells are unable to excrete a water-soluble form of bilirubin called conjugated bilirubin, which can lead to jaundice.⁴

The test includes the two most common mutations in the ABCC2 gene. The I1173F mutation is very common in Iranian Jews with Dubin-Johnson syndrome⁵ and the R1150H mutation is very common in Moroccan Jews with Dubin-Johnson syndrome⁵.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes two mutations in the ABCC2 gene.

ABCC2 [R1150H and I1173F]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
ABCC2	Moroccan Jew	100%	1 in 18	0
ABCC2	Iranian Jew	100%	1 in 18	0

^aPercentage of affected patients carrying mutations detected by this test⁵.

^bCarrier risk before testing.⁶

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other very rare mutations associated with Dubin-Johnson syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.4 Disorders of bilirubin excretion Applies to: • Hyperbilirubinemia: ◦ congenital ◦ constitutional • Syndrome: ◦ Crigler-Najjar ◦ Dubin-Johnson ◦ Gilbert's ◦ Rotor's	V82.71 Screening for genetic disease carrier status

References

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Ehlers-Danlos syndrome, dermatosparaxis

Report Type: Carrier Status

About: Ehlers-Danlos syndromes (EDS) comprise a diverse group of diseases that affect the connective tissues of the skin, joints and blood vessels. EDS is characterized by varying degrees of skin elasticity, easy bruising and delayed wound healing with abnormal scarring, highly-bendable joints and generally fragile tissues.¹ Mutations in many genes can cause EDS because many genes are involved in the formation of connective tissue, both as enzymes and as structural components.

EDS is further classified into six well-defined subtypes (Classical, Hypermobility, Vascular, Kyphoscoliotic, Arthrochalasia and Dermatosparaxis) and a few variant overlap syndromes based on the overall presentation of the disease in an individual or a family. Dermatosparaxis EDS is also associated with sagging, redundant skin (excessive skin that folds) in patients. The condition may cause large umbilical and inguinal hernias, and premature rupture of the fetal membrane.

Genetics: Dermatosparaxis EDS is caused by mutations in the ADAMTS2 gene,² which encodes the enzyme procollagen I N-proteinase (PNPI) that processes the precursor of collagen (procollagen) into collagen. Without proper processing, procollagen forms abnormal fibrils (tissue components) that lack tensile strength. Fine structure observations of the affected skin show collagen chains that are larger than usual and apparently caused by faulty processing of procollagen.³ The disease was initially classified “Ehlers- Danlos syndrome type VIIc” but is now known as dermatosparaxis Ehlers-Danlos syndrome.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes two mutations in the ADAMTS2 gene.

ADAMTS2 [Q225X, W795X]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with dermatosparaxis Ehlers-Danlos syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
756.83 Ehlers-Danlos syndrome	V82.71 Screening for genetic disease carrier status

References

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Ehlers-Danlos syndrome, hypermobility

Report Type: Carrier Status

About: Ehlers-Danlos syndromes (EDS) comprise a diverse group of diseases that affect the connective tissues of the skin, joints and blood vessels. EDS is characterized by varying degrees of skin elasticity, easy bruising and delayed wound healing with abnormal scarring, highly-bendable joints and generally fragile tissues.¹ Mutations in many genes can cause EDS because many genes are involved in the formation of connective tissue, both as enzymes and as structural components.

EDS is further classified into six well-defined subtypes (Classical, Hypermobility, Vascular, Kyphoscoliotic, Arthrochalasia and Dermatosparaxis) and a few variant overlap syndromes based on the overall presentation of the disease in an individual or a family. Hypermobility (or type III) EDS is considered the least severe EDS. Patients with this disease have pronounced joint hypermobility but show no deformations of their skeletal systems. Skin pathologies are minimal, distinguishing it from Classical EDS. The condition leads to recurring dislocations, even with minimum trauma, and chronic pain.²

Genetics: Hypermobility EDS is caused by mutations in the TNXB gene, which encodes the tenascin-X protein that localizes in the matrix between cells.³ The function of tenascin-X is largely unknown but may be important in organizing and maintaining the connective tissue structure in the muscles, joints, skin and organs. The TNXB gene is also mutated in classic-like EDS, a disease with symptoms that overlap with hypermobility EDS but primarily manifests in the skin.²

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes two mutations in the TNXB gene.

TNXB [3551_3552delAA, 2116_2117dupGT]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with hypermobility Ehlers-Danlos syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
756.83 Ehlers-Danlos syndrome	V82.71 Screening for genetic disease carrier status

References

1. Callewaert B, Malfait F, Loeys B, De Paepe A. Ehlers-Danlos syndromes and Marfan syndrome. *Best practice & research. Clinical rheumatology*. 2008;22:165-89.
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Ehlers-Danlos syndrome, kyphoscoliotic

Report Type: Carrier Status

About: Ehlers-Danlos syndromes (EDS) comprise a diverse group of diseases that affect the connective tissues of the skin, joints and blood vessels. EDS is characterized by varying degrees of skin elasticity, easy bruising and delayed wound healing with abnormal scarring, highly-bendable joints and generally fragile tissues.¹ Mutations in many genes can cause EDS because many genes are involved in the formation of connective tissue, both as enzymes and as structural components.

EDS is further classified into six well-defined subtypes (Classical, Hypermobility, Vascular, Kyphoscoliotic, Arthrochalasia and Dermatosparaxis) and a few variant overlap syndromes based on the overall presentation of the disease in an individual or a family. Kyphoscoliotic (or type VI) EDS may overlap in symptoms with classical EDS (extensible skin, easy bruising, abnormal scarring, highly bendable joints) and vascular EDS (arterial rupture and complications), but it is mainly recognized by progressive scoliosis and severely limited muscle tone that are often evident soon after birth.² In some patients, the globe of the eye is also very fragile.³

Genetics: Kyphoscoliotic EDS is caused by mutations in the PLOD1 gene, which encodes an enzyme that adds hydroxyl groups to lysine residues in collagen molecules (procollagen-lysine,2-oxoglutarate 5-dioxygenase 1). Collagen derives its strength from the cross-linking of collagen fibrils, and without hydroxylysine, the ability of the fibrils to cross-link with each other is compromised.⁴ 100% of patients who are homozygous for disease-causing mutations in PLOD1 develop kyphoscoliotic EDS.³

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes 16 mutations in the PLOD1 gene.

PLOD1 [A667T, H706R, W446G, 1362delC, 1702insC, R670X, Y142X, Q327X, 467-2delA, Q49X, 153dupC, 975+2_975+3insTT, W612C, G678R, Y511X, R319X]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with kyphoscoliotic Ehlers-Danlos syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing

laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
756.83 Ehlers-Danlos syndrome	V82.71 Screening for genetic disease carrier status

References

1. Callewaert B, Malfait F, Loeys B, De Paepe A. Ehlers-Danlos syndromes and Marfan syndrome. *Best practice & research. Clinical rheumatology*. 2008;22:165-89.
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Estrogen supplementation

(DC:TB-0228.001 06DEC2012)

Report Type: Pharmacogenetics

About: Combined hormonal contraceptives and post-menopausal hormone replacement therapy products contain estrogen. These medications by themselves pose an increased risk of blood clots (venous thrombosis), but the risk is even greater when they are used by individuals with certain inherited blood clotting disorders. Relatively common variants in two genes that code for components of the blood clotting cascade confer this increased risk.¹

Genetics: The Factor V Leiden variant in the F5 gene, which encodes the factor V coagulation cofactor, and the G20210A mutation in the F2, or prothrombin gene, are associated with an increased risk of venous thrombosis in women using combined oral contraceptives or hormone replacement therapy.^{2,3,4} Both the Factor V Leiden and the G20210A variants have dominant inheritance patterns, meaning that inheriting only one copy of the variant places a woman at increased risk of experiencing venous thrombosis if she uses estrogen supplementation.

By themselves, combined oral contraceptives increase the risk for blood clots in women 4-fold. Women who carry the Factor V Leiden mutation alone have an 8-fold increase in the risk for blood clots. Women who carry the Factor V Leiden mutation and who use combined oral contraceptives increase their risk for blood clots 35-fold.^{1,5} In a meta-analysis of six case-control studies and one cohort study, presence of Factor V Leiden alone increased the risk of venous thromboembolism in combined oral contraceptive users over non-users.¹ In three case-control studies and one cohort study, the F2 G20210A variant alone also increased the risk of venous thromboembolism in combined oral contraceptive users over non-users.⁶

Post-menopausal hormone replacement therapy with oral estrogen also presents a risk to women with the Factor V Leiden and G20210A mutations. In women undergoing estrogen hormone replacement therapy, the Factor V Leiden mutation is associated with increased risk for deep vein thrombosis.^{1,7} Additionally, a meta-analysis of six independent studies found that the Factor V Leiden and G20210A mutations increased the risk of blood clots in women undergoing estrogen hormone replacement therapy.⁴ In an observational study of postmenopausal women carrying the Factor V Leiden or G20210A mutations, oral estrogen but not transdermal estrogen conferred additional risk of venous thromboembolism.⁸

Recommendations: According to the World Health Organization (WHO),⁹ the U.K. Medical Eligibility Criteria¹⁰ and the U.S. Centers for Disease Control and Prevention (CDC),¹¹ the use of combined oral contraceptives, the combined contraceptive patch or the combined contraceptive vaginal ring in individuals with known thrombogenic mutations (e.g., Factor V Leiden, prothrombin mutation, protein S, protein C and antithrombin deficiencies) is an unacceptable health risk (level 4). The WHO also concludes that the evidence for combined oral contraceptives applies to combined injectable contraceptives. The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group recommends selecting alternative therapies to estrogen-containing oral contraceptives when a patient has the Factor V Leiden mutation and a family history of thrombotic events.¹²

The North American Menopause Society¹³ and the Endocrine Society¹⁴ acknowledge that thrombogenic mutations, such as Factor V Leiden, can increase the risk of venous thromboembolism, but they make no recommendations against using hormone replacement therapy in women with thrombogenic mutations. They do recommend thrombophilia screening prior to hormone replacement therapy use for women with a personal or family history of venous thromboembolism. For women with thromboembolic risk factors, the International Menopause Society suggests non-oral routes of estrogen or tibolone may be used if hormone replacement therapy is considered appropriate.¹⁵

The prevalence of individuals with one copy of both the Factor V Leiden and G20210A mutations is 1 in 1,000.¹¹

Possible Outcomes: Increased Risk of Venous Thrombosis, Normal Risk of Venous Thrombosis

Markers and Alleles Tested: F5 [Factor V Leiden/R506Q]; F2 [G20210A]

Ethnic Distribution of Tested Alleles: The carrier rate for Factor V Leiden is 1 in 19 U.S. Caucasians, 1 in 45 Hispanic Americans, 1 in 83 African Americans, 1 in 222 Asian Americans and 1 in 80 Native Americans. In Europe, the mutation is particularly common with a carrier rate of 1 in 6 to 1 in 10 in southern Sweden and Greece and 1 in 33 to 1 in 50 in Italy and Spain. Similar high numbers have been found in many Middle Eastern countries.¹⁶

The carrier rate for G20210A is 2% to 5% in U. S. Caucasians. The mutation is found in 2% to 4% of healthy individuals in southern Europe, which is twice as high as the prevalence in northern Europe. G20210A is rare in Far Eastern populations, in Africa, and in indigenous populations of Australia and the Americas.¹⁶

Limitations and Warnings: Genetic variants in other proteins, such as protein S, protein C and antithrombin are known to increase the risk of venous thrombosis, but are not part of this test. Non-genetic factors known to increase the risk of venous thrombosis include age, obesity, trauma/surgery, smoking, pregnancy and airplane travel.⁴

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
E932.2 Ovarian hormones and synthetic substitutes causing adverse effects in therapeutic use	V78.9 Screening for unspecified disorder of blood and blood-forming organs
Applies to: • Contraceptives, oral • Estrogens • Estrogens and progestogens combined • Progestogens	

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Exfoliation glaucoma

Report Type: Health Conditions

About: Exfoliation glaucoma (XFG), also known as pseudoexfoliation glaucoma, accounts for about 12% of glaucoma cases and mainly affects older people.¹ Clinically, XFG is considered a symptom of a systemic condition called exfoliation syndrome (XFS), also known as pseudoexfoliation syndrome. One risk factor for XFS is a family history of the condition,² and research indicates that genetic factors, such as variants in the LOXL gene, are also associated with XFG.³

Genetics: The genetic contribution to different forms of glaucoma is believed to include both rare Mendelian mutations and common susceptibility alleles.⁴ For XFG, a common susceptibility allele has been identified.

The genetic marker rs2165241 in the LOXL1 gene, which encodes lysyl oxidase-like protein 1, was found to be associated with XFS in a large study of Caucasians from Iceland and Sweden.³ The LOXL1 protein is believed to assist in the construction and maintenance of the extracellular matrix, which provides structural support to cells. LOXL1 is expressed by many cell types in the eye, and changes in the LOXL1 gene may lead to defective processing of extracellular matrix proteins.³ Approximately 35% of people with European ancestry carry one copy of the risk allele of rs2165241 and about 22% carry two copies. However, the prevalence of XFS in most countries is much lower than the frequency of this allele, indicating that other genetic and environmental factors contribute to risk for XLS. Interestingly, the amount of risk associated with rs2165241 has been observed to be lower in Caucasians in Australia compared to Caucasians in Nordic countries.⁵ The rs2165241 marker is not associated with the risk of developing non-XFS types of glaucoma.³

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
LOXL1	rs2165241	T	3.62	Caucasian	43.8%	Preliminary	17690259

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in

genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
365.9 Unspecified glaucoma	V80.1 Screening for glaucoma

References

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Factor XI deficiency

Report Type: Carrier Status

About: Factor XI deficiency, also called hemophilia C, is a mild form of hemophilia.¹ The condition is especially prevalent among Ashkenazi Jews, and bleeding occurs more frequently after surgery or trauma in tissues with mucosal surfaces (e.g., the mouth, nose, urinary tract, genital tract). In contrast to hemophilia A and B, spontaneous bleeding, deep muscle bleeding and joint bleeding are uncommon in factor XI deficiency. Also in contrast to hemophilia A and B, the severity of bleeding does not correspond to the level of coagulation factor activity in the blood.²

Genetics: Factor XI deficiency is caused by mutations in the F11 gene, which encodes the coagulation factor XI that is involved in blood clot formation. Severe factor XI deficiency is an injury-related bleeding disorder and is characterized by complications due to excessive bleeding, following injury.³

The test includes four mutations in the F11 gene. Two alleles, E117X and F283L are responsible for 98% of Factor XI deficiencies in Ashkenazi Jews.⁴ The E117X allele has been found in both Ashkenazi and non-Ashkenazi Jews, suggesting that the E117X allele arose in an individual who lived in ancient times before the divergence of the Ashkenazi and Sephardic Jews.⁵ In contrast, the F283L allele is restricted to Ashkenazi Jews, suggesting that it arose more recently in an Ashkenazi Jewish individual.⁵ The C128X allele accounts for 10% to 15% of abnormal alleles in non-Jewish patients in the U.K.⁶

The estimated incidence of factor XI deficiency in the American population is 1 in 100,000.⁷ The frequency is much higher in certain ethnic groups. One in 11 Ashkenazi Jews is a carrier for one of the two most common factor XI mutations (E117X and F283L).⁸ Fewer common mutations have been found in non-Jewish population groups. In a study of 116 ethnically diverse factor XI deficient patients in the U.K., Mitchell et al.⁶ found that 40% of the mutations were one of the three common mutations (E117X, F283L and C128X). The remaining 60% of mutations included 31 novel mutations and whole gene deletions.

Although some factor XI deficiency mutations have an autosomal dominant inheritance pattern, the test only includes factor XI deficiency mutations that have an autosomal recessive pattern of inheritance.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes four mutations in the F11 gene.

F11 [E117X, F283L, C128X, IVS14+1G>A]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
F11	Ashkenazi Jew	98%	1 in 11	1 in 501
F11	U.K. Panethnic	39%	1 in 500	1 in 819

^aPercentage of affected patients carrying mutations detected by this test.^{6,9}

^bCarrier risk before testing. Ashkenazi Jew.^{8,10} U. K. panethnic (The true carrier rate is unknown for this extremely rare disease. The carrier rate of 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.^{11,12} The actual carrier rate and the post-test residual risk are likely to be lower.).

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with factor XI deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
286.2 Congenital factor XI deficiency Applies to: • Hemophilia C • Plasma thromboplastin antecedent [PTA] deficiency • Rosenthal's disease	V82.71 Screening for genetic disease carrier status

References

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Familial dysautonomia

Report Type: Carrier Status

About: Familial dysautonomia (FD), also known as Riley Day syndrome, is an inherited disease found almost exclusively in Ashkenazi Jews and leads to the progressive deterioration of nerve cells in the autonomic and sensory nervous systems. In infants with FD, the most distinctive symptom is the absence of overflow tears with emotional crying. Older children may display delayed speech and walking, excessive drooling and sweating, frequent lung infections, and dry eyes. Lung disease and unexplained sudden death are the main causes of shortened lifespan in patients with FD. At present, there is no cure and only 50% of patients survive to age 40.^{1,2}

Genetics: FD is caused by mutations in the IKBKAP gene, which encodes the ELP1 protein.^{1,3} ELP1 is important for regulating neuronal development, which can explain the neuronal degeneration associated with FD.^{4,5}

The IVS20+6T>C mutation is responsible for almost all occurrences (greater than 99%) of familial dysautonomia in Ashkenazi Jews.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) recommends offering prenatal and preconception carrier screening for familial dysautonomia to individuals with Ashkenazi Jewish ancestry or a positive family history of the disease.^{6,7}

Mutations Tested: The test includes two mutations in the IKBKAP gene. ACMG recommends screening in Ashkenazi Jews for both mutations, which are underlined below.⁸

IKBKAP [IVS20+6T>C, R696P]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c	Incidence ^d
IKBKAP	Ashkenazi Jew	99%	1 in 31	1 in 3,001	1 in 3,600

^aPercentage of affected patients carrying mutations detected by this test.⁸

^bCarrier risk before testing.⁸

^cCarrier risk after a “not a carrier” test result.

^dNumber of familial dysautonomia patients born in one year.⁹

Limitations and Warnings: Since there are other very rare mutations associated with familial dysautonomia, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
742.8 Other specified congenital anomalies of nervous system Applies to: • Agenesis of nerve • Displacement of brachial plexus • Familial dysautonomia • Jaw-winking syndrome • Marcus-Gunn syndrome • Riley-Day syndrome	V82.71 Screening for genetic disease carrier status

References

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Familial Mediterranean fever

Report Type: Carrier Status

About: Familial Mediterranean fever (FMF) is an inherited disease that causes recurrent episodes of fever and painful inflammation of the membranes that enclose several body cavities. Membranes in the abdomen, joints, and chest are most commonly affected. FMF patients typically experience their first inflammation episode as children, but the first attack can also happen later in life. Although the symptoms usually resolve within one to four days, the acute inflammation induces a buildup of immune response proteins in the plasma and may cause amyloidosis in the kidneys and other organs of some patients. Kidney failure caused by amyloidosis is the major life-threatening complication of FMF.^{1,2}

Genetics: FMF is caused by mutations in the MEFV gene, which encodes a protein called pyrin or marenostrin that is found in some types of white blood cells. Without the regulation of pyrin, the immune response is unchecked and leads to attacks of fever and inflammation. Most FMF cases are found in people of Eastern Mediterranean descent. In non-Ashkenazi Jewish, Armenian, Arab and Turkish populations, the prevalence of FMF varies from 1 in 200 to 1 in 1,000.^{1,3,4}

The test includes prevalent MEFV mutations found in various ethnic groups. M694V, which is associated with amyloidosis and more severe forms of FMF, is the most common mutation in Jordan, Lebanon, Turkey, Arabs from Morocco and Tunisia, and the Jewish populations in Iraq and North Africa. Other common mutations found in Jewish and Arab patients include V726A, M680I, and M694I.^{1,5}

The prevalence of the disease in those of Ashkenazi Jewish descent is estimated at 1 case per 73,000 individuals, which is a disease prevalence much lower than would be expected given the frequency of MEFV mutations identified in that population. This suggests that some MEFV gene mutations have relatively low penetrance, meaning that they do not always cause disease.⁶

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes eight mutations in the MEFV gene.

MEFV [R653H, M680I, M694I, M694V, V726A, K695R, A744S, R761H]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
MEFV	Arab	53%	1 in 7	1 in 13
MEFV	Armenian	79%	1 in 3	1 in 9

MEFV	Non-Ashkenazi Jew	69%	1 in 4	1 in 11
MEFV	Turkish	76%	1 in 6	1 in 22
MEFV	Ashkenazi Jew	54%	1 in 4	1 in 8

^aPercentage of affected patients carrying mutations detected by this test.⁵

^bCarrier risk before testing.⁵

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are many mutations associated with familial Mediterranean fever, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.31 Familial Mediterranean fever Applies to: • Benign paroxysmal peritonitis • Hereditary amyloid nephropathy • Periodic familial polyserositis • Recurrent polyserositis	V82.71 Screening for genetic disease carrier status

References

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Fanconi anemia

Report Type: Carrier Status

About: Fanconi anemia (FA) is a rare inherited disease that is characterized by aplastic anemia, an increased risk for cancer and leukemia, and cellular hypersensitivity to drugs or agents that act by crosslinking DNA. FA patients may have short stature, developmental delay and congenital anomalies of the limbs, heart and/or kidney.^{1,2} Other FA patients are free from any visible disorder except for bone marrow failure that typically occurs before the age of 10. The median survival age of FA patients is 30 years, and at least 20% of FA patients also develop cancer. The definitive test for FA is a chromosome breakage test.³

Genetics: FA is caused by mutations in thirteen genes that encode proteins in the FA-BRCA pathway, which is a DNA damage-activated signaling pathway that regulates DNA repair. This DNA repair defect in Fanconi anemia cells removes an important protection against the development of cancer and leukemia. Less is known about why bone marrow failure occurs in FA, but one possibility that has been suggested is that FA genes somehow function to protect blood progenitor cells from oxidative stress.^{1,4,5}

In the U.S. and Canada, 50 percent of FA patients are Ashkenazi Jews,^{3,6} although FA is found in all ethnic groups.

The test includes six mutations in the FANCC gene; mutations in the FANCC gene (Fanconi anemia, complementation group C) are responsible for 10% to 15% of all cases of Fanconi anemia.^{7,8} The most common FANCC mutation, IVS4+4A>T, is unique to FA patients of Ashkenazi Jewish background and has a carrier frequency of greater than 1 in 100 in this population.^{6,9} The 322delG mutation is the next most common FANCC mutation after IV4+4A>T. Together with IVS4+4A>T, 322delG makes up approximately 85% of all FANCC mutations.⁷ The R548X mutation is the third most common FANCC mutation.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics (ACMG) recommends offering carrier screening for Fanconi anemia to individuals with Ashkenazi Jewish ancestry.⁹

Mutations Tested: The test includes six mutations in the FANCC gene. ACMG recommends screening in Ashkenazi Jews for one mutation, which is underlined.⁹

FANCC [322delG, L554P, R185X, R548X, Q13X, IVS4+4A>T]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c

FANCC	Ashkenazi Jew	99%	1 in 89	1 in 8,801

^aPercentage of affected patients carrying mutations detected by this test.⁹

^bCarrier risk before testing.⁹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with Fanconi anemia, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
284.1 Constitutional red blood cell aplasia Applies to: • Aplasia, (pure) red cell: ◦ congenital ◦ of infants ◦ primary • Blackfan-Diamond syndrome • Familial hypoplastic anemia	V82.71 Screening for genetic disease carrier status

References

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Galactokinase deficiency

Report Type: Carrier Status

About: Galactokinase deficiency, also called galactosemia type 2, is one of the three inborn errors of metabolism that results in hypergalactosemia and the subsequent buildup of galactose and galactitol in the lens of the eye. The major clinical symptoms are the development of cataracts in children who are not maintained on a lactose-free diet and the appearance of presenile cataracts in adults. The disease is preventable in infants through early diagnosis and treatment with a galactose-restricted diet, which includes the avoidance of all milk products since lactose is a major source of galactose.^{1,2}

Genetics: Galactokinase deficiency is caused by mutations in the GALK1 gene, which encodes the enzyme galactokinase that catalyzes the first step in galactose metabolism. Mutations in GALK1 reduce the activity of galactokinase and cause high levels of galactose to build up in the blood.^{3,4} In the lens of the eye, an enzyme called aldose reductase converts galactose to galactitol. High levels of galactitol in the lens causes increased uptake of water by osmosis which leads to cell swelling, lysis and cataracts.

The test includes several mutations in the GALK1 gene. Of these, the Q382X mutation was found in six out of thirteen different individuals of European descent in Costa Rica. All patients but one were homozygous for the mutation.¹

Please also see the carrier status test for the related condition, galactosemia.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes four mutations in the GALK1 gene.

GALK1 [G349S, R256W, T344M, Q382X]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other rare mutations associated with galactokinase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

271.1 Galactosemia	V77.4 Screen for galactosemia
Applies to:	
- Galactose-1-phosphate uridyl transferase deficiency - Galactosuria	

References

1. Kolosha V, Anoia E, de Cespedes C, et al. Novel mutations in 13 probands with galactokinase deficiency. *Human mutation*. 2000;15:447-53.
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Galactosemia

Report Type: Carrier Status

About: Galactosemia is a hereditary disease that is characterized by high levels of galactose in the blood. Because breast milk or dairy products are usually the primary source of nutrition for newborns, galactosemia can cause life-threatening and irreversible damages in affected infants immediately after birth. Common symptoms of untreated patients include feeding difficulties, diarrhea, vomiting, failure to gain weight, liver failure, bleeding, severe bacterial infection, cataracts, and mental retardation. Severe symptoms and complications can be avoided if the diagnosis is prompt and sources of lactose or galactose are immediately eliminated from food intake.¹

Genetics: Classic and Duarte variant forms of galactosemia are caused by mutations in the GALT gene, which encodes the enzyme galactose-1-phosphate uridylyltransferase that metabolizes galactose.¹ Depending on the mutation, galactosemia can be categorized into classic galactosemia and a milder form called “Duarte variant galactosemia”, which typically does not cause complications as severe as those seen in the classic form of the disease. The incidence of classic galactosemia is about 1 in 30,000 live births,¹ whereas Duarte variant galactosemia has an incidence as high as 1 in 4,000 live births.²

The test includes 10 mutations in the GALT gene. Seven of them (Q188R, S135L, K285N, L195P, Y209C, F171S, and IVS2-2A>G) are common mutations found in classic galactosemia patients.^{1,3,4,5} A GALT mutation that causes classic galactosemia is called a “G allele”. In individuals with two G alleles, GALT enzyme activity is less than 5% of normal. Carrier individuals, who have one G allele and one normal copy of the GALT gene, have about 50% of the enzyme activity compared to people who have two normal copies. The Q188R mutation accounts for about 70% of G alleles found in people of northern European descent. S135L is prevalent in Africa and is the second most common mutation in the U.S. IVS2-2A>G is common among the Hispanic population.¹

The Duarte variant form of galactosemia is typically caused by a combination of one G allele with a D2 allele. The D2 allele, also called the Duarte variant allele, is a haplotype in the GALT gene that includes a N314D mutation and a 4-bp deletion in the 5' upstream region. Current research suggests that the 4-bp deletion is the causative mutation for Duarte variant galactosemia.² The N314D mutation and a L218L (c.652C>T) mutation are found in the more benign D1 or Los Angeles allele, which has normal GALT enzyme activity. Individuals with Duarte variant galactosemia have about 5% to 20% of the normal GALT enzyme activity.

The GALT enzyme is one of three enzymes required for the conversion of galactose to glucose.^{4,6} Genetic variants in the other two enzymes, galactokinase and UDP-galactose-4-epimerase, encoded by the GALK1 and GALE genes, respectively, can cause other forms of galactosemia that differ from the classic galactosemia described here.¹ Please see the carrier status report for galactokinase deficiency for more information on GALK1 variants.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified galactosemia as one of 29 diseases for which newborn screening should be mandated.⁷

Mutations Tested: The test includes 10 mutations in the GALT gene.

GALT [L218L (c.652C>T), Q188R, F171S, L195P, K285N, N314D, S135L, E203K, Y209C, IVS2-2A>G]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Galactosemia Type	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
GALT	Classic	African American	80%	1 in 1,010	1 in 5,046
GALT	Classic	Northern European	80%	1 in 111	1 in 551
GALT	Classic	Western European	80%	1 in 270	1 in 1,346
GALT	Classic	Eastern European	80%	1 in 1,016	1 in 5,076
GALT	Classic	Southern European	80%	1 in 234	1 in 1,166
GALT	Duarte variant	Northern European	100%	1 in 9	0
GALT	Duarte variant	Western European	100%	1 in 11	0
GALT	Duarte variant	Eastern European	100%	1 in 12	0
GALT	Duarte variant	Southern European	100%	1 in 18	0
GALT	Duarte variant	Asian	100%	1 in 56	0

^aPercentage of affected patients carrying mutations detected by this test.⁸

^bCarrier risk before testing.^{8,9}

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are many rare mutations associated with galactosemia, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing

laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
271.1 Galactosemia	V77.4 Screen for galactosemia
Applies to: - Galactose-1-phosphate uridyl transferase deficiency - Galactosuria	

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3. Tyfield L, Reichardt J, Fridovich-Keil J, et al. Classical galactosemia and mutations at the galactose-1-phosphate uridyl transferase (GALT) gene. *Human mutation*. 1999;13:417-30.
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Gaucher disease

Report Type: Carrier Status

About: Gaucher disease (GD) is an inherited lysosomal storage disease that is characterized by a variety of symptoms, including enlarged spleen and liver, anemia due to the spleen breaking down red blood cells, osteoporosis, and yellowish-brown skin pigmentation. Gaucher disease is classified as one of three types based on clinical symptoms and degree of neurological involvement. Type I is characterized by the above-listed symptoms and does not involve the nervous system, with age of onset from early life into adulthood. Types II and III have neurological involvement and vary from early to late age of onset, with moderate to severe symptoms. Types I and III GD can be treated with enzyme replacement therapy to reduce symptoms.^{1,2}

Genetics: GD is caused by mutations in the GBA gene, which encodes an enzyme called glucocerebrosidase that is necessary for breaking down the fatty acid glucocerebroside.¹ When the enzyme is defective, cells cannot clear metabolites. As a consequence, the cells become damaged and produce the symptoms of the disease.

The incidence of Gaucher disease type 1 is approximately 1 in 50,000 and 1 in 855 live births in the general population and in Ashkenazi Jews, respectively.² Type 2 and type 3 are more rare with an incidence of about 1 in 100,000 live births each.²

Gaucher disease symptoms are highly variable due to variations in the penetrance and the expression of the mutated GBA gene. Some people who are homozygous for Gaucher disease type 1 mutations may not know that they have the condition because they experience few, if any, of the symptoms, while others with the same genotype will be affected. Thus, the symptoms can vary from very mild to severe in people with the same genotype for Gaucher disease.

The N370S mutation is the most common variant in Ashkenazi Jews and is associated only with Gaucher disease type 1. People with N370S may have mild or unnoticeable disease.² The test does not include the L444P mutation, which is found in about 50% of Gaucher disease type 2 and type 3 and is more frequent among non-Jewish patients but is sometimes found in Ashkenazi individuals.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote.

Recommendations: The American College of Medical Genetics (ACMG) recommends offering carrier screening for Gaucher disease to individuals with Ashkenazi Jewish ancestry.³

Mutations Tested: The test includes six mutations in the GBA gene. ACMG recommends screening in Ashkenazi Jews for the three mutations that are underlined.³

GBA [R463C, V394L, 84GG, N370S, D409H, IVS2+1G>A]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
GBA	Ashkenazi Jew	87%	1 in 18	1 in 131
GBA	Panethnic	64%	1 in 50	1 in 137

^aPercentage of affected patients carrying mutations detected by this test^{2,3}

^bCarrier risk before testing^{2,3}

^cCarrier risk after a “not a carrier” test result

Limitations and Warnings: Since there are other rare mutations, it is possible to carry a mutation that is not on the test. The test does not include the L444P mutation, which is found in about 50% of type II and type III Gaucher disease and is more frequent among non-Jewish patients, but is sometimes found in Ashkenazi individuals. Further sequencing may be required to confirm positive test results for N370S⁴ and D409H.⁵ These test results may be confounded by the GBAP pseudogene that is located near GBA on the same chromosome. GBA and GBAP have high sequence similarity.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.7 Lipidoses Applies to: - Chemically induced lipidosis - Disease: - Anderson's - Fabry's - Gaucher's - I cell [mucopolipidosis I] - lipoid storage NOS - Niemann-Pick - pseudo-Hurler's or mucopolipidosis III - triglyceride storage, Type I or II - Wolman's or triglyceride storage, Type III - Mucopolipidosis II - Primary familial xanthomatosis	V82.71 Screening for genetic disease carrier status

References

1. Campbell TN, Choy FY. Gaucher disease and the synucleinopathies: refining the relationship. *Orphanet journal of rare diseases*. 2012;7:12.

2. Pastores GM, Hughes DA. Gaucher disease. GeneReviews web site. <http://www.ncbi.nlm.nih.gov/books/NBK1269/>. Updated July 2011. Accessed July 9, 2012.
3. Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2008;10:54-6.
4. Torralba MA, Alfonso P, Pérez-Calvo JI, et al. High prevalence of the 55-bp deletion (c.1263del55) in exon 9 of the glucocerebrosidase gene causing misdiagnosis (for homozygous N370S (c.1226A > G) mutation) in Spanish Gaucher disease patients. *Blood cells, molecules & diseases*. 2002;29:35-40.
5. Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). *Human mutation*. 2008;29:567-83.

Genetic risk for decreased folate

Report Type: Nutrition

About: Folate, a B-vitamin, plays a role in protein metabolism and DNA repair¹ and can lower the blood level of homocysteine, a substance linked to cardiovascular disease at high levels.² Diets rich in folate have also been associated with reduced risk of cardiovascular disease.³ The vitamin is particularly important early in pregnancy for preventing some birth defects¹. The recommended dietary allowance for most adults is 400 micrograms per day, while 600 micrograms of folate per day is recommended by the Institute of Medicine for pregnant women.

Genetics: The C677T variant in the methylenetetrahydrofolate reductase gene (MTHFR, which encodes a folate-metabolizing enzyme), has been associated with lowered folate levels in the blood in a study that included over six thousand Caucasian, African and Hispanic individuals from the third National Health and Nutrition Examination Survey (NHANES III).² The study also showed that dietary intake of folic acid could significantly reduce the negative impact of this variant on serum folate levels in individuals taking supplements containing greater than 400 micrograms folate per day. Therefore, people with a T allele are recommended to optimize their intake of folate by eating foods rich in folate. People who are homozygous for the C allele should maintain a healthy, balanced diet.

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: Please also see the genetic test results for the related phenotypes: methotrexate toxicity, MTHFR deficiency.

Markers Tested and Scientific Strength: MTHFR [rs1801133]

The rs1801133 marker is rated a “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for decreased folate levels. Other tests are available to assess a patient’s levels of blood folate. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual blood folate levels are too low, but rather that the patient may be genetically predisposed to have lower blood folate levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual blood folate levels are optimal.

These interpretations and recommendations are made in the context of studies that included Caucasian, African and Hispanic participants, and the results may or may not be relevant to tested individuals who are of Asian ancestry.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test,

nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
266.2 Other B-complex deficiencies	N/A
Applies to: - Deficiency: - cyanocobalamin - folic acid - vitamin B12	

References

1. Bailey LB, Gregory JF 3rd. Folate metabolism and requirements. *The Journal of nutrition*. 1999;129:779-82.
2. Yang QH, Botto LD, Gallagher M, et al. Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: findings from the third National Health and Nutrition Examination Survey DNA Bank. *The American journal of clinical nutrition*. 2008;88:232-46.
3. Voutilainen S, Rissanen TH, Virtanen J, Lakka TA, Salonen JT. Low dietary folate intake is associated with an excess incidence of acute coronary events: The Kuopio Ischemic Heart Disease Risk Factor Study. *Circulation*. 2001;103:2674-80.

Genetic risk for decreased HDL cholesterol

Report Type: Metabolic Health Factors

About: High levels of high-density lipoprotein (HDL) cholesterol may protect against heart attack, while low levels may increase the risk of heart disease.¹ Though multiple mechanisms are known to account for the effects of HDL cholesterol levels, the major one is thought to be the role of HDL in transporting excess cholesterol away from the arteries and back to the liver, where it is passed from the body.² According to the National Cholesterol Education Program (NCEP) guidelines, levels lower than 40 mg/dl (for men) and lower than 50 mg/dl (for women) are considered risk factors for heart disease.³

Genetics: Fourteen genetic variants associated with decreased HDL cholesterol levels were identified in a large genome-wide association study that included over 19,000 Caucasian individuals from the Framingham Heart Study.⁴ The association was replicated in another set of over 20,000 Caucasian individuals within the same study. While the function of these genetic variants is still being investigated, most are in genes such as CETP (cholesteryl ester transfer protein), FADS1 (fatty acid desaturase 1), LIPC (hepatic lipase), LIPG (endothelial lipase), LPL (lipoprotein lipase), PLTP (phospholipid transfer protein), amongst others, that are known to be involved in lipid metabolism.

An allele counting algorithm, in which risk alleles are weighted based on their effect size, was used to assign risk outcomes for each patient. An outcome of "High Risk" indicates that the patient has a genetic profile similar to individuals in the study whose HDL cholesterol levels were, on average, below 46 mg/dl; approximately 37% of individuals in this group had levels below 40 mg/dl.⁴ An outcome of "Above Average Risk" indicates that the patient has a genetic profile similar to individuals in the study whose HDL cholesterol levels were, on average, below 50 mg/dl HDL; approximately 30% of individuals in this group had levels below 40 mg/dl HDL cholesterol.⁴ An outcome of "Average Risk", "Below Average Risk" or "Low Risk" indicates that the patient has a genetic profile similar to individuals in the study whose HDL cholesterol levels were, on average, above 50 mg/dl.⁴

Possible Outcomes: High Risk, Above Average Risk, Average Risk, Below Average Risk, Low Risk

Recommendations: Routine screening for blood cholesterol levels should be performed at appropriate ages, as recommended by the U.S. Preventive Services Task Force and other groups.⁵

Markers Tested and Scientific Strength

Gene/Locus ^a	Marker ^b	Scientific Strength ^c
ABCA1	rs1883025	4
ANGPTL4	rs2967605	4
CETP	rs173539 ^d	4
FADS1	rs174547	4
GALNT2	rs4846914	4

HNF4A	rs1800961	4
KCTD10	rs2338104	4
LCAT	rs2271293	4
LIPC	rs10468017	4
LIPG	rs4939883	4
LPL	rs12678919	4
PLTP	rs7679	4
TTC39B	rs471364	4
ZNF259	rs964184	4

^aGene or locus containing the tested marker

^bMarker tested

^c"Scientific Strength" refers to the strength of research evidence for the genetic marker and the associated result. A rating of "4" indicates a study of over 2,000 people and at least one study that replicated the results. A rating of "3" indicates a study of over 400 people. A rating of "2" indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of "1" indicates that results are extremely preliminary.

^dA proxy marker may be used on the test.

Limitations and Warnings: These genetic variants together account for approximately 9.3% of the variance in HDL cholesterol levels⁴ and, therefore, need to be considered together with other known risk factors for decreased HDL cholesterol levels. Specifically, an outcome of "High Risk" or "Above Average Risk" does not indicate that the patient has decreased HDL cholesterol levels; rather it indicates that the patient may have a genetic propensity for decreased HDL cholesterol levels. Similarly, an outcome of "Low" or "Below Average" does not indicate that the patient has optimal HDL cholesterol levels; rather it indicates that the patient has a lower than average genetic likelihood for decreased HDL cholesterol levels. To identify a patient's actual blood HDL cholesterol levels, a standard blood test could be considered.

The genetic risk for decreased HDL cholesterol has been studied and observed in Caucasian populations. The interpretation and recommendations are made in the context of Caucasian studies, and the results may or may not be relevant to tested individuals who are of non-Caucasian or mixed ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
N/A	V77.91 Screening for lipoid disorders

References

1. Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease: current and future therapies. *Journal of the American College of Cardiology*. 2010;55:1283-99.
2. Alwaili K, Awan Z, Alshahrani A, Genest J. High-density lipoproteins and cardiovascular disease: 2010 update. *Expert review of cardiovascular therapy*. 2010;8:413-23.
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5. U.S. Preventative Services Task Force. Screening for lipid disorders in adults: U.S. Preventative Services Task Force recommendation statement. National Guideline Clearinghouse web site. <http://guideline.gov/content.aspx?id=12634>. Accessed July 10, 2012.

Genetic risk for elevated LDL cholesterol

Report Type: Metabolic Health Factors

About: At high levels, low-density lipoprotein (LDL) cholesterol can put a patient at risk for conditions such as heart attack or stroke. According to the National Cholesterol Education Program (NCEP) guidelines,¹ optimal LDL levels should be less than 100 mg/dl. Near-optimal levels range from 100 to 129 mg/dl and borderline-high from 130 to 159 mg/dl. A score greater than 160 mg/dl is high and greater than 190 mg/dl is considered very high.

Genetics: Ten genetic variants associated with elevated LDL cholesterol levels were identified in a large genome-wide association study that included over 19,000 Caucasian individuals from the Framingham Heart Study.² The association was replicated in another set of over 20,000 Caucasian individuals within the same study. While the function of these genetic variants is still being investigated, most are in genes that are directly involved in lipid metabolism, such as APOB (apolipoprotein B) and LDLR (low density lipoprotein receptor). Others, such as HNF1A (hepatic nuclear transcription factor 1A), regulate genes involved in lipid metabolism.

An allele counting algorithm, in which risk alleles are weighted based on their effect size, was used to assign risk outcomes for each patient. An outcome of "High Risk" indicates that the patient has a genetic profile similar to individuals in the study whose LDL cholesterol levels were on average borderline-high; approximately 25% of individuals in this group had levels in the high range.² An outcome of "Above Average Risk" indicates that the patient has a genetic profile similar to individuals in the study whose LDL cholesterol levels were on average borderline-high; approximately 17% of individuals in this group had levels in the high range.² An outcome of "Average Risk", "Below Average Risk" or "Low Risk" indicates that the patient has a genetic profile similar to individuals in the study whose LDL cholesterol levels were on average in the near-optimal range.²

Recommendations: Routine screening for blood cholesterol levels should be performed at appropriate ages, as recommended by the U.S. Preventive Services Task Force and other groups.³

Possible Outcomes: High Risk, Above Average Risk, Average Risk, Below Average Risk, Low Risk

Markers Tested and Scientific Strength

Gene/Locus ^a	Marker ^b	Scientific Strength ^c
ABCG8	rs6544713	4
APOB	rs515135	4
CELSR2	rs12740374	4
HMGCR	rs3846663	4
HNF1A	rs2650000	4
INTERGENIC	rs1501908	4

LDLR	rs6511720	4
MAFB	rs6102059	4
NCAN	rs10401969	4
PCSK9	rs11206510	4

^aGene or locus containing the tested marker

^bMarker tested

^c“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: These genetic variants together account for approximately 7.7% of the variance in LDL cholesterol levels² and, therefore, need to be considered together with other known risk factors for elevated LDL cholesterol levels. Specifically, an outcome of "High Risk" or "Above Average Risk" does not indicate that the patient has elevated LDL cholesterol levels; rather it indicates that the patient may have a genetic propensity for elevated LDL cholesterol levels. Similarly, an outcome of "Low Risk" or "Below Average Risk" does not indicate that the patient has optimal LDL cholesterol levels; rather it indicates that the patient has a lower than average genetic likelihood for elevated LDL cholesterol levels. To assess a patient's actual LDL cholesterol levels, a standard blood test could be considered.

The genetic risk for elevated LDL cholesterol has been studied and observed in Caucasian populations. The interpretation and recommendations are made in the context of Caucasian studies, and the results may or may not be relevant to tested individuals who are of non-Caucasian or mixed ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.1 Pure hypercholesterolemia Applies to: • Familial hypercholesterolemia • Fredrickson Type IIa hyperlipoproteinemia • Hyperbetalipoproteinemia • Hyperlipidemia, Group A • Low-density-lipoid-type [LDL] hyperlipoproteinemia	V77.91 Screening for lipid disorders

References

1. ATP III at-a-glance: quick desk reference. National Heart Lung and Blood Institute web site. <http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm>. Updated 2004. Accessed August 3, 2012.
2. Kathiresan S, Willer CJ, Peloso GM, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nature genetics*. 2009;41:56-65.
3. U.S. Preventative Services Task Force. Screening for lipid disorders in adults: U.S. Preventative Services Task Force recommendation statement. National Guideline Clearinghouse web site. <http://guideline.gov/content.aspx?id=12634>. Accessed July 10, 2012.

Genetic risk for elevated triglycerides

Report Type: Metabolic Health Factors

About: Elevated triglycerides are a risk factor for conditions such as coronary artery disease and type 2 diabetes. According to the National Cholesterol Education Program (NCEP) guidelines,¹ a normal triglyceride score is under 150 mg/dl. Triglyceride levels in the range of 150 to 199 mg/dl are defined as borderline-high, with over 200 mg/dl considered high and over 500 mg/dl very high.

Genetics: Eleven genetic variants associated with elevated triglyceride levels were identified in a large genome-wide association study that included over 19,000 Caucasian individuals from the Framingham Heart Study.² The association was replicated in another set of over 20,000 Caucasian individuals within the same study. While the function of these genetic variants is still being investigated, most are in genes such as APOB (apolipoprotein B), FADS1 (fatty acid desaturase 1), LPL (lipoprotein lipase), PLTP (phospholipid transfer protein), amongst others, that are known to be involved in lipid metabolism.

An allele counting algorithm, in which risk alleles are weighted based on their effect size, was used to assign risk outcomes for each patient. An outcome of "High Risk" indicates that the patient has a genetic profile similar to individuals in the study whose triglyceride levels were on average borderline-high; approximately 31% of individuals in this group had levels in the high range.² An outcome of "Above Average Risk", "Average Risk", "Below Average Risk" or "Low Risk" indicates that the patient has a genetic profile similar to individuals in the study whose triglyceride levels were on average under 150 mg/dl.²

Possible Outcomes: High Risk, Above Average Risk, Average Risk, Below Average Risk, Low Risk

Recommendations: NA

Markers Tested and Scientific Strength

Gene/Locus ^a	Marker ^b	Scientific Strength ^c
ANGPTL3	rs10889353	4
APOB	rs7557067	4
FADS1	rs174547	4
GCKR	rs1260326	4
LPL	rs12678919	4
MLXIPL	rs714052	4
NCAN	rs17216525	4
PLTP	rs7679	4
TRIB1	rs2954029	4

XKR6	rs7819412	4
ZNF259	rs964184	4

^aGene or locus containing the tested marker

^bMarker tested

^c“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: These genetic variants together account for approximately 7.4% of the variance in triglyceride levels² and, therefore, need to be considered together with other known risk factors for elevated triglyceride levels. Specifically, an outcome of "High Risk" or "Above Average Risk" does not indicate that the patient has elevated triglyceride levels; rather it indicates that the patient may have a genetic propensity for elevated triglyceride levels. Similarly, an outcome of "Low Risk" or "Below Average Risk" does not indicate that the patient has optimal triglyceride levels; it indicates that the patient has a lower than average genetic likelihood for elevated triglyceride levels. To assess a patient's actual triglyceride levels, a standard blood cholesterol test could be considered.

The genetic risk for elevated triglyceride levels has been studied and observed in Caucasian populations. The interpretation and recommendations are made in the context of Caucasian studies, and the results may or may not be relevant to tested individuals who are of non-Caucasian or mixed ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.2 Mixed hyperlipidemia Applies to: • Broad- or floating-betalipoproteinemia • Combined hyperlipidemia • Elevated cholesterol with elevated triglycerides NEC • Fredrickson Type IIb or III hyperlipoproteinemia • Hypercholesterolemia with endogenous hyperglyceridemia • Hyperbetalipoproteinemia with prebetalipoproteinemia • Tubo-eruptive xanthoma • Xanthoma tuberosum	V77.91 Screening for lipid disorders

References

1. ATP III at-a-glance: quick desk reference. National Heart Lung and Blood Institute web site. <http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm>. Updated 2004. Accessed August 3, 2012.
2. Kathiresan S, Willer CJ, Peloso GM, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nature genetics*. 2009;41:56-65.

Glutaric acidemia, type 1

Report Type: Carrier Status

About: Glutaric acidemia type 1 (GA1) is an inherited disease that is caused by a defect in protein metabolism. Accumulation of glutaric acid and 3-hydroxyglutaric acid to toxic levels can lead to brain damage in infants and young children. Other symptoms may include poor appetite, nausea, vomiting, extreme sleepiness, irritability, low muscle tone and muscle weakness. If not treated, breathing problems, seizures, swelling of the brain, subdural hematoma, coma and sometimes even death can occur. With prompt and lifelong treatment, children with GA1 can often live normal lives. Some people with GA1 have very mild or no symptoms and are only identified when a sibling is diagnosed.^{1,2}

Genetics: GA1 is caused by mutations in the GCDH gene, which encodes the glutaryl-CoA dehydrogenase enzyme that is necessary for catabolizing certain amino acids (lysine, hydroxylysine and tryptophan).² A defective protein can cause toxic levels of glutaric acid and 3-hydroxyglutaric acid to accumulate in body fluids and be excreted in the urine.

The R402W mutation is the most common variant in Caucasians; it comprised 40% of mutations found in German patients. A421V is prevalent in the Pennsylvania Amish.³

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified glutaric acidemia type 1 as one of 29 diseases for which newborn screening should be mandated.⁴

Mutations Tested: The test includes five mutations in the GCDH gene.

GCDH [R227P, A293T, V400M, R402W, A421V]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
GCDH	Caucasian	38%	1 in 159	1 in 254

^aPercentage of affected patients carrying mutations detected by this test.^{5,6}

^bCarrier risk before testing.⁶

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with type 1 glutaric acidemia, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.7 Other disturbances of straight-chain amino-acid metabolism Applies to: • Glucoglycinuria • Glycinemia (with methylmalonic acidemia) • Hyperglycinemia • Hyperlysinemia • Pipecolic acidemia • Saccharopinuria • Other disturbances of metabolism of glycine, threonine, serine, glutamine, and lysine	V82.71 Screening for genetic disease carrier status

References

1. Hedlund GL, Longo N, Pasquali M. Glutaric acidemia type 1. *American journal of medical genetics. Part C, Seminars in medical genetics*. 2006;142C:86-94.
2. Seahore MR. The organic acidemias: an overview. GeneReviews web site. <http://www.ncbi.nlm.nih.gov/books/NBK1134/>. Updated December 2009. Accessed July 10, 2012.
3. Biery BJ, Stein DE, Morton DH, Goodman SI. Gene structure and mutations of glutaryl-coenzyme A dehydrogenase: impaired association of enzyme subunits that is due to an A421V substitution causes glutaric acidemia type I in the Amish. *American journal of human genetics*. 1996;59:1006-11.
4. Newborn screening: toward a uniform screening panel and system. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2006;8 Suppl 1:1S-252S.
5. Zschocke J, Quak E, Guldberg P, Hoffmann GF. Mutation analysis in glutaric aciduria type I. *Journal of medical genetics*. 2000;37:177-81.
6. Kölker S, Christensen E, Leonard JV, et al. Guideline for the diagnosis and management of glutaryl-CoA dehydrogenase deficiency (glutaric aciduria type I). *Journal of inherited metabolic disease*. 2007;30:5-22.

Glycogen storage disease, type 1a

Report Type: Carrier Status

About: Glycogen storage disease type 1a (GSD1a) is an inherited disorder caused by impaired metabolism of glucose and glycogen. The resulting hypoglycemia can cause seizures, and the accumulation of glycogen and fat in the liver and kidneys can lead to enlargement of these organs (hepatomegaly and renomegaly). Other biochemical changes in the blood include abnormally high levels of lactate (lactic acidosis), uric acid (hyperuricemia) and lipids (hyperlipidemia). Some affected newborns may present with severe hypoglycemia, but symptoms are more commonly noticed at three to four months of age. Affected patients usually have fat faces, thin legs and arms, short stature and suffer from bleeding problems. Untreated patients can have severe complications in multiple organs; however, normal growth and survival to adulthood can be achieved with proper treatment.¹

Genetics: GSD1a is caused by mutations in the G6PC gene, which encodes a subunit of glucose-6-phosphatase. This enzyme is responsible for the last step in both glycogenolysis and gluconeogenesis. Mutations in the G6PC gene that abolish or reduce G6PC enzyme activity cause the aforementioned hypoglycemia and glycogen accumulation.¹

The test includes nine common mutations in the G6PC gene. The R83C mutation accounts for 93% to 100% of all disease-causing G6PC mutations in the Ashkenazi Jewish population.² The carrier frequency of this mutation is about 1.4% in people of Ashkenazi Jewish descent. In Caucasian patients, R83C accounts for about 30% of disease-causing mutations, whereas three other mutations, 79delC (also known as 158delC), G188R and Q347X, account for about 20%.^{2,3,4,5} The mutation 378_379dupTA (also known as 59insTA) has been found to be common in the Hispanic population of the United States (50% of disease causing mutations).²

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes nine mutations in the G6PC gene

G6PC [R83C, R83H, c.378_379dupTA, c.79delC, G188R, Q347X, G270V, Q242X, deltaF327]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
G6PC	Ashkenazi Jew	93%	1 in 71	1 in 1,001
G6PC	non-Jewish	62%	1 in 158	1 in 414

^aPercentage of affected patients carrying mutations detected by this test.^{1,6}

^bCarrier risk before testing.¹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with glycogen storage disease type 1A, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
271.1 Glycogenosis Applies to: • Amylopectinosis • Glucose-6-phosphatase deficiency • Glycogen storage disease • McArdle's disease • Pompe's disease • von Gierke's disease	V82.71 Screening for genetic disease carrier status

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GM1-gangliosidosis

Report Type: Carrier Status

About: GM1-gangliosidosis is an inherited lysosomal storage disease that affects the central nervous system. There are three clinical phenotypes of GM1-gangliosidosis. The infantile type shows symptoms, at birth or in early infancy, which include low muscle tone, cherry-red spots on the skin, severe degeneration of the CNS and death by the age of 1 to 2. The late-infantile/juvenile type presents between the age of 7 months and 3 years, with slower progression of psychomotor deterioration. The adult/chronic type has late onset and is mostly found in Japanese, with normal neurologic development early on and slow development of dementia with features of Parkinson's syndrome.¹

Genetics: GM1 gangliosidosis is caused by mutations in the GLB1 gene, which encodes the lysosomal enzyme beta-galactosidase-1 that helps break down GM1 ganglioside by converting it to GM2 ganglioside. Mutations in GLB1 result in reduced or deficient enzyme activity that causes the accumulation of toxic GM1 ganglioside and its derivatives in different tissues, particularly in the central nervous system (CNS).¹

The test includes a common mutation in the GLB1 gene. The R59H mutation accounts for a significant proportion (16% to 100%) of the mutant GLB1 alleles found in Brazilians, Iberians, South Americans and Roma patients of Gypsy origin.^{2,3,4,5} The carrier rate is about 2% in the general Gypsy population and about 10% in the Rudari sub-isolate, a specific Gypsy group found in both Bulgaria and Brazil.⁵

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: NA

Mutations Tested: The test includes the R59H mutation in the GLB1 gene.

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with GM1 gangliosidosis, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

330.1 Cerebral lipidoses	V82.71 Screening for genetic disease carrier status
Applies to: • Amaurotic (familial) idiocy • Disease: ◦ Batten ◦ Jansky-Bielschowsky ◦ Kufs' ◦ Spielmeyer-Vogt ◦ Tay-Sachs ◦ Gangliosidosis	

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Hearing loss, DFNB1 and DFNB9 nonsyndromic

Report Type: Carrier Status

About: Hearing loss is the most common sensory disorder. The impact of hearing loss is most significant if it occurs before a child learns to talk; most prelingual hearing loss is congenital and can now be detected by newborn hearing screening programs. More than half of hearing loss cases have genetic causes and are considered hereditary.¹

About 1% of genes in the human genome are believed to function in the hearing process. Hereditary hearing loss can be associated with additional clinical features in other tissues or organs and is associated with more than 400 syndromes. These make up about 30% of hereditary hearing loss cases. Nonsyndromic hearing loss (NSHL) accounts for the remaining 70% of hereditary hearing loss cases and is predominantly sensorineural. NSHL is usually caused by mutations in a single gene (monogenic).¹ Scientists believe that changes in more than 100 genes can lead to NSHL. Autosomal recessive mutations account for about 80% of NSHL cases, and each genetic locus of autosomal recessive NSHL is designated with a name composed of “DFNB” and a number. Generally, autosomal recessive NSHL is congenital, severe-to-profound, and non-progressive.

Genetics: DFNB1 nonsyndromic hearing loss is caused by mutations in the GJB2 gene, which encodes the connexin 26 protein. Connexins form channels between neighboring cells called gap junctions. These channels in the inner ear are involved in the maintenance of the normal ionic environment that is essential for the auditory hair cells to survive and function.^{2,3}

In people of European descent, the most common DFNB1 mutation is 35delG (sometimes also called 30delG) in the GJB2 gene. Mutations in GJB2 account for more than a half of all autosomal recessive NSHL in Caucasian populations, and about 70% of these mutations are 35delG.² The combined carrier rate of all recessive deafness-causing GJB2 mutations has been estimated at 3% in the general population of the Midwestern United States.⁴

The prevalence of GJB2 mutations as a cause of deafness varies in other ethnic groups, and other GJB2 mutations may be found more often than 35delG. For example, 167delT is the most common GJB2 mutation in the Ashkenazi Jewish population with a carrier rate of about 4%. In the Japanese and Chinese populations, 235delC is the most common deafness-causing GJB2 mutation. V37I is also common in the Chinese population (carrier rate 11.5%) and causes mild to moderate hearing loss.²

DFNB9 nonsyndromic hearing loss is caused by mutations in the OTOF gene, which encodes a membrane-anchored cytosolic protein called otoferlin. This protein is believed to play a role in neurotransmitter release from nerve cells in the ear. DFNB9 is typically congenital, with severe-to-profound effects on hearing, and bilateral.⁵ The Q829X mutation in the OTOF gene accounts for 3% (the third most frequent) of mutations causing recessive prelingual deafness in Spain.⁶

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified hearing loss as one of 29 diseases for which newborn screening should be mandated.⁷

Mutations Tested: The test includes five mutations in the GJB2 gene and one mutation in the OTOF gene.

GJB2 [V37I, 35delG, 167delT, 235delC, L90P]

OTOF [Q829X]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with DFNB1 and DFNB9 nonsyndromic hearing loss, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
389.8 Other specified forms of hearing loss	V19.2 Family hx-deafness

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Hearing loss, DFNB59 nonsyndromic

Report Type: Carrier Status

About: Hearing loss is the most common sensory disorder. The impact of hearing loss is most significant if it is prelingual; most prelingual hearing loss is congenital and can now be detected by newborn hearing screening programs. More than half of hearing loss cases have genetic causes and are considered hereditary.¹

Genetics: DFNB59 nonsyndromic hearing loss is caused by mutations in the DFNB59 gene, which encodes the pejvakin protein of unknown function. The DFNB59 protein is present in the nerves leading from the inner ear to the brain and in the part of the brain that is connected to the spinal cord (the brainstem). Mutations in DFNB59 affect the function of mechanosensory cells and sensory neurons.²

About 1% of genes in the human genome are believed to function in the hearing process. Hereditary hearing loss can be associated with additional clinical features in other tissues or organs and is associated with more than 400 syndromes. These make up about 30% of hereditary hearing loss cases. Nonsyndromic hearing loss (NSHL) accounts for the remaining 70% of hereditary hearing loss cases and is predominantly sensorineural. NSHL is usually caused by mutations in a single gene (monogenic).¹ Scientists believe that changes in more than 100 genes can lead to NSHL. Autosomal recessive mutations account for about 80% of NSHL cases, and each genetic locus of autosomal recessive NSHL is designated with a name composed of “DFNB” and a number. Generally, autosomal recessive NSHL is congenital, severe-to-profound, and non-progressive.

DFNB59 nonsyndromic hearing loss is a type of auditory neuropathy that was originally discovered in families from different regions in Iran carrying nonsyndromic, bilateral, prelingual, sensorineural hearing impairment. Affected individuals have a profound deafness involving all sound frequencies and have trouble learning to speak.³

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified hearing loss as one of 29 diseases for which newborn screening should be mandated.⁴

Mutations Tested: The test includes six mutations in the DFNB59 gene.

DFNB59 [988delG, 726delT, L244R, R167X, 509_512delCACT, 113dupT]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with DFNB59 nonsyndromic hearing loss, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
389.14 Central hearing loss	V82.71 Screening for genetic disease carrier status V19.2 Family history of deafness or hearing loss

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Hemochromatosis

Report Type: Carrier Status

About: Hereditary hemochromatosis is a potentially fatal disorder caused by mutations in any one of several genes that result in abnormally high absorption of iron into the body. Excess iron can damage many organ systems, including the liver, skin, pancreas, endocrine glands, joints, and heart. If therapeutic phlebotomy is started in time, affected individuals will have a normal lifespan. Therefore, early diagnosis is essential.¹

Genetics: Hereditary hemochromatosis can be caused by mutations in several different genes, which lead to a difference in the age of disease onset.²

HFE-associated hereditary hemochromatosis (HFE-HHC) presents in men between 40 and 60 years of age and after menopause for women. The HFE gene encodes a protein that helps regulate the absorption of iron into the small intestine and may also help control the levels of an iron regulatory protein called hepcidin. Many individuals carrying two HFE variants do not develop clinical symptoms.¹ The prevalence of hereditary hemochromatosis associated with mutations in the HFE gene (HFE-HHC) is 1 in 200 for Caucasians, 1 in 6,667 for non-Hispanic blacks and 1 in 3,333 for Mexican Americans. Compared to HFE-HHC, hereditary hemochromatosis from mutations in other genes, such as HFE2 and TFR2, is rare.³

Juvenile hereditary hemochromatosis (JHHC) presents between 10 and 30 years of age. The HFE2 gene encodes the hemojuvelin protein that may regulate the level of hepcidin. Most mutations of HFE2 causing JHHC are carried in individual families or small populations. The only recurrent mutation is G320V.⁴

TFR2-related hereditary hemochromatosis (TFR2-HHC) presents before age 30. The TFR2 gene is a member of the transferrin receptor-like family and encodes a membrane protein that mediates cellular uptake of transferrin-bound iron. Some individuals carrying two TFR2 variants do not develop clinical symptoms (penetrance is incomplete). Like the HFE and the HFE2 gene product, the TFR2 gene product also appears to regulate the level of iron-regulatory protein hepcidin. Fifteen disease-associated mutations of TFR2 have been found, but most of them are rare or private.⁵

The test includes 3 mutations in the HFE gene, 1 mutation in the HFE2 gene and 2 mutations in the TFR2 gene. The C282Y and H63D variants of the HFE gene are the most common cause of hereditary hemochromatosis. The C282Y mutation is thought to have originated by chance in a single Celtic (or Viking) ancestor in northwestern Europe about 2,000 years ago.² Homozygosity for the C282Y mutation is now found in approximately 5 of every 1,000 persons of northern European descent. The carrier rate for C282Y is 1 in 9 for Caucasians, 1 in 33 for Hispanics, 1 in 43 for African-Americans, and 1 in 1,000 for Asians.¹

The H63D mutation is an older, more prevalent mutation with a worldwide distribution and a carrier rate of 1 in 4 for Caucasians, 1 in 6 for Hispanics, 1 in 17 for African-Americans, and 1 in 12 for Asians. About 60%-90% of individuals with HFE-HHC carry two copies of C282Y. 87% of individuals of European origin with HFE-HHC either carry two copies of the C282Y variant or carry one copy of the C282Y variant and one copy of the H63D variant.⁶

Conventional wisdom is that most individuals with two copies of C282Y do not show clinical symptoms.² However, a study in 2008 of Australians found that, among individuals homozygous for C282Y, 28% of men as compared to 1% of women showed clinical symptoms of hemochromatosis.⁷ Thus, men who are homozygous for C282Y should be aware of this possibility. Most individuals with one copy of C282Y and one copy of H63D as well as individuals with two copies of H63D do not show clinical symptoms.

More than 90% of all juvenile hereditary hemochromatosis cases are caused by mutations in the HFE2 gene. G320V is the most prevalent HFE2 mutation reported to date, representing more than 50% of all detected mutations in affected individuals worldwide.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes six mutations in three genes.

TFR2 [Y250X, M172K]; HFE2 [G320V]; HFE [H63D, C282Y, S65C]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
HFE	Northern European	63%	1 in 3	1 in 6
HFE2	Greek	70%	<1 in 500	1 in 1,664
HFE2	French-Canadian	100%	<1 in 500	0
HFE2	Italian	4%	<1 in 500	1 in 520

^aPercentage of affected patients carrying mutations detected by this test.^{1,8,9}

^bCarrier risk before testing. HFE carrier rate.^{1,10} HFE2 carrier rate (The true carrier rate is unknown for this extremely rare disease. The carrier rate of 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.¹¹ The actual carrier rate and the post-test residual risk are likely to be lower.).

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with hemochromatosis, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
275.1 Hereditary hemochromatosis Applies to: • Bronzed diabetes • Pigmentary cirrhosis (of liver) • Primary (hereditary) hemochromatosis	V82.71 Screening for genetic disease carrier status

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Hemoglobin C

Report Type: Carrier Status

About: Hemoglobin C disease is an inherited blood disorder characterized by a mild hemolytic anemia and mild to moderate enlargement of the spleen. The high prevalence (10% to 20%) of the HbC mutation in certain West Africa populations is likely due to the protection against malarial infection conferred by the two copies of the HbC variant in individuals with HbC disease.^{1,2}

Genetics: Hemoglobin C disease is caused by the HbC mutation in the HBB gene that encodes the beta subunit of hemoglobin.³ Hemoglobin C disease is a type of hemoglobinopathy. Other mutations in the HBB gene give rise to other hemoglobinopathies including sickle cell anemia (HbS), hemoglobin E (HbE) disease and various beta-thalassemias.^{1,2,4}

Hemoglobin C disease is more common in African Americans and people of West African descent than in other ethnic populations. Accordingly, the HbC mutation is found in approximately 1 in 50 African Americans.^{2,5}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: The American College of Obstetricians and Gynecologists (ACOG) recommends offering carrier screening for hemoglobinopathies to people of African, Southeast Asian and Mediterranean ancestry.⁶ The American College of Medical Genetics identified hemoglobin C disease as one of 29 diseases for which newborn screening should be mandated.⁷

Mutations Tested: The test includes one mutation in the HBB gene.

HBB [Hemoglobin C]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
HBB	African American	100%	1 in 52	0
HBB	Native American	100%	1 in 489	0
HBB	Hispanic American	100%	1 in 1,517	0
HBB	Middle Eastern	100%	1 in 5,476	0
HBB	Caucasian	100%	1 in 2,754	0
HBB	Asian Indian	100%	1 in 4,768	0
HBB	Filipino	100%	1 in 4,775	0

HBB	Asian	100%	1 in 6,607	0
HBB	Southeast Asian	100%	1 in 14,200	0

^aPercentage of affected patients carrying mutations detected by this test.⁵

^bCarrier risk before testing.⁵

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Hemoglobin C disease carriers may have misleading results in the hemoglobin A1C test (also known as glycated hemoglobin, glycosylated hemoglobin and HbA1c) that is used to diagnose diabetes and to monitor blood glucose levels in diabetics. False hemoglobin A1C test results can lead to false diagnosis, over-treatment or under-treatment of diabetes in people with hemoglobin variants).⁸

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
282.7 Other hemoglobinopathies Applies to: • Abnormal hemoglobin NOS • Congenital Heinz-body anemia • Disease: ◦ hemoglobin C [Hb-C] ◦ hemoglobin D [Hb-D] ◦ hemoglobin E [Hb-E] ◦ hemoglobin Zurich [Hb-Zurich] • Hemoglobinopathy NOS • Hereditary persistence of fetal hemoglobin [HPFH] • Unstable hemoglobin hemolytic disease	V82.71 Screening for genetic disease carrier status

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Hemoglobin E

Report Type: Carrier Status

About: Hemoglobin E disease is an inherited disorder characterized by a mild, hemolytic anemia, abnormally small red blood cells (microcytosis) and mild enlargement of the spleen. The high prevalence of the HbE mutation in areas of the world where malaria is endemic is likely due to the protection against malarial infection conferred by the presence of one copy of HbE variant in carriers of hemoglobin E disease.^{1,2}

Genetics: Hemoglobin E disease is caused by a mutation in the HBB gene that encodes the beta subunit of hemoglobin.³ Hemoglobin E disease is a type of hemoglobinopathy. Other mutations in the HBB gene give rise to other hemoglobinopathies, including sickle cell disease (HbS), hemoglobin C (HbC) disease and various beta-thalassemias.^{2,4,5,6}

Hemoglobin E disease is the second most common abnormal hemoglobin disease after sickle cell disease (HbS). HbE is common in Southeast Asia with a carrier rate as high as 1 in 3 in some parts of Thailand, Cambodia and Laos. HbE is also found in Sri Lanka, Northeast India, Bangladesh, Pakistan, Nepal, Vietnam and Malaysia.⁷ From 1998 to 2006 in California, the incidence of HbE disease was 11 per 100,000 infants screened.⁸

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: The American College of Obstetricians and Gynecologists (ACOG) recommends offering carrier screening for hemoglobinopathies to people of African, Southeast Asian and Mediterranean ancestry.⁹ The American College of Medical Genetics recommends newborn screening for hemoglobin E.¹⁰

Mutations Tested: The test includes one mutation in the HBB gene.

HBB [Hemoglobin E]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Carrier Rate ^b	Residual Risk ^c
HBB	White British	100%	1 in 9091	0
HBB	Bangladeshi	100%	1 in 24	0
HBB	Pakistani	100%	1 in 529	0
HBB	Chinese	100%	1 in 221	0
HBB	White Irish	100%	1 in 1,961	0
HBB	Asian Indian	100%	1 in 578	0

HBB	African	100%	1 in 10,000	0

^aPercentage of affected patients carrying mutations detected by this test.¹

^bCarrier risk before testing.¹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Hemoglobin E disease carriers may have misleading results in the hemoglobin A1C test (also known as glycated hemoglobin, glycosylated hemoglobin and HbA1c) that is used to diagnose diabetes and to monitor blood glucose levels in diabetics. False A1C test results can lead to false diagnosis, over-treatment or under-treatment of diabetes in people with hemoglobin variants.¹¹

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
282.47 Hemoglobin E-beta thalassemia	V82.71 Screening for genetic disease carrier status

References

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HMG-CoA lyase deficiency

Report Type: Carrier Status

About: HMG-CoA lyase deficiency, also known as 3-hydroxy-3-methyl glutaric aciduria, is a rare and severe disease. The disruption of leucine processing and ketone body synthesis that is associated with the condition causes damage to many organs, especially the brain. The defect in leucine processing can cause metabolic acidosis, which can damage many types of cells, particularly brain cells. The defect in ketone body synthesis can lead to a metabolic crisis with typical symptoms of vomiting, sleepiness and muscle weakness. This crisis is usually triggered by a period of feeding disruption or a common infection. The first episode usually occurs within the first year of life, and the symptoms can quickly worsen and result in life-threatening seizures and coma.¹

Genetics: HMG-CoA lyase deficiency is caused by mutations in the HMGCL gene, which encodes 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase.¹ This enzyme is required for the breakdown of the amino acid leucine.¹ If leucine cannot be processed normally, acidic byproducts can accumulate to toxic levels, causing metabolic acidosis.¹ The HMG-CoA lyase enzyme is also required for the generation of ketone bodies, which are used as fuel for many organs, particularly the brain, when the body experiences a shortage of sugar-based energy. Thus, if sugar-based energy sources are depleted, individuals with HMG-CoA lyase deficiency may have a metabolic crisis due to the absence of an alternative energy supply.¹

The test includes three prevalent mutations in the HMGCL gene. The R41Q mutation is the most frequent one worldwide, but it is mostly found in individuals of Saudi Arabian descent. The next most prevalent HMGCL mutation in the world is E37X; it is the most frequent (38%) disease-causing mutation in non-Saudi patients. The 504_505delCT mutation in the HMGCL gene is the second most frequent (10%) mutation in non-Saudi patients.¹

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes the three mutations in the HMGCL gene.

HMGCL [504_505delCT, E37X, R41Q]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with HMB-CoA lyase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test,

nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
N/A	V82.71 Screening for genetic disease carrier status

References

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Homocystinuria, cbIE type

Report Type: Carrier Status

About: Homocystinuria of the cbIE type is an inherited metabolic disorder that results from the accumulation of homocysteine in the blood. Symptoms of homocysteinemia, which lead to homocystinuria, include megaloblastic anemia, developmental delay, failure to thrive and a variety of neurological defects, including cerebral atrophy accompanied by white matter abnormalities. Most patients exhibit symptoms in the first weeks to first two years of life.¹ Patients typically respond to treatments including vitamin B12 supplementation, but as with other progressive diseases, are managed better when treatment begins early in life.

Genetics: cbIE type homocystinuria is caused by mutations in the MTRR gene, which encodes the methionine synthase reductase enzyme that is dependent on cobalamin (vitamin B12 or cbl) for its function.² Methionine synthase converts homocysteine, a potentially toxic amino acid, to methionine. Methionine synthase reductase (MTRR) is responsible for maintaining methionine synthase in its active state.³ Disease-causing mutations in the MTRR gene have decreased enzyme activity, which prevents the methionine synthase from being activated and results in a buildup of homocysteine in the body. Unlike classic homocystinuria where patients also have increased levels of methionine, patients who have homocystinuria of the cbIE type typically have normal to reduced levels of methionine.¹

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes five mutations in the MTRR gene.

MTRR [c.1953-6_1953-2del5, c.1622_1623dupTA, 1726delTTG, R3W, R525X]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with cbIE type homocystinuria, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

270.4 Disturbances of sulphur-bearing amino-acid metabolism Applies to: • Cystathioninemia • Cystathioninuria • Disturbances of metabolism of methionine, homocystine, and cystathionine • Homocystinuria • Hypermethioninemia • Methioninemia	V82.71 Screening for genetic disease carrier status

References

1. Zavadáková P, Fowler B, Suormala T, et al. cblE type of homocystinuria due to methionine synthase reductase deficiency: functional correction by minigene expression. *Human mutation*. 2005;25:239-47.
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Homocystinuria, classic

Report Type: Carrier Status

About: Classic homocystinuria is an inherited disorder that results in the accumulation of homocysteine and methionine in the blood and urine.¹ The clinical manifestations of homocystinuria include dislocation of the lens of the eyes which usually occurs after the age of 2, skeletal abnormalities including scoliosis and long, thin extremities that give patients a Marfan-like appearance, mental retardation, developmental delay and vascular disorders including thromboembolic events and accelerated atherosclerosis.² Patient symptoms vary greatly in their severity, with lens dislocation often being the first classic symptom, leading to a diagnosis in patients who are not detected by newborn screening. Newborn screening using the Guthrie blood spot card can identify hypermethioninemia, one symptom of homocystinuria, which can then be diagnosed upon further testing.¹

Genetics: Classic homocystinuria is caused by mutations in the CBS gene, which encodes cystathionine beta-synthase.¹ This enzyme normally acts to convert homocysteine, a potentially toxic amino acid, to cysteine, a non-toxic amino acid.³ Disease-causing mutations in the CBS gene decrease or eliminate the activity of cystathionine beta-synthase, resulting in a buildup of homocysteine in the blood and urine.

Classic homocystinuria is treatable with a combination of therapies, including dietary restrictions of certain amino acids, supplementation with vitamin B6 and B12, and betaine treatment. When patients are treated, they are classified as being vitamin B6 responsive or non-responsive based on whether supplementation with vitamin B6 alone results in the lowering of homocysteine levels. The I278T mutation is generally indicative of being B6-responsive, while the G307S mutation is generally indicative of B6 non-responsiveness.³ Patients who are B6 responsive typically have milder clinical manifestations. However, newborn screening typically identifies B6 non-responsive patients more frequently than B6-responsive patients possibly due to a lack of elevated methionine in the blood in the first few days of life in B6-responsive patients.¹ Thus compared to newborn screening, genetic carrier testing may be useful for identifying newborns that may be at risk of homocystinuria, regardless of B6-responsive status.

The test includes some of the most common mutations in the CBS gene that cause classic homocystinuria: I278T, G307S, IVS11-2A>C, T191M.¹ The I278T mutation is the most common one and has a worldwide distribution accounting for up to 25% of mutant alleles worldwide, and representing up to 50% of affected alleles in the Netherlands. The G307S allele accounts for approximately 70% of mutant alleles in Irish patients and has been observed in patients of 'Celtic' origin from other countries. The IVS11-2A>C mutation, the third most common allele, is found mainly in patients of Eastern European origins. The T191M mutation is prevalent in persons of Spanish, Portuguese and South American origin.⁴

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified homocystinuria as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test includes 64 mutations in the CBS gene.

CBS [T191M, D47E, W43X, P78R, R58W, K102N, P88S, R121C, G116R, E128D, M126V, P145L, G139R, A155V, E176K, V168A, A226T, S217F, IVS8+1G>A, E239K, IVS9+1G>T, R266G, 298fsX329, P290L, V354M, R336H, A355P, D376N, R369H, R379W, IVS12+1G>A, I435T, K384E, R491C, S466L, L539S, 1591delTTTCG, 1622ins4, G85R, P49L, C109R, L101P, E144K, A114V, G151R, G148R, C165Y, T257M, H232D, E302K, R266K, R336C, V320A, G347S, R336C, T353M, S349N, V371M, R369C, 1566delG, D444N, G307S, I278T, IVS11-2A>C]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
CBS	US	26%	1 in 500	1 in 675
CBS	UK	50%	1 in 500	1 in 999

^aPercentage of affected patients carrying mutations detected by this test.^{1,6}

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.⁷ The actual carrier rate and the post-test residual risk are likely to be lower.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with classic homocystinuria, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.4 Disturbances of sulphur-bearing amino-acid metabolism Applies to: • Cystathioninemia • Cystathioninuria • Disturbances of metabolism of methionine, homocystine, and cystathionine • Homocystinuria • Hypermethioninemia • Methioninemia	V82.71 Screening for genetic disease carrier status

References

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Hurler syndrome

Report Type: Carrier Status

About: Hurler syndrome is the most severe form of mucopolysaccharidosis type I (MPS I), which is an inherited metabolic disorder.¹ Clinically, Hurler syndrome affects many systems due to the ubiquitous nature of lysosomal degradation of large sugar molecules called glycosaminoglycans (GAGs).² The symptoms of Hurler syndrome are progressive with age and often begin to occur in early life (ages 1 to 2). These include skeletal dysplasia (abnormal bone growth), hearing loss, mental retardation, and severe cardiopulmonary failure. Some therapeutic interventions such as enzyme therapy have been reported for this disease.³

Genetics: Hurler syndrome, the most severe form of MPS I, is caused by mutations in the IDUA gene, which encodes alpha-L-iduronidase.¹ This enzyme cleaves certain carbohydrate residues so that GAGs can be properly degraded in the lysosome. Individuals diagnosed with Hurler syndrome have little to no detectable levels of this active enzyme.^{3,4}

The test includes two key mutations, W402X and Q70X, in the IDUA gene that are known to account for the majority of all cases of Hurler syndrome.^{5,6,7}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes five mutations in the IDUA gene.

IDUA [1695_1705delTCTGGTCTGGT, 1814_1815delTT, 1044_1049delCGACAA, Q70X, W402X]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
IDUA	Caucasian	79%	1 in 159	1 in 753

^aPercentage of affected patients carrying mutations detected by this test.⁷

^bCarrier risk before testing.¹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with Hurler syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.5 Mucopolysaccharidosis Applies to: • Gargoylism • Hunter's syndrome • Hurler's syndrome • Lipochoondrodystrophy • Maroteaux-Lamy syndrome • Morquio-Brailsford disease • Osteochondrodystrophy • Sanfilippo's syndrome • Scheie's syndrome	V82.71 Screening for genetic disease carrier status

References

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Hypertension

Report Type: Health Conditions

About: The prevalence of hypertension, also known as high blood pressure, is estimated to be 29% in the U.S.¹ This condition can lead to stroke, heart attack and kidney failure. Risk factors for hypertension include high salt intake, being overweight and high alcohol consumption.² Research indicates that genetic factors are also associated with risk for the condition.^{3,4,5,6}

Genetics: Over 90% of individuals who develop hypertension are considered to have essential or primary hypertension, meaning that no underlying medical cause can be identified. Hypertension can also be secondary to existing medical problems, such as kidney disease. Some rare forms of hypertension are caused by mutations in single genes. Individuals with these mutations usually have a family history of the disease and hypertension occurs at a younger age. This genetic test focuses on essential hypertension, for which several susceptibility alleles have been identified through large population studies.^{3,4,5,6}

Because of the complex interactions of different physiologic pathways regulating blood pressure, it has been difficult to definitively identify risk alleles in candidate genes for hypertension. Contradictory results have been reported for many genes identified in an early study but not replicated in further research. A few large population-based genome-wide scans and candidate gene association studies have identified two genes as risk factors for hypertension: PPARGC1A and BCAT1.^{3,4,5,6}

The PPARGC1A gene encodes the protein PPAR-gamma coactivator 1,⁷ which regulates the expression of genes involved in several metabolic processes related to blood pressure homeostasis. The Gly482Ser (rs7961152) allele causes an amino acid change in the protein, but the functional consequence of this change is unknown. The Ser allele was associated with decreased risk for essential hypertension in a Danish population.⁵ The same allele was also modestly associated with decreased risk for severe essential hypertension in a Chinese population.⁶

The BCAT1 gene encodes branched-chain aminotransferase 1, which catalyzes the first reaction in the catabolism of the essential branched-chain amino acids leucine, isoleucine and valine. The rs7961152 marker is in a non-coding region of the BCAT1 gene, making it difficult to discern the functional impact of a nucleotide change. The variant may be linked to another causative mutation in the same gene or a neighboring gene. The A allele of the rs7961152 marker was associated with an increased risk for essential hypertension in a study of a British Caucasian population.⁴ In a Korean population, the same allele was moderately associated with increased blood pressure.³

Recommendations: The U.S. Preventive Services Task Force recommends screening for high blood pressure in adults aged 18 and older.⁸

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
BCAT1	rs7961152	A	1.29	Asian	16.9%	Preliminary	19424278
BCAT1	rs7961152	A	1.16	Caucasian	46.5%	Preliminary	17554300
PPARGC1A	rs8192678	A	0.60	Asian	40.5%	Preliminary	17971240
PPARGC1A	rs8192678	A	0.70	Caucasian	35.0%	Preliminary	15738346

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
401.1 Benign essential hypertension	N/A

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Interferon-alpha/ribavirin

(DC:TB-0218.001 06DEC2012)

Report Type: Pharmacogenetics

About: Hepatitis C virus (HCV) infection is the most common chronic, blood-borne infection in the US and affects 170 million worldwide.¹ The standard treatment for HCV infection, particularly in resource-limited settings, is a combination of pegylated (polyethylene glycol) IFN-alpha (PEG-IFN-alpha) and ribavirin (RBV).² IFN-alpha stimulates the natural defense against the viral infection, and pegylation enhances its antiviral potency.² Ribavirin is a nucleoside antimetabolite that inhibits replication of the virus.³ Telaprevir and boceprevir are HCV NS3/4A protease inhibitors that require co-administration with PEG-IFN-alpha/RBV.^{4,5}

IFN-based therapies are expensive and can induce severe side effects; therefore, it would be beneficial to distinguish responders from non responders prior to treatment screening.^{6,7}

Genetics: A variant in the rs12979860 marker near the IL28B gene is a strong predictor of response to PEG-IFN-alpha/RBV.^{4,5} The IL28B gene encodes a cytokine called interleukin 28B (IL28B), also known as IFN-lambda-3.

A meta-analysis of seven studies containing a total of approximately 4,700 patients found that variants at rs12979860 near the IL28B gene could be used as a predictor of treatment response,⁸ as measured by sustained virological response (SVR). SVR is defined as an absence of hepatitis C viral RNA six months after therapy. SVR was higher in patients who were homozygous for the C allele of rs12979860 compared to patients who were heterozygous. Additionally, rs12979860 can explain some of the variability in the response rate between different ethnic groups.⁸ Individuals of European ancestry have a higher chance of successful treatment than African Americans,⁹ consistent with higher C allele frequency in European Americans (70%) compared to African Americans (40%) (see "Allele Frequency" table below).⁹ Moreover, East Asians have a higher C allele frequency and higher SVR rate than European patients.¹⁰

Patients who are homozygous for the C allele also have higher rates of clearing HCV without treatment¹¹ and may have an increased SVR rate after liver transplantation.¹² Conversely, carriers of the T allele are at an increased risk of therapeutic failure,¹³ and being homozygous for the T allele is associated with a more severe recurrence of hepatitis after transplantation.¹⁴

Precisely how rs12979860 variation affects response to PEG-IFN-alpha/RBV is not well understood.¹⁵ Other variants near the IL28B gene have been shown to alter the expression, stability or receptor binding of IL28B.¹⁵ Rs12979860 is located in a DNA methylation site, and it has been speculated that the C variant may decrease expression of IL28B.¹⁶

The association of IL28B variants with treatment response varies with the strain of the HCV virus. The association is strongest for patients infected with the HCV-1 virus, the viral strain most commonly found worldwide. In patients infected

with HCV-2, -3 or -6, however, IL28B variants are weakly associated with response to PEG-IFN-alpha/RBV.^{15,17,18} For patients infected with HCV-5 virus, IL28B variants have not been shown to be associated with response to PEG-IFN alpha/RBV.

Telaprevir and boceprevir are newly approved drugs for treatment of Hepatitis C. They are inhibitors of the viral NS3/4A protease and are indicated for patients with a null or partial response to PEG-IFN-alpha/RBV treatment.^{4,5} These drugs require co-administration with PEG-IFN-alpha/RBV. In addition, many candidate drugs for treating hepatitis C are in various phases of clinical trials.² Thus, genotyping may help determine the best treatment strategy for HCV-infected patients.⁷

Recommendations: NA

Possible Outcomes: Poor Responder, Responder

Markers or Alleles Tested: IL28B [rs12979860]

Ethnic Distribution of Tested Alleles:

Population	C allele frequency (rs12979860) ¹
Biaka Pygmies	23.5%
Zaramo	37.2%
Yoruba	31.2%
Hungarians	65.1%
Irish	73.9%
European-American	67.4%
Druze	77.6%
Yemenite Jews	69.5%
Indians	65.5%
Laotians	93.6%
Chinese, San Francisco	97.5%
Koreans	93.5%
Micronesians	98.6%
Pima, Mexico	55.5%
Mayans	37.5%
Ticuna	20.2%
Karitiana	82.4%

Limitations and Warnings: In patients infected with HCV-2, -3 or -6 strains, the IL28B variants are weakly associated with treatment response.^{15,17,18}

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to:	
Unspecified adverse effect of medicinal substance NEC properly administered	

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Leukemia, chronic lymphocytic

Report Type: Health Conditions

About: Chronic lymphocytic leukemia is the most common leukemia in adults in Western countries. This type of leukemia is characterized by the accumulation of immunoincompetent lymphocytes in the blood, bone marrow, lymph nodes and spleen.¹ Individuals with the condition usually lack symptoms, but symptoms may include painless swollen lymph nodes, tiredness, pain below the ribs, fever and weight loss.² No environmental risk factors have been identified, but research indicates that genetic factors are associated with the disease.^{1,3}

Genetics: Genetics may play a bigger role in the risk of chronic lymphocytic leukemia (CLL) compared to other types of leukemia. While CLL incidence varies with geographical location, ethnic groups retain the risk associated with their country of origin rather than their new home.⁴ The importance of genetics in CLL is also illustrated by the increased risk (2- to 8-fold) associated with a family history.⁵ Though there are many families with CLL, no autosomal dominant, high risk alleles, like those in BRCA1 for breast cancer, have been identified for CLL.⁶ In addition, patients with a strong family history of CLL have similar symptoms and survival rates compared to patients with no family history. These data suggest that many common susceptibility alleles, each associated with a small amount of risk, account for the genetic risk of CLL. The test includes four common low-risk alleles for CLL.

A study in Caucasians identified the first low-risk variants associated with CLL.⁷ It is not known whether the identified alleles are associated with CLL in other ethnic groups, but the G allele of the rs13397985 marker may also be associated with a younger age of diagnosis (less than 63 years old).⁷

The rs872071 marker is located in a noncoding region of the IRF4 gene (also known as multiple myeloma oncogene 1 or MUM1), which regulates lymphocyte development and carcinogenesis and is implicated in multiple myeloma. The G allele in the rs872071 marker was shown to reduce IRF4 expression in lymphocytes.⁷ One hypothesis is that reduced IRF4 expression might lead to the high number of abnormal lymphocytes that occurs in CLL.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
PRKD2	rs11083846	A	1.35	Caucasian	25.9%	Preliminary	18758461
SP140	rs13397985	G	1.41	Caucasian	20.5%	Preliminary	18758461
Intergenic_11q24	rs735665	A	1.45	Caucasian	17.3%	Preliminary	18758461

IRF4	rs872071	G	1.54	Caucasian	50.9%	Preliminary	18758461

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
204.11 Chronic lymphoid leukemia, in remission	V76.89 Special screening for other malignant neoplasms

References

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Lipoprotein lipase deficiency, familial

Report Type: Carrier Status

About: Lipoprotein lipase deficiency is a severe disease that is usually diagnosed in childhood.¹ The affected child may have abdominal pain, inflammation of the pancreas (pancreatitis), an enlarged liver and spleen (hepatosplenomegaly) and fatty deposits in the skin (eruptive xanthomas).² Hypertriglyceridemia is commonly diagnosed, but genetically inherited defects in the LPL gene that result in lipoprotein lipase deficiency are rarely identified. The condition is easily treated by following a low-fat diet and avoiding alcohol and medications known to increase fat levels in the blood.

Genetics: Familial lipoprotein lipase deficiency is caused by mutations in the LPL gene, which encodes the lipoprotein lipase enzyme that is required for the breakdown of fat in the body.³ Affected individuals have increased levels of fat in the blood and an increased risk for coronary artery disease.⁴

The test includes the G188E mutation, which is the most common disease-causing mutation in LPL.¹

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: NA

Mutations Tested: The test includes the G188E mutation in the LPL gene.

Ethnic Prevalence and Frequency of Mutations Tested:

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
LPL	Caucasian	46%	1 in 500	1 in 928

^aPercentage of affected patients carrying mutations detected by this test.⁴

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.⁵ The actual carrier rate and the post-test residual risk are likely to be lower.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with familial lipoprotein lipase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing

laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.5 Lipoprotein deficiencies Applies to: • Abetalipoproteinemia • Bassen-Kornzweig syndrome • High-density lipoid deficiency • Hypoalphalipoproteinemia • Hypobetalipoproteinemia (familial)	V82.71 Screening for genetic disease carrier status

References

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Lung cancer

Report Type: Health Conditions

About: Lung cancer is the most common cancer in the world and the leading cause of cancer-related death in the U.S.^{1,2} Symptoms include a chronic cough, constant chest pain, hemoptysis, shortness of breath, swelling of the face and neck, weight loss, recurring pneumonia or bronchitis and fatigue.³ Cigarette smoking is the major risk factor for lung cancer, but research indicates that genetic factors are also associated with the disease.²

Genetics: Lung cancer has long been described as a disease caused mostly by exposure to tobacco smoke.⁴ However, people who have never smoked are estimated to account for 10% to 15% of all lung cancer deaths in the U.S.⁵ For both smokers and non-smokers, a family history of lung cancer has been shown to result in a 2-fold higher risk for being diagnosed with the disease.⁶ This risk may reflect shared environmental as well as genetic influences, but the risk of lung cancer was found to be higher for children, parents and siblings compared to spouses, suggesting a genetic component.⁶

The test includes low susceptibility alleles which are each associated with small amounts of risk for lung cancer. Two of these alleles are highlighted below.

The CHRNA3 gene encodes a subunit of the nicotinic acetylcholine receptor, which binds to nicotine.⁷ In addition to mediating addiction to cigarette smoking and related products, nicotine has been reported to promote cancer cell proliferation, migration, survival and tumor angiogenesis. The rs1051730 marker is located in the coding region of CHRNA3 and was associated with lung cancer in a study of Caucasians.⁸ Follow-up studies have replicated the association and have revealed that the risk of developing lung cancer is independent of smoking behavior.⁹ Thus, both nonsmokers and smokers with the risk allele at rs1051730 may have increased risk for developing lung cancer.

The TERT gene encodes an essential component of telomerase, which is important for replacing ends of chromosomes that are lost during cell division.¹⁰ Variation in the TERT gene has been shown to be associated with an increased risk for many cancers. In addition, increased expression of chromosomal region 5p15.33, which includes TERT, has been shown to occur in the early stages of lung cancer.¹¹ The rs2736100 marker in the TERT gene was found to be associated with lung cancer in studies of Caucasians and of Han Chinese.^{12,13}

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
CHRNA3	rs1051730	T	1.32	Caucasian	38.5%	Validated	18385676

TERT	rs2736100	C	1.26	Asian	42.1%	Validated	19369581
TERT	rs2736100	C	1.07	Caucasian	52.7%	Validated	18978790
BAT3	rs3117582	C	1.20	Caucasian	8.0%	Validated	18978787

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
212.3 Benign neoplasm of bronchus and lung Applies to: • Carina • Hilus of lung	V76.0 Special screening for malignant neoplasms of respiratory organs

References

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Maple syrup urine disease

Report Type: Carrier Status

About: Maple syrup urine disease (MSUD) is an inherited metabolic disorder that is characterized by a sweet, maple syrup-like odor in earwax and urine. The most severe and also most common type of the disease is classic MSUD. The characteristic sweet smell can be detected in affected newborns within the first day of birth. If untreated, affected infants quickly develop symptoms, including poor feeding, vomiting, and lack of energy, which can develop into life-threatening symptoms, such as coma and seizures, by 10 days of age. Variant types of MSUD usually present milder symptoms at a later age of onset, but they can still lead to severe symptoms and complications if not properly monitored. Mental retardation and psychiatric disorders are the major long-term complications of MSUD. Death by the age of 7 to 10 days can occur if untreated. Treatment includes a diet restricted in particular amino acids and frequent biochemical monitoring.¹

Genetics: MSUD is caused by mutations in four genes, BCKDHA, BCKDHB, DBT and DLD. These genes encode subunits of the branched-chain alpha-ketoacid dehydrogenase complex, which is responsible for the second step in the breakdown of branched-chain amino acids.¹ In patients with maple syrup urine disease, these amino acids and their byproducts build up and reach toxic levels, resulting in a characteristic sweet, maple syrup-like odor in earwax and urine. This accumulation is toxic to many organs, especially the nervous system.¹

The test includes three mutations that cause MSUD. R183P, E372X and G278S are mutations found in BCKDHB and are prevalent disease-causing mutations in the Ashkenazi Jewish population, accounting for more than 99% of disease-causing mutations in this ethnic group.²

MSUD affects about 1 in 185,000 newborns in the general population. In the Ashkenazi Jewish population, the incidence is approximately 1 in 27,600, and in the Old Order Mennonite population in the US, the frequency is about 1 in 380.^{1,3}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified maple syrup urine disease as one of 29 diseases for which newborn screening should be mandated.⁴

Mutations Tested: The test includes three mutations in the BCKDHB gene

BCKDHB [R183P, G278S, E372X]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
BCKDHB	Ashkenazi Jew	99%	1 in 97	1 in 1,921

^aPercentage of affected patients carrying mutations detected by this test.^{1,2,5}

^bCarrier risk before testing.^{1,5}

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with maple syrup urine disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.3 Disturbances of branched-chain amino-acid metabolism Applies to: • Disturbances of metabolism of leucine, isoleucine, and valine • Hypervalinemia • Intermittent branched-chain ketonuria • Leucine-induced hypoglycemia • Leucinoses • Maple syrup urine disease	V82.71 Screening for genetic disease carrier status

References

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Medium-chain acyl-CoA dehydrogenase deficiency

Report Type: Carrier Status

About: Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is a genetic disease that disrupts the breakdown of a type of medium-chain fatty acids. Symptoms may include vomiting, drowsiness and hypoglycemia and can quickly worsen to include seizures, coma and even death. Sudden death is often the first and only presentation of the disease. Episodes of energy shortage can lead to long-term complications that include damage to the brain and muscles and problems in the liver. People with MCAD deficiency typically experience their first episode between 3 months to 2 years of age.¹

Genetics: Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is caused by mutations in the ACADM gene, which encodes the medium-chain acyl-coenzyme A dehydrogenase enzyme that is required for the first step in the metabolism of medium-chain fatty acids. Individuals with this disease may experience an energy crisis when other energy stores are depleted, causing symptoms such as vomiting drowsiness and hypoglycemia. Individuals suffering from MCAD deficiency have increased risk of hypoketotic hypoglycemia, which may lead to coma or death.²

MCAD deficiency is one of the most frequently diagnosed diseases in newborn screening programs with an estimated incidence of 1 in 17,000 live births in the U. S. MCAD deficiency is more common among individuals of northern European ancestry than in people of other ethnicities.¹

The K304E mutation is especially prevalent in the Caucasian population with a carrier rate of 1 in 40.^{3,4} The Y42H mutation has an allele frequency of approximately 7% in newborns with MCAD deficiency.¹ Unlike K304E, Y42H reduces but does not completely abolish the enzyme's activity. Notably, Y42H has only been found in infants as a result of newborn screening. All infants discovered to carry Y42H were immediately treated, so the natural disease progression associated with this mutation is not known.⁵

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified medium-chain acyl-CoA dehydrogenase deficiency as one of 29 diseases for which newborn screening should be mandated.⁶

Mutations Tested: The test includes two mutations in the ACADM gene.

ACADM [Y42H, K304E]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
ACADM	Caucasian	70%	1 in 40	1 in 131

^aPercentage of affected patients carrying mutations detected by this test.¹

^bCarrier risk before testing.¹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with medium-chain acyl-CoA dehydrogenase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.85 Disorders of fatty acid oxidation Applies to: • Carnitine palmitoyltransferase deficiencies (CPT1, CPT2) • Glutaric aciduria type II (type IIA, IIB, IIC) • Long chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHAD) • Long chain/very long chain acyl CoA dehydrogenase deficiency (LCAD, VLCAD) • Medium chain acyl CoA dehydrogenase deficiency (MCAD) • Short chain acyl CoA dehydrogenase deficiency (SCAD)	V82.71 Screening for genetic disease carrier status

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Melanoma

Report Type: Health Conditions

About: Melanoma has been on the rise in developed countries for the past 50 years. It is now the eighth most common cancer in developed countries and, in the U.S., is ranked fifth and sixth in men and women, respectively.^{1,2} Risk factors for melanoma include sun exposure, being blond or red-headed with fair skin, having a family history of melanoma. Research indicates that genetic factors are also associated with the disease.³

Genetics: Genetic markers for cutaneous melanoma fall into two categories: rare, high risk alleles and common, low risk susceptibility alleles.^{4,5} Rare mutations in high penetrance genes such as CDKN2A or CDK4 are associated with risk for familial melanoma. However, known high risk alleles explain only a very small fraction of the incidence of melanoma. The genetic risk for most individuals who develop melanoma is hypothesized to be due to multiple common susceptibility alleles, each conferring a small amount of risk.

The test includes four low risk susceptibility alleles for cutaneous melanoma.^{6,7,8,9,10}

The melanocortin-1 receptor (MC1R) gene is a susceptibility locus for melanoma in Caucasians.⁷ The R151C variant (rs1805007) of the MC1R gene was found to be associated with melanoma.⁶ In addition, the C variant is known to be a “red hair variant”, characterized by association with the occurrence of red hair, freckles and a poor tanning ability, which are known risk factors for melanoma. The risk of melanoma was not wholly explained by association with the red hair phenotype, however, and the variant shows association with increased melanoma risk in both lighter-skinned and darker-skinned Caucasians.

The tyrosinase-related protein 1 (TYRP1) and tyrosinase (TYR) genes encode proteins that are critical for melanin production.¹¹ Variants in these genes are associated with eye color in Europeans^{8,9} and risk for melanoma in populations of European ancestry, including individuals from Iceland, Sweden and Spain.⁶ The association with melanoma risk was similar in individuals with fair skin and hair compared to those with darker skin and hair.

The rs910873 marker in the phosphatidylinositol glycan anchor biosynthesis, class U (PIGU) gene is also associated with melanoma risk.¹⁰ PIGU, also known as CDC91L1, is also an oncogene for bladder cancer.¹² It is unclear what role PIGU might play in melanoma, but the gene is expressed in melanoma tumor cells. Moreover, rs910873 may not directly impact melanoma itself, but be linked to a causative variant.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested^{6,10}

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
TYR	rs1126809	A	1.21	Caucasian	21.7%	Validated	18488027
MC1R	rs1805007	T	1.47	Caucasian	12.1%	Validated	18488027
TYRP1	rs1408799	C	1.15	Caucasian	69.5%	Preliminary	18488027
PIGU	rs910873	T	1.75	Caucasian	8.4%	Preliminary	18488026

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
172.8 Malignant melanoma of other specified sites of skin	N/A
Applies to: Malignant melanoma of contiguous or overlapping sites of skin whose point of origin cannot be determined	

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Methotrexate toxicity

(DC:TB-0226.001 06DEC2012)

Report Type: Pharmacogenetics

About: Methotrexate (MTX) is a chemotherapeutic agent used in the treatment of lymphoma and leukemia, as well as uterine, breast, skin, ovarian and other cancers. MTX is also used to treat very severe and disabling psoriasis or in hematopoietic stem cell transplantation to prevent graft-versus-host disease. Some patients taking MTX may experience many and/or severe side effects, which are often referred to as MTX toxicity.¹

Genetics: The T allele of the rs1801133 marker (C677T variant) in the MTHFR (5,10-methylenetetrahydrofolate reductase) gene, which is important for folate metabolism, was shown to be associated with MTX toxicity in patients with rheumatoid arthritis. The T allele results in an amino acid change that leads to reduced enzyme activity. Homozygotes for the T allele have approximately 30% of the expected MTHFR enzyme activity, and heterozygotes have approximately 65% activity, compared to the most common genotype, C allele homozygotes. Reduced MTHFR enzyme activity may result in reduced elimination of MTX, thus resulting in higher than expected MTX plasma concentrations and increasing the likelihood of MTX toxicity.²

While other MTHFR mutations are associated with MTHFR deficiency, only the C677T variant has shown significant association with methotrexate toxicity. In a meta-analysis of eight small studies, individuals with a T allele were shown to have a 1.7-fold increased risk for MTX-induced side effects.³ These studies included patients from India, Japan, South Korea, Israel and the Netherlands. Additionally, a meta-analysis of 14 studies demonstrated that the T allele was associated with an increased risk of MTX-induced toxicity (liver toxicity, myelosuppression, oral mucositis, gastrointestinal toxicity and skin toxicity) in patients with acute lymphoblastic leukemia (ALL).⁴

Most studies with statistically significant data indicate an association between the T allele with MTX-induced side effects in patients with rheumatoid arthritis and ALL. It should be noted, however, that a 2011 meta-analysis did not identify a significant association between the C677T variant and MTX toxicity in patients with rheumatoid arthritis.⁵ Association of the T allele with MTX toxicity has also been observed in patients undergoing hematopoietic cell transplantation and in patients with high-grade non-Hodgkin's lymphoma, acute leukemia, ovarian cancer, breast cancer, or juvenile idiopathic arthritis.² However, these studies are relatively small and controversial. In addition to MTX toxicity, the T allele has been associated with lowered efficacy of MTX, such as reduced anti-tumor activity or reduced survival in some studies but not others. The T allele has also been shown to be associated with therapeutic response to a different chemotherapy, fluorouracil (5-FU), in some studies but not others.^{6,7,8,9}

Recommendations: Varying the MTX dose or supplementing with folic or folinic acid (leucovorin) has been shown to reduce the risk of toxicity-related discontinuation of MTX treatment in patients with and without the T allele.^{10,11,12}

Please also see the related tests: MTHFR deficiency and Genetic risk for decreased folate.

Possible Outcomes: Increased Risk, Typical Risk

Markers or Alleles Tested: MTHFR [rs1801133]

Ethnic Distribution of Tested Alleles: The minor allele frequency was approximately 29.4% to 33.5% in Caucasians.⁵

Limitations and Warnings: Some variants not reported in the test also result in altered MTHFR activity. Therefore, a negative result for the reported MTHFR variant does not rule out the presence of additional variants that can cause altered MTHFR activity related adverse effects upon MTX treatment.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to:	
Unspecified adverse effect of medicinal substance NEC properly administered	

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Methylmalonic acidemia

Report Type: Carrier Status

About: Methylmalonic acidemia is an inherited metabolic disease that causes brain damage in infants and young children. A defect in protein and fat metabolism leads to the accumulation of toxic levels of methylmalonic acid and its byproducts in body fluids, which can provoke a crisis that causes brain damage. Other symptoms of the crisis may include poor appetite, nausea, vomiting, extreme sleepiness, irritability, low muscle tone and muscle weakness. If not treated, breathing problems, seizures, stroke, coma and sometimes even death can occur. With prompt and lifelong treatment, children with methylmalonic acidemia can often live normal lives.¹

Genetics: Methylmalonic acidemia is caused by mutations in multiple genes, including MUT and MMAA.¹ The MUT gene encodes the enzyme methylmalonyl-CoA mutase that converts methylmalonyl-CoA to succinyl-CoA during the metabolic degradation of certain amino acids (valine, isoleucine, methionine, threonine) and fats (odd-chain fatty acids, cholesterol). The MMAA gene encodes a protein (methylmalonic aciduria type A) that helps methylmalonyl-coA mutase function.² When one of these genes is mutated, toxic levels of methylmalonic acid and its byproducts accumulate in body fluids and are excreted in the urine.

The test includes mutations in the MMAA and MUT genes. In the MUT gene, the N219Y mutation has been observed in Caucasian populations while the E117X mutation occurs in Japanese populations.^{3,4}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified methylmalonic acidemia as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test includes two mutations in the MMAA gene and five mutations in the MUT gene.

MMAA [503delC, R145X]

MUT [N219Y, R369C, R108C, G717V, E117X]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
MMAA	Caucasian	43%	1 in 568	1 in 996
MMAA	Japanese	64%	1 in 448	1 in 1243
MUT	Caucasian	19%	1 in 237	1 in 292
MUT	Japanese	22%	1 in 187	1 in 239

MUT	Black	35%	1 in 237	1 in 361
MUT	Hispanic	41%	1 in 237	1 in 399

^aPercentage of affected patients carrying mutations detected by this test.^{4,6,7,8,9}

^bCarrier risk before testing.¹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other genes and mutations associated with methylmalonic aciduria, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.7 Other disturbances of straight-chain amino-acid metabolism Applies to: • Glucoglycinuria • Glycinemia (with methylmalonic acidemia) • Hyperglycinemia • Hyperlysinemia • Pipecolic acidemia • Saccharopinuria • Other disturbances of metabolism of glycine, threonine, serine, glutamine, and lysine	V82.71 Screening for genetic disease carrier status

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Metoprolol metabolism

(DC:TB-0217.001 06DEC2012)

Report Type: Pharmacogenetics

About: Metoprolol (MET) is one of the most commonly used beta-blockers for treatment of heart failure.¹ This cardioselective beta(1)-adrenergic blocker is also used for treatment of acute myocardial infarction, angina pectoris and mild to moderate hypertension.² Metoprolol is metabolized to inactive forms by a member of the cytochrome P450 superfamily, the CYP2D6 enzyme, which is responsible for 70% to 80% of the metabolism of metoprolol.³

Genetics: CYP2D6 variants play a major role in the pharmacokinetics of metoprolol, which translates into relevant clinical outcomes.^{3,4,5,6} A wide range of variants in the CYP2D6 gene affect the enzyme activity, and individuals can be classified based on this activity into three metabolizer groups: Extensive Metabolizer (normal enzyme activity), Intermediate Metabolizer (intermediate enzyme activity) and Poor Metabolizer (low or no enzyme activity).

CYP2D6 poor and intermediate metabolizers treated with standard doses of metoprolol have increased plasma concentration of the drug and increased risk for bradycardia.^{7,8,9,10,11,12,13} They may also have greater reductions in heart rate, diastolic blood pressure, and arterial pressure at typical doses.^{3,6,14,15,16,17,18}

The largest and most representative study on CYP2D6-metabolized beta-blockers demonstrates that the CYP2D6 poor metabolizer status is associated with lower heart rate and blood pressure.³ The association between CYP2D6 genotype and metoprolol response or side effects was not confirmed in some much smaller studies.^{7,11,19,20}

Recommendations: The FDA-approved labels of metoprolol^{12,13} indicate that concomitant use of CYP2D6 inhibitors (see "Known CYP2D6 Inhibitors" table below) with metoprolol may lead to higher than normal plasma levels of metoprolol at standard doses. CYP2D6 inhibitors are also likely to decrease the cardioselectivity of metoprolol. The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group also suggests dose adjustment or alternative medications for CYP2D6 poor metabolizers and intermediate metabolizers.²¹ CYP2D6 genotype and metabolizer status may also affect a patient's response to other drugs (see "Known CYP2D6 Substrates" table below).

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2D6 alleles are classified as non-functional (*3, *4, *6 and *8), reduced-function (*9, *10, *17, *29 and *41), and normal-function (*1, *2 and *35). CYP2D6 phenotype prediction follows conventional guidelines (See below).

Predicted CYP2D6 Metabolizer Status

CYP2D6 Diplotype	Predicted Metabolizer Status

Two non-functional alleles	Poor metabolizer
One non-functional allele plus one reduced-function allele, or two reduced-function alleles	Intermediate metabolizer
One or two normal-function copies of the CYP2D6 gene	Extensive metabolizer

Ethnic distribution of CYP2D6 phenotypes

Ethnicity	Poor Metabolizer	Intermediate Metabolizer	Extensive Metabolizer
African American	2-8%	~30%	60-70%
Caucasian	5-10%	10-17%	70-80%
East Asian	<2%	50-60%	40-50%
Hispanic	3-10%	no data	no data

Limitations and Warnings: This test detects common CYP2D6 alleles that have a combined frequency of over 90% in major ethnic groups. Other alleles that may also affect CYP2D6 enzyme activity are not tested. For example, the test does not include alleles that are associated with higher than normal enzyme activity. As such, a small percentage of patients with the test result of CYP2D6 "Extensive Metabolizer" may metabolize metoprolol at higher than normal rates. This may result in failure to achieve optimal plasma concentrations at standard doses and an increased risk of therapeutic failure.^{4,7,16}

Known CYP2D6 Inhibitors and Substrates Tables

Known CYP2D6 Inhibitors ^{22,23,24}		
amiodarone	escitalopram	paroxetine
bupropion	flecainide acetate	perphenazine
celecoxib	fluoxetine	primaquine phosphate
chloroquine phosphate	fluphenazine	propafenone
chlorpheniramine	fluvoxamine maleate	propoxyphene
chlorpromazine	halofantrine	quinacrine
cimetidine	haloperidol	quinidine
cinacalcet	histamine H1 receptor antagonists	ranitidine
citalopram	hydroxychloroquine	reduced haloperidol
clemastine	hydroxyzine	ritonavir
clomipramine	imatinib mesylate	sertraline
cocaine	labetalol	terbinafine
codeine	levomepromazine	thioridazine
darifenacin hydrobromide	lomustine	ticlopidine
delavirdine mesylate	lumefantrine	tripelennamine
desipramine	methadone	valdecoxib
diphenhydramine	metoclopramide	vinblastine sulfate
doxepin	mibefradil	vincristine sulfate

doxorubicin dronedarone duloxetine	midodrine moclobemide norfluoxetine	vinorelbine tartrate yohimbine

Known CYP2D6 Substrates ^{22,24,25}		
alprenolol amitriptyline amoxapine amphetamine aripiprazole atomoxetine betaxolol bisoprolol bufuralol captopril carvedilol cevimeline chlorpheniramine chlorpromazine chlorpropamide cinacalcet clomipramine clonidine clozapine codeine cyclobenzaprine cyclophosphamide darifenacin hydrobromide debrisoquine delavirdine mesylate desipramine dexfenfluramine dextromethorphan diphenhydramine dolasetron donepezil doxazosin mesylate doxepin duloxetine encainide	fenfluramine fentanyl flecainide fluoxetine fluphenazine fluvoxamine formoterol galantamine haloperidol hydrocodone hydrocortisone hydroxyamphetamine hydrobromide iloperidone imipramine labetalol lidocaine loratadine maprotiline meperidine methadone methamphetamine methoxyamphetamine metoclopramide metoprolol mexiletine minaprine mirtazapine molindone morphine nebivolol nortriptyline olanzapine ondansetron orphenadrine citrate	oxycodone paliperidone paroxetine penbutolol sulfate pentazocine lactate perhexiline perphenazine phenacetin phenformin pindolol promethazine propafenone propoxyphene propranolol protriptyline quetiapine ranolazine risperidone ropivacaine selegiline S-metoprolol sparteine tamoxifen tamsulosin thioridazine tiagabine timolol tolterodine tramadol trazodone trimipramine maleate venlafaxine yohimbine zuclopenthixol

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
N/A	V58.83 Encounter for therapeutic drug monitoring

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Mucopolidosis II

Report Type: Carrier Status

About: Mucopolidosis II alpha/beta is a fatal, inherited disorder that results in the abnormal accumulation of carbohydrates and lipids in lysosomes.^{1,2} Cells in the skeletal system are the most sensitive to this defect. At birth, infants with mucopolidosis II alpha/beta may show abnormal skeletal development, restricted joint movement and coarse facial features (flat nasal bridge, puffy eyelids, enlarged gums and tongue).^{1,2} The liver, spleen and heart may be enlarged. Affected children fail to grow and develop, have eye problems and suffer respiratory tract infections. There is no cure for mucopolidosis II alpha/beta. Children with mucopolidosis II alpha/beta usually die of congestive heart failure or respiratory tract infections before the age of seven.³

Genetics: Mucopolidosis II alpha/beta, the severe form of mucopolidosis, is caused by mutations with complete loss of activity in the GNPTAB gene, which encodes the alpha and beta subunits of the enzyme N-acetylglucosamine-1-phosphotransferase (GNPT).^{4,5,6} This enzyme is responsible for making a molecular tag that directs enzymes to the lysosome. Mutations in GNPTAB that eliminate GNPT enzyme activity result in disrupted lysosomal function and accumulation of toxic levels of lipids and acid mucopolysaccharides in the lysosome.¹

The test includes the most common mutations in the GNPTAB gene that are responsible for mucopolidosis II alpha/beta. The 3503_3504delTC mutation in the GNPTAB gene is the most common mutation worldwide in all ethnic groups.¹ The 3503_3504delTC mutation is also responsible, as a founder mutation, for the high incidence of mucopolidosis II alpha/beta in a French-Canadian population in the northeastern part of Quebec province.⁷ The R1189X mutation in the GNPTAB gene is common in the Japanese population.⁸

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes seven mutations in the GNPTAB gene.

GNPTAB [Q104X, 1581delC, 616_619delACAG, 3503_3504delTC, Q845X, R1205X, R1189X]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
GNPTAB	Predominantly white	56%	1 in 500	1 in 1138
GNPTAB	Japanese	60%	1 in 500	1 in 1249

^aPercentage of affected patients carrying mutations detected by this test.^{8,9}

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of in 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.¹⁰ The actual carrier rate and the post-test residual risk are likely to be lower.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with mucopolipidosis II, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.7 Lipidoses Applies to: - Chemically induced lipidoses - Disease: - Anderson's - Fabry's - Gaucher's - I cell [mucopolipidosis I] - lipoid storage NOS - Niemann-Pick - pseudo-Hurler's or mucopolipidosis III - triglyceride storage, Type I or II - Wolman's or triglyceride storage, Type III - Mucopolipidosis II - Primary familial xanthomatosis	V82.71 Screening for genetic disease carrier status

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Mucopolidosis III

Report Type: Carrier Status

About: Mucopolidosis III alpha/beta is an inherited disease that results in a mild, late-onset form of mucopolidosis. At 3 to 5 years of age, children with mucopolidosis III alpha/beta begin showing symptoms such as skeletal abnormalities, coarse facial features, short stature and eye problems. Individuals with mucopolidosis III alpha/beta may live into their forties.^{1,2,3}

Genetics: Mucopolidosis III is caused by mutations that lead to a partial loss of N-acetylglucosamine-1-phosphotransferase (GNPT) activity. The GNPT enzyme makes a molecular tag that directs enzymes to the lysosome. When normal lysosomal function is disrupted, toxic levels of lipids and acid mucopolysaccharides accumulate in the lysosome.^{1,2,3}

Because the GNPT enzyme is composed of three distinct subunits encoded by two different genes (GNPTAB and GNPTG), it is possible for mutations in either gene to cause the same symptoms. The inherited disease caused by mutations in the GNPTAB gene is called mucopolidosis III alpha/beta.^{2,4} The inherited disease caused by mutations in the GNPTG gene is called mucopolidosis III gamma and is clinically indistinguishable from mucopolidosis III alpha/beta.^{5,6,7}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes four mutations in two genes.

GNPTAB [K4Q, IVS17+6T>G]; GNPTG [499dupC, 347_349_delACA]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there might be other mutations associated with mucopolidosis III, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.7 Lipidoses	V82.71 Screening for genetic disease carrier status
Applies to:	

- Chemically induced lipidosis
- Disease:
 - Anderson's
 - Fabry's
 - Gaucher's
 - I cell [mucopolipidosis I]
 - lipid storage NOS
 - Niemann-Pick
 - pseudo-Hurler's or mucopolipidosis III
 - triglyceride storage, Type I or II
 - Wolman's or triglyceride storage, Type III
- Mucopolipidosis II
- Primary familial xanthomatosis

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Mucopolipidosis IV

Report Type: Carrier Status

About: Mucopolipidosis IV is an inherited disease of the nervous system that is characterized by developmental delay and vision loss. Most patients with this disease have intellectual disability, psychomotor delay and, by their early teens, lose their eyesight as a result of retinal degeneration.¹ Mucopolipidosis IV can also be classified as a lysosomal storage disease and an ion channel disease. There is no cure.

Genetics: Mucopolipidosis IV is caused by mutations in the MCOLN1 gene, which encodes an ion channel protein called mucolipin-1.¹ Defects in this protein can alter the function of the lysosome and lead to an abnormal accumulation of a wide variety of lipids and acid mucopolysaccharides. The result is disrupted development of the brain and the reduced maintenance of retina and optic nerve cells.¹

Two mutations in MCOLN1 account for 95% of mucopolipidosis IV in Ashkenazi Jews: IVS3-2A>G and del6.4kb.² This test currently detects the IVS3-2A>G mutation, which accounts for approximately 77% of Ashkenazi mucopolipidosis IV alleles, and does not include del6.4kb.²

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: NA

Mutations Tested: The test includes the IVS3-2A>G mutation in the MCOLN1 gene.

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
MCOLN1	Ashkenazi Jewish	77%	1 in 127	1 in 549

^aPercentage of affected patients carrying mutations detected by this test.²

^bCarrier risk before testing.²

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with mucopolipidosis IV, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing

laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.8 Other disorders of lipid metabolism	V82.71 Screening for genetic disease carrier status
Applies to: - Hoffa's disease or liposynovitis prepatellaris - Launois-Bensaude's lipomatosis - Lipoid dermatoarthritis	

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Multiple carboxylase deficiency

Report Type: Carrier Status

About: Multiple carboxylase deficiency (MCD) is a potentially life-threatening, inherited disease of newborns caused by a defect in the way the body processes the vitamin biotin. MCD can develop from soon after birth to 15 months of age and involves an episode of illness called a metabolic crisis. The symptoms may include poor appetite, vomiting, lack of energy, irritability, low muscle tone and severe peeling skin rash. If not treated, breathing problems, seizures, swelling of the brain, coma and sometimes even death can occur. The treatment is effective and simple: high doses of biotin daily for life. Even without metabolic crises, untreated children can suffer mental retardation, hearing loss or vision loss that cannot be reversed by biotin supplementation.¹

Genetics: MCD is caused by mutations in the HLCS gene, which encodes biotin-protein ligase, also known as holocarboxylase synthetase.^{1,2} Mutations in HLCS reduce the enzyme's ability to attach biotin to carboxylase enzymes. Without biotin, carboxylase enzymes remain inactive and are unable to effectively process proteins, fats and carbohydrates. Mutations in HLCS also compromise the enzyme's ability to attach biotin to chromosomal proteins called histones, which may alter the regulation of genes that are important for normal development.^{3,4}

The 780delG and L237P mutations account for 50% of the alleles found in Japanese patients, but are never found in other ethnic groups.² The R508W, V550M, D571N and G581S mutations are recurrent in several ethnic groups.²

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified multiple carboxylase deficiency as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test includes seven mutations in the HLCS gene.

HLCS [R665X, 780delG, L237P, R508W, V550M, D571N, G581S]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with multiple carboxylase deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
271.8 Other specified disorders of carbohydrate transport and metabolism Applies to: • Essential benign pentosuria • Fucosidosis • Glycolic aciduria • Hyperoxaluria (primary) • Mannosidosis • Oxalosis • Xylosuria • Xylulosuria	V82.71 Screening for genetic disease carrier status

References

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Multiple sclerosis

Report Type: Health Conditions

About: Multiple sclerosis is a chronic inflammatory disease that is presumed to be an autoimmune disorder.^{1,2} This neurodegenerative disease damages the myelin sheaths surrounding neurons, which leads to muscle weakness, difficulties with balance and numbness, among others.³ Though the cause of multiple sclerosis is unknown, genetic factors are associated with the disease.^{2,4}

Genetics: Genetic variation in the major histocompatibility complex region of Chromosome 6 has long been known to play a role in susceptibility to multiple sclerosis. The human leukocyte antigen (HLA) region, a set of genes within the major histocompatibility complex, has been associated with an increased risk for multiple sclerosis in people of European descent.² The HLA region is also associated with other auto-immune conditions, such as type 1 diabetes and rheumatoid arthritis.^{5,6} Two other genes, interleukin 2 receptor alpha (IL2RA) and interleukin 7 receptor (IL7R), are also involved in the immune system and associated with the risk for multiple sclerosis.² Variants in these genes were examined in families of European descent from the U.S. and U.K. While HLA had the strongest association, both IL2RA and IL7R also appeared to play a role in susceptibility to multiple sclerosis.² The test includes variants in the HLA region, as well as the IL2RA and IL7R genes.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
IL2RA	rs12722489	G	1.25	Caucasian	82.7%	Validated	17660530
HLA	rs3135388	T	1.99	Caucasian	19.0%	Validated	17660530
IL7RA	rs6897932	C	1.18	Caucasian	75.7%	Validated	17660530
KIF1B	rs10492972	C	1.34	Caucasian	33.6%	Preliminary	18997785
EVI5	rs10735781	G	1.11	Caucasian	34.5%	Preliminary	17660530
ANKRD15	rs10975200	G	1.14	Caucasian	16.4%	Preliminary	17660530
FAM69A	rs11164838	C	1.11	Caucasian	58.4%	Preliminary	17660530
CD58	rs12044852	C	1.24	Caucasian	87.2%	Preliminary	17660530
CBLB	rs12487066	T	1.09	Caucasian	67.7%	Preliminary	17660530
PDE4B	rs1321172	G	1.08	Caucasian	54.9%	Preliminary	17660530

KLRB1	rs4763655	A	1.10	Caucasian	33.2%	Preliminary	17660530

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: Multiple sclerosis is rare in non-European populations and, thus, has not been widely studied in people of African or Asian descent. Therefore, only data from studies using large populations of European descent are represented. Genetic risk factors found in Caucasians may well apply to people of other ethnicities, but this has not been proven. Only the most common relapsing-remitting form of multiple sclerosis has been well studied, and all the information provided here relates to relapsing-remitting multiple sclerosis.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
340 Multiple sclerosis Applies to: - Disseminated or multiple sclerosis: - NOS - brain stem - cord - generalized	V82.9 Screening for unspecified condition

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Myocardial infarction

Report Type: Health Conditions

About: Myocardial infarction (MI) kills approximately half a million people in the U.S. each year.¹ Symptoms of this condition include chest pain, shortness of breath and other symptoms.^{1,2} Risk factors include a family history of MI, diabetes, hypertension and hypercholesterolemia.² Research indicates that genetic factors are also associated with MI.^{2,3}

Genetics: Genetic susceptibility factors contribute to the risk of MI. Their importance is highlighted by the fact that about 15% to 20% of individuals who have an MI lack conventional risk factors.⁴ Studies suggest that many genetic variations associated with the disease are in genes involved in processes involving endothelial cell function, inflammation, lipid metabolism, thrombosis and fibrinolysis.^{2,3}

Many SNPs associated with heart disease are in genes involved in inflammation. A marker in the CXCL12 gene, which encodes a chemokine molecule important for attracting lymphocytes,⁵ was shown to be also associated with the risk for MI in a large study of Caucasians.⁶ Additionally, in a large genome-wide association study identifying markers affecting eosinophil counts, a marker at 12q24 (rs3184504) in the SH2B3 gene, which encodes a protein important for cytokine pathway inhibition, was associated with risk for MI in six different populations.⁷

A number of high-impact studies have identified 9p21.3 as an important genetic region associated with risk for MI or coronary artery disease.⁸ This region contains no annotated genes but lies close to the CDKN2A and CDKN2B genes, which regulate important cell cycle pathways. An allele of the rs10757278 marker in the 9p21.3 region is associated with MI in Icelandic, U.S. Caucasian, and Italian populations.^{9,10,11} When the Italian patient group was subdivided into those with and without a family history of MI, only the individuals with a family history of MI still showed a significant association with the allele.¹¹ This research suggests that in cases with a family history of heart disease and heart attack, the relative risk for an individual carrying a risk allele can be significantly higher.

Another large study carried out by the Myocardial Infarction Genetics Consortium replicated the region of 9p21, as well as identified or replicated other markers in MIA3 (rs17465637), 1p13 (rs646776), 10q11 in CXCL12 (rs1746048), 21q22 (rs9982601), 6p24 in PHACTR1 (rs12526453), and 2q33 in WDR12 (rs6725887).⁶

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
PSMA6	rs1048990	G	1.21	Asian	37.8%	Validated	16845397

Intergenic_9p21	rs10757278	G	1.28	Caucasian	50.0%	Validated	17478679
PCSK9	rs11206510	T	1.15	Caucasian	83.6%	Validated	19198609
PHACTR1	rs12526453	C	1.12	Caucasian	63.3%	Validated	19198609
CXCL12	rs1746048	C	1.17	Caucasian	85.4%	Validated	19198609
MIA3	rs17465637	C	1.14	Caucasian	26.8%	Validated	19198609
SH2B3	rs3184504	T	1.13	Caucasian	44.5%	Validated	19198610
Intergenic_1p13	rs646776	T	1.19	Caucasian	74.6%	Validated	19198609
WDR12	rs6725887	C	1.17	Caucasian	15.9%	Validated	19198609
LGALS2	rs7291467	C	1.23	Asian	73.3%	Validated	15129282
Intergenic_21q22	rs9982601	T	1.20	Caucasian	20.6%	Validated	19198609
LTA	rs1041981	A	1.00	Asian	43.5%	Preliminary	12426569
OR13G1	rs1151640	G	1.31	Caucasian	46.0%	Preliminary	16175505
PRR4	rs1376251	C	1.23	Caucasian	65.3%	Preliminary	16175505
MIAT	rs2331291	T	1.38	Asian	13.1%	Preliminary	17066261

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
410.9 Acute myocardial infarction of unspecified site	V81.2 Screening for other and unspecified cardiovascular conditions

Applies to:

- Acute myocardial infarction NOS
- Coronary occlusion NOS
- Myocardial infarction NOS

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Nephrotic syndrome, steroid-resistant

Report Type: Carrier Status

About: Steroid-resistant nephrotic syndrome (SRNS) is a subgroup of the idiopathic nephrotic syndrome and is identified based on the patient's response to a standard steroid therapy.¹ SRNS is defined when patients remain unresponsive to the therapy after eight weeks of treatment.² The symptoms of this inherited disease include progressive kidney failure, proteinuria, edema, hypoalbuminemia and hyperlipidemia. Additional complications include infections, anemia, and hypertension.² SRNS occurs mainly in early childhood.^{3,4}

Genetics: SRNS is caused by mutations in the NPHS2 gene, which encodes a membrane-bound structural protein found in the kidney called podocin. This protein plays an important role in molecular signaling and assists in the formation of the scaffolding complex of the slit diaphragm, a structure that is important for the filtration barrier in the kidneys.^{5,6,7}

In 42 of 73 families with two disease-causing NPHS2 mutations, the most common mutation was the R138Q founder mutation, which is associated with an early onset of the disease (0 to 5.4 years).^{1,8}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes three mutations in the NPHS2 gene.

NPHS2 [436delA, R138Q, 1036delC]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with steroid-resistant nephrotic syndrome, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
581.9 Nephrotic syndrome with unspecified pathological lesion in kidney	V82.71 Screening for genetic disease carrier status

Applies to:

- Glomerulonephritis with edema NOS
- Nephritis:
 - nephrotic NOS
 - with edema NOS
- Nephrosis NOS
- Renal disease with edema NOS

References

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Niemann-Pick disease

Report Type: Carrier Status

About: Niemann-Pick disease (NPD) causes organ damage because of a defect in fat metabolism. In NPD patients, some types of lipids are not properly transported to lysosomes or are not degraded efficiently in the lysosomes. These undegraded lipids accumulate in cells and cause symptoms in multiple organs, including liver, lung, spleen, and the nervous system.^{1,2} NPD is categorized into three main types according to the genetic defect and symptoms.

NPD-A is the most severe form and refers to affected individuals who develop neurologic symptoms during infancy and usually do not survive beyond age three. NPD-B generally has milder symptoms and a later age of onset compared to NPD-A. NPD-B patients do not usually present neurologic symptoms or the nervous system is affected only later in life. Survival into adulthood is common for NPD-B patients.¹ NPD-C typically manifests first in childhood, but infant or adult onset is also possible. Pneumonia is the most life-threatening complication for NPD-C patients, who survive to their late second or third decade.³

Genetics:

Both Niemann-Pick disease type A (NPD-A) and Niemann-Pick disease type B (NPD-B) are caused by mutations in the SMPD1 gene, which encodes a lysosomal enzyme called acid sphingomyelinase that degrades sphingomyelin. The disease name “acid sphingomyelinase deficiency” covers both NPD-A and NPD-B.¹

Niemann-Pick disease type C (NPD-C) is caused by mutations in the NPC1 and NPC2 genes. Approximately 90% of NPD-C cases are caused by mutations in the NPC1 gene, whereas a small number of NPD-C cases are caused by mutations in NPC2. The proteins encoded by the NPC1 and NPC2 genes are involved in the transportation of lipids inside the cell, although their exact functions are not well understood.³

Mutations causing NPD-A are especially prevalent in the Ashkenazi Jewish population.⁴ Implementation of carrier screening programs has significantly reduced the incidence of NPD-A in this population.¹ NPD-B has a wide ethnic and regional distribution and is found frequently found in people of Turkish, Arabic and North African descent.⁵ The combined incidence of NPD-A and NPD-B in non-Ashkenazi Jewish populations is about 1 in 250,000.¹ The incidence of NPD-C is 1 in 150,000 in Western Europe.³

The test includes three SMPD1 mutations (R496L, L302P, P330SfsX382) that cause NPD-A in the Ashkenazi Jewish population⁴ as well as two SMPD1 mutations (H421Y, deltaR608) associated with NPD-B. The H421Y mutation causes relatively severe symptoms and accounts for as much as 71% of disease-causing mutations in Saudi Arabian NPD-B cases.⁵ The deltaR608 mutation is prevalent among patients descended from the Maghreb region of North Africa. Patients who are homozygous for deltaR608 usually present with mild symptoms.⁵

The test also includes three mutations that cause NPD-C. The I1061T mutation in NPC1 accounts for about 15% to 20% of pathogenic NPC1 mutations in Western Europe and the U. S.³ The G992W mutation in NPC1 is predominant in Acadian patients from Nova Scotia.³ E20X accounts for about half of pathogenic mutations in NPC2.⁶

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote.

Recommendations: The American College of Medical Genetics (ACMG) recommends offering carrier screening for Niemann-Pick (Type A) disease to individuals with Ashkenazi Jewish ancestry.⁴

Mutations Tested: The test includes eight mutations in three genes. ACMG recommends screening in Ashkenazi Jews for three mutations, which are underlined below.⁴

SMPD1 [deltaR608, P330SfsX382, H421Y, R496L, L302P]; NPC1 [G992W, I1061T]; NPC2 [E20X]

Ethnic Prevalence and Frequency of Mutations Tested⁴

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
SMPD1	Ashkenazi Jew	97%	1 in 90	1 in 2,968

^aPercentage of affected patients carrying mutations detected by this test.

^bCarrier risk before testing.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with Niemann-Pick disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
272.7 Lipidoses Applies to: - Chemically induced lipidosis - Disease: - Anderson's - Fabry's	V82.71 Screening for genetic disease carrier status

◦ Gaucher's ◦ I cell [mucopolipidosis I] ◦ lipid storage NOS ◦ Niemann-Pick ◦ pseudo-Hurler's or mucopolipidosis III ◦ triglyceride storage, Type I or II ◦ Wolman's or triglyceride storage, Type III • Mucopolipidosis II • Primary familial xanthomatosis	

References

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Obesity

Report Type: Health Conditions

About: Obesity (BMI > 30 kg/m²) affects at least 20% of individuals in Western countries, while 50% of people are classified as overweight (BMI > 25 kg/m²) or obese by the World Health Organization's definition. This condition is characterized by an increase in fat mass that can result in adverse health consequences. Obesity is associated with increased risks for cardiovascular disease, type 2 diabetes and various types of cancer. Risk factors for obesity include low physical activity and consumption of high-energy foods. Research indicates that genetic factors are also associated with the disease.¹

Genetics: Some rare inherited forms of obesity are caused by a mutation in a single gene.¹ However, these monogenic forms of obesity only account for a small fraction of obesity cases. The genetic predisposition for obesity is thought to arise from multiple, common variants in several genes.^{2,3} These common variants are referred to as low risk susceptibility alleles because they each contribute a relatively small amount of risk to developing obesity. Low risk susceptibility alleles for obesity have been successfully identified by screening large numbers of individuals in genome-wide association studies.^{4,5}

The FTO gene was the first gene shown to be associated with common obesity in genome-wide association studies.⁵ This association was quickly replicated in many other studies.^{6,7} How FTO affects obesity is not understood,⁸ but studies in rodents suggest that FTO has a role in regulating food intake. Mice genetically engineered to overexpress FTO show increased food intake, which leads to obesity.⁹ The function of FTO in the central nervous system is also supported by the finding that human children carrying an obesity-associated FTO variant have increased energy intake.¹⁰ Besides its effects in the brain, the FTO protein may also have functions in other tissues where it is also expressed.⁸

Genome-wide association studies have also implicated the MC4R gene in obesity.⁴ The MC4R gene encodes the melanocortin 4 receptor, which is expressed in neurons that modulate food intake. Interestingly, rare mutations in this gene can cause monogenic obesity.

Recommendations: The U.S Preventative Services Task Force recommends screening all adults and children aged 6 years and older for obesity.¹¹

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
MC4R	rs17782313	C	1.12	Caucasian	26.5%	Validated	18454148
FTO	rs9939609	A	1.38	Asian	14.9%	Validated	18379722
FTO	rs9939609	A	1.31	Caucasian	46.0%	Validated	17434869

PCSK1	rs6232	G	1.34	Caucasian	4.4%	Preliminary	18604207
INSIG2	rs7566605	C	1.29	Caucasian	26.5%	Preliminary	17465681

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
278.1 Obesity, unspecified	V77.8 Screening for obesity
Applies to:	
• Obesity NOS	

References

1. Farooqi IS, O'Rahilly S. Monogenic obesity in humans. *Annual review of medicine*. 2005;56:443-58.
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Osteoarthritis

Report Type: Health Conditions

About: Osteoarthritis is the most common form of arthritis and is a major cause of disability in the U.S.¹ This progressive bone disease is characterized by cartilage loss, which can lead to pain and reduced joint function. Risk factors for osteoarthritis include age, obesity, gender and trauma. Research indicates that genetic factors are also associated with the disease.²

Genetics: Some rare forms of early-onset osteoarthritis (OA) are caused by mutations in single genes, but uncovering the genetic basis of the most common form of OA, which appears after age 45, has been more elusive. Variants in three genes that have been shown to increase the risk of developing OA are included on the test: GDF5, DVWA and PTGS2.

The GDF5 gene encodes a member of the transforming growth factor-beta superfamily and is involved in the development and maintenance of bone and cartilage. Mutations in GDF5 are known to cause disorders of skeletal development including chondrodysplasia, synphalangism and type C brachydactyly. In the largest meta-analysis study of OA to date, researchers found an association of a variant in the GDF5 gene with OA of the knee in Caucasian and Asian women.³

The DVWA gene encodes a protein that binds beta-tubulin, which is the building block of the microtubules that serve a structural and kinetic role in the cell. In Asians, a variant in the DVWA gene is associated with susceptibility to OA of the knee.⁴

The PTGS2 gene encodes prostaglandin G/H synthase 2, which is involved in a key step in the synthesis of prostaglandins. Prostaglandins are regulators of important biological processes such as inflammation, cell division, and formation of new blood vessels. In Caucasians, a variant in the PTGS2 gene is associated with OA in the knee.⁵

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
GDF5	rs143383	T	1.55	Asian	77.9%	Preliminary	18299287
GDF5	rs143383	T	1.13	Caucasian	66.7%	Preliminary	19479880
PTGS2	rs4140564	C	1.55	Caucasian	8.0%	Preliminary	18471798
DVWA	rs7639618	G	1.43	Asian	54.2%	Preliminary	19181678

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
715.89 Osteoarthritis involving, or with mention of more than one site, but not specified as generalized, multiple sites	N/A

References

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Parkinson's disease

Report Type: Health Conditions

About: By the year 2030, the prevalence of Parkinson's disease (PD) is projected to double from numbers in 2005 (4.1 to 4.6 million).¹ This neurodegenerative disease is characterized by tremors, akinesia, bradykinesia and balance difficulties.² Risk factors include age and head trauma,³ and research indicates that genetic factors, such as a variant in the LRRK2 gene, are also associated with the disease.²

Genetics: The genetic contribution to PD includes high-risk genetic mutations as well as low-risk susceptibility factors.² Familial PD, which accounts for 15% to 25% of individuals with PD, is caused by rare, high-penetrance mutations (LRRK2, SNCA, parkin, UCHL1, PINK1 and DJ-1). Most PD patients, however, do not have known high-risk mutations, have no family history of the disease and are classified as having sporadic or idiopathic PD. Compared to familial PD, individuals with sporadic PD tend to have a later age of onset but still exhibits similar clinical and pathological features.⁴

The test includes a common variant (rs34778348) in the LRRK2 gene that is associated with sporadic PD in Asians.^{5,6} The LRRK2 (leucine-rich repeat kinase 2) gene, also known as dardarin, encodes a kinase that is found in the brain. High-risk genetic mutations in LRRK2 are pathogenic for familial PD in families of European descent.⁷ In Asians, high risk PD-causing mutations of the LRRK2 gene appear to be extremely rare.

The A allele of rs34778348 in the LRRK2 gene has been found in PD patients in three Asian populations (Han Chinese, Japanese and Malay) but has not yet been found in other ethnic populations. This allele is associated with only a small increase in PD risk. Thus, rs34778348 is considered a low-risk susceptibility marker. Many people who carry the A allele may not develop PD. The A allele leads to an LRRK2 protein that causes cell death only when combined with oxidative stress.⁸ This finding is consistent with the idea that the A allele may result in PD only when additional environmental, lifestyle or other personal risk factors are present.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
LRRK2	rs34778348	A	2.55	Asian	3.0%	Validated	19343804

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: The test does not include high-penetrance pathogenic mutations that cause PD and are inherited in a dominant manner. Most notably, the test does not include pathogenic mutations of the LRRK2 gene, which have been identified in PD families of European descent.⁷

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
332.1 Paralysis agitans	N/A
Applies to:	
• Parkinsonism or Parkinson's disease: ◦ NOS ◦ idiopathic ◦ primary	

References

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Perindopril

(DC:TB-0236.001 06DEC2012)

Report Type: Pharmacogenetics

About: Perindopril is an angiotensin-converting enzyme (ACE) inhibitor that is used to manage or treat hypertension, stable coronary artery disease, myocardial infarction and heart failure.^{1,2} ACE is a zinc metallopeptidase that plays a role in the production of angiotensin II, the primary blood pressure effector in the renin-angiotensin-aldosterone system.³ It also acts in the degradation of bradykinin, a strong vasodilator of the Kinin-Kallikrein cascade.⁴ By preventing the production of angiotensin II and blocking the degradation of bradykinin, ACE inhibitors prevent arteriolar vasoconstriction and promote vasodilation.⁵

Genetics: Two markers located in the angiotensin II receptor type I (AGTR1) gene and one in the bradykinin type I receptor (BDKRB1) gene are associated with perindopril's treatment benefit. The benefit of perindopril in stable coronary artery disease patients is calculated using these three markers to generate a pharmacogenetic score.⁶

In a study that examined the effect of perindopril (8 mg/day) in predominantly Caucasian male patients with stable coronary artery disease, markers in AGTR1 (rs275651 and rs5182) and BDKRB1 (rs12050217) were associated with the treatment benefits of perindopril. Combining these three markers in a pharmacogenetic score demonstrated a stepwise decrease in treatment benefit of perindopril. A pronounced treatment benefit was observed in a subgroup of 73.5% of patients, whereas no benefit was apparent in the remaining 26.5%, with a trend towards a harmful effect.⁶ Prospective studies are yet to be completed to test whether patients with a "non-responder" genetic profile should avoid treatment with ACE inhibitors.⁷

Recommendations: NA

Possible Outcomes: Likely Non-Responder, Likely Responder

Markers or Alleles Tested: AGTR1 [rs275651, rs5182]; BDKRB1 [rs12050217]

Limitations and Warnings: This test can inform perindopril treatment optimization for stable coronary artery disease patients only. The results of this test do not apply to patients that are being treated with perindopril for other indications.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to:	
Unspecified adverse effect of medicinal substance NEC properly administered	

References

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Peripheral arterial disease

Report Type: Health Conditions

About: Peripheral arterial disease (PAD) affects 20% of individuals in the U.S. over the age of 55 and is strongly associated with a risk for myocardial infarction and stroke.¹ This progressive disease is characterized by the accumulation of plaque in the arterial system, especially the abdominal aorta and arteries in the legs.^{1,2} Risk factors for PAD include age, sex, smoking, diabetes, hypertension and hyperlipidemia.¹ Research indicates that genetic factors are also associated with PAD.³

Genetics: Peripheral arterial disease (PAD) is caused by atherosclerosis, a complex disorder involving both genetic risk factors as well as traditional risk factors, such as cigarette smoking, cholesterol levels, hypertension and stress. Within various populations, genetic differences are thought to account for greater than 50% of the risk for atherosclerosis.³ It is estimated that the genetic risk of atherosclerosis involves variants in hundreds of genes with a variety of functions in regulating blood pressure, lipid and cholesterol metabolism, pro-inflammatory processes, cell adhesion and migration.³

The CHRNA3 gene encodes a subunit of the nicotinic acetylcholine receptor, which binds to nicotine.⁴ A large study of PAD in Caucasians from Iceland, New Zealand, Austria, Sweden and Italy⁵ showed that a variant in CHRNA3 increased the risk for PAD by approximately 20%. No significant differences in risk were shown between males and females. The results from this study suggest that this variant may also partly confer a risk for cardiovascular disease indirectly through its relationship with exposure to nicotine as a function of smoking history.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
CHRNA3	rs1051730	T	1.19	Caucasian	38.5%	Validated	18385739

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in

genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
443.9 Peripheral vascular disease, unspecified Applies to: • Intermittent claudication NOS • Peripheral: ◦ angiopathy NOS ◦ vascular disease NOS • Spasm of artery	V81.2 Screening for other and unspecified cardiovascular conditions

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Phenylketonuria

Report Type: Carrier Status

About: Phenylketonuria (PKU) is the most common hereditary disorder of amino acid metabolism. Classical PKU is the most severe form of the disease, and untreated newborns can develop irreversible mental retardation, psychiatric problems and seizures. Symptoms are usually noticed several months after birth. Milder forms of the disease, including non-PKU hyperphenylalaninemia and variant PKU, also present high blood levels of phenylalanine, but they have lower risks for neuropsychiatric disorders. PKU can be successfully diagnosed during newborn screening and treated by restricting phenylalanine intake.^{1,2,3}

Genetics: PKU is caused by mutations in the PAH gene, which encodes an enzyme called phenylalanine hydroxylase that converts phenylalanine to tyrosine. Defects in this protein can lead to the accumulation of phenylalanine, which can cause irreversible brain damage and lead to profound impaired cognitive development.^{1,2,3}

Reported incidence of PKU at birth varies among ethnic groups. Generally, the incidence is 1 in 10,000 for Caucasians and East Asians, and about 1 in 100,000 for people of African descent. Newborn screening can detect most PKU cases. Consequently, most patients are treated immediately upon diagnosis and severe symptoms are prevented.¹

The combined frequency of the 14 mutations in the PAH gene that are included in the test is about 50% in Caucasian PKU patients.⁴ R408W, IVS10-11G>A and Y414C are the most prevalent mutations in the Midwestern region of the U.S.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Screening Recommendations: The American College of Medical Genetics identified phenylketonuria as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test includes 14 mutations in the PAH gene.

PAH [R408W, R158Q, E280K, R243X, F39L, L48S, R261Q, P281L, Y414C, I65T, R408Q, A403V, V245A, IVS10-11G>A]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
PAH	U. S. Caucasian	51%	1 in 62	1 in 124
PAH	Irish	72%	1 in 34	1 in 120
PAH	German	56%	1 in 45	1 in 101
PAH	Danish	43%	1 in 55	1 in 96

PAH	Spanish	41%	1 in 51	1 in 86
PAH	Polish	78%	1 in 45	1 in 201
PAH	Turkish	65%	1 in 34	1 in 96
PAH	Chinese	3%	1 in 53	1 in 55
PAH	Korean	4%	1 in 102	1 in 106
PAH	Japanese	60%	1 in 174	1 in 124

^aPercentage of affected patients carrying mutations detected by this test.^{4,6,7,8,9,10,11}

^bCarrier risk before testing (PMID 20971365, PMID [Mitchell JJ, Scriver CR. Phenylalanine hydroxylase deficiency. GeneReviews web site. <http://www.ncbi.nlm.nih.gov/books/NBK1504/>. Updated May 2010. Accessed June 29,2012.](#) , PMID 12655544, PMID 8445616, PMID 15061917, PMID 15503242, PMID 21307867)

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are many mutations associated with phenylketonuria, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.1 Phenylketonuria PKU Applies to: • Hyperphenylalaninemia	V77.3 Screening for phenylketonuria (PKU)

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Phenytoin hypersensitivity

(DC:TB-0221.001 06DEC2012)

Report Type: Pharmacogenetics

About: Phenytoin is used to treat epilepsy, accounting for approximately 52% of all prescriptions for antiepileptic drugs.¹ It acts by blocking voltage-sensitive sodium channels in neurons.² Monitoring phenytoin levels is often necessary due to the drug's narrow therapeutic range and large individual variability in clearance.¹ Use of phenytoin can lead to cutaneous adverse reactions that vary from mild maculopapular eruption with increasing severity to hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS and TEN are rare but life-threatening.³

Genetics: The HLA-B*1502 allele of the HLA-B gene has been shown to be associated with phenytoin-induced cutaneous adverse reactions in Asians. The association between HLA-B*1502 and phenytoin-induced SJS/TEN has been found in both Thai and Chinese populations.^{4,5,6} The HLA-B gene encodes a human leukocyte antigen protein that is involved in immune response. The HLA-B*1502 allele has also been shown to be associated with increased risk of SJS/TEN for antiepileptic drugs that are related to phenytoin, such as carbamazepine and oxcarbazepine.^{4,5,6,7}

Recommendations: FDA advises that alternative therapies should be considered for HLA-B*1502-positive patients, who are at an increased risk of phenytoin-induced adverse reactions.⁸

Possible Outcomes: Hypersensitive, Typical, Unknown

Markers or Alleles Tested: HLA-B [HLA-B*1502]

This test includes rs3909184 and rs2844682, which together tag the HLA-B*1502 allele in Han Chinese.⁹ Patients with one or two HLA-B*1502 alleles are assigned a "Hypersensitive" result. Patients with no HLA-B*1502 alleles are assigned a "Typical" result.

For patients with a particular genotype (rs3909184 (G/C), rs2844682 (C/T)), the HLA-B*1502 status cannot be determined, and thus these patients are assigned an "Unknown" result. These patients may require further evaluation.

Ethnic Distribution of Tested Alleles: The HLA-B*1502 allele is more prevalent in individuals of Asian ancestry.¹⁰ The HLA-B*1502 allele has been observed in about 10% to 15% of patients in parts of China, Thailand, Malaysia, Indonesia, the Philippines and Taiwan. The frequency of this allele in South Asian individuals, such as Indians, is about 2% to 4%, but the frequency may be higher in some groups. The frequency of HLA-B*1502 is much lower (less than 1%) in Japan and Korea.¹¹ The HLA-B*1502 allele is also less frequently found (less than 1%) in those of African, European, Hispanic or Native American descent.¹⁰

Limitations and Warnings: The markers tested for HLA-B*1502 are most applicable to patients of Han Chinese descent.⁹ If clinically indicated, patients of other Asian ethnicities could be advised to undergo HLA sequencing to assess their risk of

phenytoin hypersensitivity. There are insufficient data to associate HLA-B*1502 with phenytoin hypersensitivity in other non-Asian ethnicities. Many HLA-B*1502-positive Asian patients treated with phenytoin will not develop SJS/TEN. Conversely, these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. Therefore, healthcare professionals are advised to watch for symptoms in all patients.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
E936.1 Hydantoin derivatives causing adverse effects in therapeutic use	N/A
Applies to:	
• Phenytoin	

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Phenytoin metabolism

(DC:TB-0222.001 06DEC2012)

Report Type: Pharmacogenetics

About: Phenytoin is used to treat epilepsy, accounting for approximately 52% of all prescriptions for antiepileptic drugs.¹ Monitoring phenytoin levels is often necessary due to the drug's narrow therapeutic range and large individual variability in clearance.¹ Phenytoin acts by blocking voltage-sensitive sodium channels in neurons² and is primarily metabolized to hydroxyphenytoin (p-HPPH)³ by the CYP2C9 enzyme, which accounts for up to 90% of the drug's metabolism.⁴ p-HPPH has no anticonvulsant properties but is associated with some side effects, such as gingival hyperplasia, somnolence, dry mouth and fatigue.⁵

Genetics: The most common reduced function CYP2C9 variants are the CYP2C9*2 and CYP2C9*3 alleles. *In vitro* studies have shown that CYP2C9*2 and CYP2C9*3 are associated with approximately 29% and 95% reductions in phenytoin clearance, respectively, as compared to the wild-type allele, CYP2C9*1.² The CYP2C9*6 allele is a rare loss-of-function variant found in African populations.^{6,7} Different combinations of CYP2C9 alleles give rise to different levels of CYP2C9 enzyme activity. For example, individuals with two wild-type alleles (e.g., CYP2C9*1/ CYP2C9*1) are extensive metabolizers. Individuals with one wild-type and one reduced function allele (e.g., CYP2C9*1/ CYP2C9*2) are intermediate metabolizers. Individuals with two reduced function alleles (e.g., CYP2C9*2/ CYP2C9*2 or CYP2C9*2/ CYP2C9*3) are poor metabolizers. These genetically determined differences in phenytoin metabolism can lead to toxicity and variable efficacy.^{8,9}

CYP2C9 intermediate and poor metabolizers have increased plasma concentrations of phenytoin^{10,11,12,13,14} and increased risk of phenytoin-induced neurological toxicity.^{4,8,15,16,17,18,19} Symptoms of neurological toxicity may include dizziness, nystagmus (lateral and vertical), ataxia, slurred speech, lethargy and mental confusion.⁸

Recommendations: The Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy recommends a 25% dose decrease of phenytoin for CYP2C9*1/CYP2C9*2 and CYP2C9*1/CYP2C9*3 individuals and a 50% dose decrease of phenytoin for CYP2C9*2/CYP2C9*2, CYP2C9*3/CYP2C9*3 and CYP2C9*2/ CYP2C9*3 individuals.²⁰ The German AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) strongly recommends therapeutic drug monitoring (TDM) of plasma phenytoin in all patients, regardless of CYP2C9 genotype, in their Consensus Guidelines for Therapeutic Drug Monitoring.²¹ According to the Guidelines, the therapeutic reference range for phenytoin is 10 to 20 µg/ml and the alert level is 25 µg/ml, indicating a narrow therapeutic range.²¹

CYP2C9 metabolizer status may affect response to other drugs, such as warfarin, tolbutamide, glipizide, celecoxib and fluvastatin.^{22,23}

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2C9 [CYP2C9*2, CYP2C9*3, CYP2C9*6]

Ethnic Distribution of Alleles:²⁴

Gene	Allele	African	Caucasian	Japanese	Chinese
CYP2C9	*1	80.6	77.9	96.5	95.8
CYP2C9	*2	1.2	15.9	0	0.1
CYP2C9	*3	0	5.7	3.4	4.1
CYP2C9	*6	1.2	0	0	0

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to:	
Unspecified adverse effect of medicinal substance NEC properly administered	

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Polycystic kidney disease

Report Type: Carrier Status

About: Autosomal recessive polycystic kidney disease (ARPKD) leads to the development of enlarged and multi-cystic kidneys in the fetus or in infants. Most individuals with ARPKD are identified before birth or during the neonatal period.¹ The cysts can be detected in fetuses or infants by ultrasound imaging. Cysts can also be found in liver, spleen and other organs. A major complication of the kidney disease before birth is a lack of amniotic fluid, which leads to underdeveloped lungs. A malfunctioning respiratory system is the major cause of death in about a third of ARPKD newborns.² More than half of the ARPKD patients who survive infancy die from end-stage renal disease, usually before 10 years of age. Because of improved treatment and kidney transplantation, many patients can now survive to the second decade.³ ARPKD is less common than the autosomal dominant form of polycystic kidney disease.⁴

Genetics: Autosomal recessive polycystic kidney disease (ARPKD) is caused by mutations in the PKHD1 gene, which encodes the protein fibrocystin, also known as polyductin.^{5,6} This protein is found on the surface of cells that line the cavities in many parts of the body, but its function is not well understood.

The test includes the most frequently recurrent mutations in the United States and Europe. Among these mutations, T36M is the most common, followed by L1966fs and R496X.^{2,7} The P805L mutation has been detected in patients who also had the I3177T mutation, though it is not certain if P805L by itself is disease-causing.⁸ The test does not currently include the recurrent mutation L1966fs.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes eleven mutations in the PKHD1 gene.

PKHD1 [R496X, I3177T, R3482C, V3471G, T36M, Q3392X, I2944fs, D3230fs, I222V, P805L, I2957T]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
PKHD1	Caucasians	35%	1 in 145	1 in 224

^aAllele frequency of tested mutations in polycystic kidney disease patients. ⁷ ^bCarrier risk before testing (in the general population). ⁹ ^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with polycystic kidney disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
753.14 Polycystic kidney, autosomal recessive	V82.71 Screening for genetic disease carrier status

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Pompe disease

Report Type: Carrier Status

About: Pompe disease is a type of glycogen storage disease. Typical symptoms including muscle weakness, low muscle tone, feeding difficulties, labored breathing, coughing, and slowed growth rate. In severe cases, accumulated glycogen in heart muscle cells causes enlargement of the heart.^{1,2}

Pompe disease is classified into two general subtypes according to the age when the symptoms appear. Infantile-onset Pompe disease typically has a poor outcome. Symptoms may be detected during pregnancy, but are more commonly noticed within the first year of life. Although symptoms worsen at variable rates in infantile-onset cases, untreated patients usually die early in childhood. In contrast, late-onset cases usually have milder symptoms, and people with this form of Pompe disease generally do not develop heart problems.^{2,3}

Genetics: Pompe disease is caused by mutations in the GAA gene, which encodes acid alpha-glucosidase, also known as acid maltase. This enzyme is critical for efficient breakdown of glycogen into glucose, and defects in the protein lead to the accumulation of glycogen inside the cell. Muscles are most prominently affected in Pompe disease patients.^{1,2}

Pompe disease is classified into two general subtypes according to the age when the symptoms appear. Individuals with infantile-onset Pompe disease typically have a poor outcome with symptoms sometimes detectable in utero, but more commonly noticed within the first year of life. Untreated patients usually die early in childhood. In contrast, individuals with late-onset disease usually have milder symptoms and people with this form of Pompe disease generally do not develop heart problems.¹

The D645E mutation is found in approximately 40% to 80% individuals of Chinese descent suffering from infantile-onset Pompe disease.^{1,2}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes three mutations in the GAA gene.

GAA [D645E, 2741AG>CAGG, G309R]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
GAA	Taiwanese, Chinese	80%	1 in 185	1 in 921

GAA	Dutch	6%	1 in 185	1 in 196

^a Allele frequency of tested mutations in Pompe disease patients test.^{4,5} ^b Carrier risk before testing (in the general population).⁶ ^c Carrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with Pompe disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
271.1 Glycogenesis Applies to: • Amylopectinosis • Glucose-6-phosphatase deficiency • Glycogen storage disease • McArdle's disease • Pompe's disease • von Gierke's disease	V82.71 Screening for genetic disease carrier status

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Prekallikrein deficiency

Report Type: Carrier Status

About: Prekallikrein deficiency is a clotting disorder that causes mild to severe bleeding symptoms. The deficiency causes a prolonged partial thromboplastin time (PTT), but patients have normal prothrombin and thrombin times. The condition is not associated with a bleeding tendency, and the long PTT can be fully corrected by the addition of normal plasma or serum.^{1,2} In some cases, patients can present with routine nose bleeds in childhood and later show severe hematomas and recurrent mucosal bleeding episodes. These symptoms can often be confused with other hemophilia-like disorders.³

Genetics: Prekallikrein deficiency is caused by mutations in the KLKB1 gene, which encodes plasma prekallikrein (or Fletcher factor). This protein acts in the blood coagulation pathway and is normally converted to kallikrein, which plays a key role in producing bradykinin, an important molecule in controlling blood pressure. Therefore, the kinin-kallikrein pathway has essential roles in both the cardiovascular system and regulation of blood clotting activity. When prekallikrein is dysfunctional, both of these pathways are affected.^{4,5,6}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes two mutations in KLKB1 gene.

KLKB1 [W383X, C529Y]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with prekallikrein deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
286.9 Other and unspecified coagulation defects	V82.71 Screening for genetic disease carrier status
Applies to: Defective coagulation NOS	

• Deficiency, coagulation factor NOS • Delay, coagulation • Disorder: ◦ coagulation ◦ hemostasis	

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Propionic acidemia

Report Type: Carrier Status

About: Propionic acidemia is an inherited disease that causes brain damage in infants and young children due to a defect in protein and fat metabolism. Symptoms may include poor appetite, nausea, vomiting, extreme sleepiness, irritability, low muscle tone and muscle weakness. If not treated, breathing problems, seizures, swelling of the brain, stroke, coma and sometimes even death can occur. With prompt and lifelong treatment, children with propionic academia can often live normal lives. A small number of people with propionic acidemia never show symptoms.¹

Genetics: Propionic acidemia is caused by mutations in the PCCA or the PCCB genes, which encode the alpha and beta protein subunits, respectively, of propionyl-CoA carboxylase. This enzyme is necessary for breaking down certain amino acids (valine, isoleucine, methionine, threonine) and fats (odd-chain fatty acids, cholesterol).^{2,3} Defects in the protein lead to toxic levels of propionic acid; by-products accumulate in body fluids and can cause brain damage.

The incidence of propionic acidemia is very low worldwide (about 1 in 50,000) but highly variable: 1 in 1,000 in the Inuit people of Greenland. The incidence of propionic acidemia is 1 in 27,264 in Saudi Arabia, and 1 in 250,000 in Germany.⁴

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified propionic acidemia as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test involves one mutation in the PCCA gene and three mutations in PCCB gene.

PCCA [R3999Q]; PCCB [R410W, T428I, 1218del14ins12, 1172_1173insT]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
PCCA, PCCB	Japanese	35%	1 in 160	1 in 246
PCCB	Spanish	50%	1 in 160	1 in 320
PCCB	U. S.	10%	1 in 160	1 in 178

^aAllele frequency of tested mutations in propionic acidemia deficiency patients;^{1,3,6,7} ^bCarrier risk before testing (in the general population). ^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with propionic academia, it is possible to carry a variant that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.9 Unspecified disorder of amino-acid metabolism	V82.71 Screening for genetic disease carrier status

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Prostate cancer

Report Type: Health Conditions

About: Prostate cancer is the most commonly diagnosed form of cancer in men of developed countries.¹ Most prostate cancer is found as a function of an elevated prostate-specific antigen (PSA) blood test. Symptoms of late stage prostate cancer include difficulty urinating, pain during ejaculation and lower back pain.² Risk factors for prostate cancer include diet and obesity,³ and research indicates that genetic factors are also associated with the disease.

Genetics: The genetic test includes more than 15 low risk susceptibility markers associated with a genetic risk for developing prostate cancer. The underlying mechanism for many of the markers in contributing to prostate cancer risk is not understood, but the data for the associations are highly reproducible. A few of these markers are highlighted below.

The 8q24 locus can be divided into three regions, each of which independently affects the risk of prostate cancer.^{4,5} There are no known genes in 8q24 regions 1-3, and it is not understood how variation in these regions is associated with cancer. In prostate cancer tumors, DNA sequences in 8q24 are often amplified and the extent of amplification is correlated with progression of the disease, suggesting that the 8q24 locus plays a role in prostate cancer progression.^{6,7} In populations of white/European ancestry, association with prostate cancer for all three 8q24 regions has been well-validated in multiple studies. Variants at 8q24 are also associated with colorectal and breast cancer.

Both the HNF1B and JAZF1 genes have alleles that are associated with an increased risk for prostate cancer.^{8,9} Interestingly, these genes have also been implicated in risk for diabetes.^{8,9} The risk of prostate cancer has been shown to decrease in men with type 2 diabetes.^{9,10} The roles of the HNF1B and JAZF1 genes in prostate cancer remain to be elucidated, and the link between prostate cancer and diabetes is the subject of ongoing research.

Expression of the MSMB gene, which encodes beta-microseminoprotein and is also known as PSP94, decreases as prostate cells become cancerous.^{11,12} The T allele of rs10993994 in the MSMB gene, which results in a greater than 80% decrease in MSMB gene expression in an in vitro assay of prostate cells,¹³ has been associated with prostate cancer in over eight studies.^{14,15} Two studies also report a strong association with higher PSA (prostate-specific antigen) levels.^{13,16}

While most of the low-risk markers were identified from Caucasian populations, one study suggests that their presence in other ethnic populations is likely to be associated with a similar risk or protection.¹⁷ However, some data suggest that there may be some markers that are specific for risk in African-Americans.¹⁸

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
intergenic_8q24, region 1	rs10090154	T	1.98	Hispanic	7.0%	Validated	17401364
JAZF1	rs10486567	C	1.12	Caucasian	75.2%	Validated	19188186
MSMB	rs10993994	T	1.23	Caucasian	34.1%	Validated	19153072
Intergenic_8q24, region 1	rs1447295	A	1.28	Asian	11.9%	Validated	18726982
Intergenic_8q24, region 1	rs1447295	A	1.43	Caucasian	7.1%	Validated	17401363
DAB21P	rs1571801	T	1.15	Caucasian	29.3%	Validated	19188186
Intergenic_17q24	rs1859962	G	1.17	Caucasian	47.3%	Validated	18199855
Intergenic_3p12	rs2660753	T	1.32	Caucasian	10.2%	Validated	19188186
NUDT11	rs5945572	A	1.23	Caucasian	38.1%	Validated	18264098
LMTK2	rs6465657	C	1.19	Caucasian	50.9%	Validated	18264097
Intergenic_8q24, region 3	rs6983267	G	1.43	African	81.1%	Validated	17401364
Intergenic_8q24, region 3	rs6983267	G	1.21	Caucasian	48.7%	Validated	18264096
intergenic_8q24, region 2	rs6983561	C	1.31	African	45.7%	Validated	19549807
intergenic_8q24, region 2	rs6983561	C	1.78	Asian	28.9%	Validated	17401364
Intergenic_8q24, region 2	rs6983561	C	1.78	Caucasian	2.5%	Validated	18483343
intergenic_8q24, region 2	rs6983561	C	1.99	Hispanic	3.0%	Validated	17401364
EHBP1	rs721048	A	1.15	Caucasian	13.7%	Validated	18264098
HNF1B	rs7501939	C	1.19	Caucasian	56.6%	Validated	17603485
Intergenic_11q13	rs7931342	T	0.90	Caucasian	46.9%	Validated	18264097
SLC22A3	rs9364554	T	1.20	Caucasian	27.4%	Validated	18708398
CLPTM1L	rs401681	C	1.07	Caucasian	56.6%	Preliminary	19151717
CTBP2	rs4962416	C	1.20	Caucasian	25.7%	Preliminary	18264096
TNRC6B	rs9623117	C	1.11	Caucasian	22.1%	Preliminary	19117981

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
222.2 Benign neoplasm of prostate	V76.44 Screening for malignant neoplasms of prostate

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Prothrombin deficiency

Report Type: Carrier Status

About: Prothrombin deficiency, also known as factor II deficiency, is a rare disorder that causes increased bleeding tendency. Symptoms range from severe to mild bleeding. Hypoprothrombinemia (type I) is associated with severe bleeding, while dysprothrombinemia (type II) is associated with variable bleeding tendency.¹ Severe symptoms include hemarthrosis or hematoma. Mild symptoms include nose bleeds and prolonged oozing after medical procedures.² Nongenetic risk factors for prothrombin deficiency include severe liver disease and low levels of vitamin K.¹

Genetics: Prothrombin deficiency is caused by mutations in the F2 gene, which encodes prothrombin, also known as coagulation factor II. This protein is an essential component of the coagulation process,^{3,4,5} and mutations that decrease prothrombin production or reduce its activity cause prothrombin deficiency.

The test includes several recurrent mutations identified in patients with prothrombin deficiency. Mutation R457Q, also called Puerto Rico 1, is associated with the disease in the Puerto Rican population.⁶

Prothrombin deficiency has been identified in patients with diverse ethnic origins. The disease prevalence is 1 in 2,000,000 in the general population.⁵ Higher frequencies of the disease have been detected in Puerto Rico.⁶ The disease prevalence is 1 in 1,000 in Iranian and Italian populations.² Prothrombin deficiency is often associated with parental consanguinity (parents with common ancestors).^{2,7}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes eight mutations in the F2 gene.

F2 [E352K, D161Y, R263C, C181Y, R457Q, R538C, R2W, R314C]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
F2	Iranian, Italian	54%	1 in 1,000	1 in 2,166

^aAllele frequency of tested mutations in prothrombin deficiency patients.² ^bCarrier risk before testing (in the general population). ^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with prothrombin deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
286.3 Congenital deficiency of other clotting factors Applies to: • Congenital afibrinogenemia • Deficiency: ◦ AC globulin ◦ factor: ▪ I [fibrinogen] ▪ II [prothrombin] ▪ V [labile] ▪ VII [stable] ▪ X [Stuart-Prower] ▪ XII [Hageman] ▪ XIII [fibrin stabilizing] ◦ Laki-Lorand factor ◦ proaccelerin • Disease: ◦ Owren's ◦ Stuart-Prower • Dysfibrinogenemia (congenital) • Dysprothrombinemia (constitutional) • Hypoproconvertinemia • Hypoprothrombinemia (hereditary) • Parahemophilia	V82.71 Screening for genetic disease carrier status

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Proton pump inhibitors

(DC:TB-0219.001 06DEC2012)

Report Type: Pharmacogenetics

About: Proton pump inhibitors (PPIs), such as omeprazole, esomeprazole (S-isomer of omeprazole), lansoprazole, rabeprazole and pantoprazole, are potent gastric acid inhibitors that are used to treat gastroesophageal reflux disease, duodenal and gastric ulcers, erosive esophagitis, and pathological hypersecretory conditions, such as Zollinger-Ellison syndrome.¹ PPIs are converted to sulfenamides by the acidic environment of the stomach. The sulfenamide is the active form of the drug and inhibits gastric acid secretion by forming a disulfide bond with the gastric acid pump H⁺ K⁺-ATPase enzyme.² PPIs, with the exception of rabeprazole, are primarily metabolized by the CYP2C19 enzyme in the liver prior to elimination from the body.²

Genetics: The CYP2C19 genotype is the most important genetic determinant for PPI treatment.¹ Individuals can be classified based on their CYP2C19 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).³

CYP2C19 PMs and IMs have lower clearance rates and higher plasma concentrations of PPIs than CYP2C19 EMs. Therefore, they are likely to benefit more from the PPI treatment and may experience stronger suppression of gastric acid secretion, an improved eradication rate of *Helicobacter pylori* infection, and improved cure rates of gastroesophageal reflux disease, esophagitis or ulcers.^{1,2,4} PPIs are very safe drugs, even in CYP2C19 PMs, who are expected to have elevated plasma concentrations of PPIs.^{1,4} In CYP2C19 EMs, the clearance of omeprazole, lansoprazole and pantoprazole is significantly increased, resulting in lower plasma concentrations, compared to PMs.¹ Thus, EMs may experience insufficient suppression of gastric acid secretion and a decreased therapeutic effect in some cases.^{1,2,4} CYP2C19 UMs have decreased drug exposure and are at increased risk of therapeutic failure.^{5,6}

For *H. pylori* eradication, PPIs are typically used in dual and triple therapies together with the antibiotics amoxicillin and/or clarithromycin;^{1,7,8} the PPIs make the antibiotics more stable by reducing intragastric acidity.² Genetic testing for CYP2C19 has been shown to predict efficacy of *H. pylori* eradication treatment. For example, one study reported that the cure rates for *H. pylori* infection were 29%, 60% and 100%, respectively, for CYP2C19 EM, IM and PM individuals.⁹ However, the success of eradication depends on additional critical factors, including patient compliance, the choice of PPI regimen, type of therapy (i.e., dual or triple) and antibiotic resistance of *H. pylori*.¹ Thus, the choice of PPI and regimen is considered to be the most practical approach for *H. pylori* eradication.¹

Recommendations: The Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy recommends dose increases for CYP2C19 UM individuals using omeprazole, esomeprazole, lansoprazole or pantoprazole for *H. pylori* eradication treatment.¹⁰

The FDA-approved label for Plavix warns against concurrent use of omeprazole or esomeprazole with clopidogrel because omeprazole can inhibit CYP2C19 activity and reduce the effectiveness of clopidogrel.¹¹ Thus, patients who are at risk for heart attack or stroke will not receive the full anti-clotting effect of clopidogrel if they are also using omeprazole.¹²

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers or Alleles Tested: CYP2C19 [CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*8, CYP2C19*17]

Ethnic Distribution of Tested Alleles

The CYP2C19 panel detects alleles that have a combined frequency of over 99% in major ethnic groups.³

CYP2C19	Allele	Caucasian	African	East Asian	Middle Eastern	Enzyme activity
Wild-type	*1	63%	68%	60%	87%	Normal
rs4244285	*2	15%	15%	29%	12%	None
rs4986893	*3	0.42%	0.52%	8.9%	1.1%	None
rs28399504	*4	0.25%	0.093%	0.049%	ND ^a	None
rs56337013	*5	0.0073%	ND	0.062%	ND	Reduced
rs72552267	*6	0.017%	0%	0%	ND	None
rs41291556	*8	0.35%	0%	0%	ND	Reduced
rs12248560	*17	21%	16%	2.7%	ND	Increased

Limitations and Warnings: Many rare CYP2C19 variants have been identified, but are not part of this test. It is possible, but unlikely, that the patient may have a variant that is not included in this test.

Other critical factors that may influence the therapeutic effect of PPIs include the following: patient compliance, choice of PPI regimen, type of therapy (i.e., dual, triple) and antibiotic used, age, sex, nutritional status, liver and kidney function, concomitant diseases and medications, pharmacogenetics of CYP3A4, and IL-1 beta polymorphisms.^{1,13,14,15,16,17}

Though the CYP2C19 genotype is associated with therapeutic efficacy for omeprazole, lansoprazole and pantoprazole, it is considered to have little or no effect on the therapeutic efficacy of rabeprazole, which is mainly metabolized by a nonenzymatic reduction.^{1,18}

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to:	
Unspecified adverse effect of medicinal substance NEC properly administered	

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Psoriasis

Report Type: Health Conditions

About: Psoriasis is a common skin disease that is characterized by itchy, scaly skin and is caused by a defect in the immune system.¹ Risk factors for psoriasis include smoking, alcohol consumption, family history, diet, BMI, infections and stress.² Research indicates that genetic factors are also associated with the disease.³

Genetics: Psoriasis has long been known to have a heritable component, with the siblings of an individual with psoriasis having a significantly greater likelihood of also developing the condition compared to unrelated individuals. For example, a study in Australia looked at psoriasis in almost 4,000 twins.⁴ They found that if one twin had psoriasis, the probability that the second twin also had the condition was 35% if they were identical, but only 12% if they were fraternal twins.

As with other autoimmune conditions, the genes in the HLA (human leukocyte antigen) region of chromosome 6 strongly influence susceptibility to psoriasis. Variants in other genes related to the immune system have also been implicated in the risk of developing the disorder.

One of the largest studies looking at HLA and psoriasis identified an association between variants in the HLA region of Chromosome 6 and susceptibility to psoriasis. HLA was also found to play a role in susceptibility to psoriatic arthritis, a subtype of psoriasis.³ The study also revealed associations between psoriasis and genes involved in the body's immune response, namely interleukin genes IL12B and IL23R. A study by a consortium of academic groups in the US and Germany that specifically looked at interleukin genes confirmed the association with psoriasis.⁵ This report also examined whether the interleukin genes were interacting with genes in the HLA region but found no evidence of such an interaction, suggesting that the HLA and the interleukin genes act as independent risk factors for psoriasis.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
HLA	rs10484554	T	2.80	Caucasian	13.4%	Validated	18369459
IL23R	rs11209026	G	1.40	Caucasian	95.9%	Validated	18219280
TNIP1	rs17728338	A	1.59	Caucasian	8.0%	Validated	19169254
STAT2	rs2066808	A	1.34	Caucasian	92.9%	Validated	19169254
IL12B	rs3212227	A	1.62	Caucasian	81.0%	Validated	18219280
TNFAIP3	rs610604	G	1.19	Caucasian	42.5%	Validated	19169254

Intergenic_1q21	rs4112788	C	1.41	Caucasian	59.7%	Preliminary	19169253
SPATA2	rs495337	C	1.25	Caucasian	57.0%	Preliminary	18364390

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
696.1 Other psoriasis Applies to: • Acrodermatitis continua • Dermatitis repens • Psoriasis: ◦ NOS ◦ any type, except arthropathic	N/A

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Rh-null syndrome

Report Type: Carrier Status

About: Rh-null syndrome is characterized by red blood cells (RBCs) lacking Rh factor, leading to a distinctive morphology pattern that includes cell swelling. This condition has been described in a few cases where abnormal RBCs have been characterized from people, typically when receiving or donating blood. Clinically, Rh-null syndrome can result in mild anemia.¹

Genetics: Rh-null syndrome is caused by mutations in the RHAG gene, which encodes a protein that is critical for the proper assembly of Rh proteins in RBCs and is required for cell surface expression of Rh antigens.² In normal red blood cells, the RHAG protein functions as an exchange system for ammonia and carbon dioxide gases in the membrane. Defects in the RHAG gene can result in a complete lack of Rh proteins and lead to altered RBC structure and function.^{1,3,4} Rh-null syndrome caused by RHAG defects is extremely rare and is often found in consanguineous families.¹

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: NA

Mutations Tested: The test includes one mutation in the RHAG gene.

RHAG [V270I]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with Rh-null syndrome, it is possible to carry a mutation that is not on the test.

References

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Rheumatoid arthritis

Report Type: Health Conditions

About: Rheumatoid arthritis (RA) affects approximately 1% of the general population in the U.S.¹ Symptoms of this autoimmune disease include joint pain, stiffness and swelling.² Risk factors for RA include diet, smoking and age, among others.³ Research indicates that genetic factors are also associated with the disease.^{4,5}

Genetics: RA is known to have a heritable component. As with other auto-immune conditions, the genes in the HLA (human leukocyte antigen) region of chromosome 6, strongly influence susceptibility to rheumatoid arthritis. The HLA Class II region contains genes that are part of the major histocompatibility complex. HLA Class II molecules are strongly associated with development of RA in all ethnic groups and account for 30% to 50% of the overall genetic risk in RA.⁶

Other genes shown to be associated with RA are also involved in the immune response. Among these, the CTLA4 (Cytotoxic T-Lymphocyte Antigen 4) gene encodes a protein that plays a key regulatory role in the immune system, particularly in T-cells. A variant in the rs3087243 marker is associated with decreased production of soluble CTLA-4.^{4,5} Abatacept is a drug used to treat RA that mimics the function of CTLA-4 by binding and inhibiting receptors on T-cells.⁷ The CTLA-4 variant and RA is rare in African populations.⁸

The CD40 and TRAF1 genes encode proteins that act together to inhibit T-cells through intracellular signaling pathways. CD40 is also involved in the development of “memory” in B-cells and is found in the synovial fluid of RA patients. A variant of the rs4810485 marker is associated with a change in the efficiency of CD40 protein production.⁴ A variant of the rs3761847 marker may impact TRAF1 protein levels.⁹

The FCRL3 gene encodes an immune receptor that has activating and inhibitory functions. Mutations in this gene are associated with RA, systemic lupus erythematosus and autoimmune thyroid disease. A variant in the rs7528684 marker may regulate FCRL3 protein levels in Asians. Evidence of a similar association has been found for some Caucasian subgroups.¹⁰

The CD244 gene encodes a receptor found on T-cells that regulates their cell-killing function. A variant in the rs3766379 marker is associated with RA in Asians.¹¹ The marker is located in a non-coding region of the gene, and the effect of the variant on protein function is unknown.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h

PADI4	rs2240340	A	1.31	Asian	41.1%	Validated	18087673
PTPN22	rs2476601	A	1.53	Caucasian	11.7%	Validated	17982455
CTLA4	rs3087243	G	1.22	Asian	80.4%	Validated	19404967
CTLA4	rs3087243	G	1.11	Caucasian	54.0%	Validated	18794853
TRAF1	rs3761847	G	1.32	Caucasian	47.8%	Validated	17804836
CD244	rs3766379	T	1.31	Asian	48.2%	Validated	18794858
MMEL1	rs3890745	T	1.12	Caucasian	66.8%	Validated	18794853
CD40	rs4810485	G	1.15	Caucasian	75.2%	Validated	18794853
HLA	rs6457617	T	2.36	Caucasian	52.2%	Validated	17554300
Intergenic_4q27	rs6822844	G	1.28	Caucasian	85.4%	Validated	19404967
Intergenic_6q23	rs6920220	A	1.24	Caucasian	16.5%	Validated	18794853
STAT4	rs7574865	T	1.27	Asian	35.2%	Validated	19404967
STAT4	rs7574865	T	1.24	Caucasian	23.4%	Validated	19404967
IL1B	rs16944	G	1.10	Caucasian	64.2%	Preliminary	18838388
FCRL3	rs7528684	G	1.16	Asian	40.5%	Preliminary	18087673

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

714.1 Rheumatoid arthritis	V82.1 Screening for rheumatoid arthritis
Applies to:	
- Arthritis or polyarthritis: - atrophic - rheumatic (chronic)	

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Rickets, pseudovitamin D-deficiency

Report Type: Carrier Status

About: Pseudovitamin D-deficiency rickets, also known as vitamin D-dependent rickets type I, is a rare inherited disorder characterized by muscle weakness, failure to thrive and early onset of rickets with hypocalcemia. Patients have normal concentrations of 25(OH)D but very low amounts of 1,25(OH)2D. The disease can be treated with physiological doses of 1,25(OH)2D or 1-alpha(OH)D.¹

Genetics: Pseudovitamin D-deficiency rickets, also known as vitamin D-dependent rickets type I, is caused by mutations in the CYP27B1 gene, which encodes an enzyme that converts 25-hydroxyvitamin D3 (25(OH)D) into bioactive vitamin D3, 1,25-dihydroxyvitamin D (1,25(OH)2D) in the kidney.² This bioactive metabolite plays a key role in the absorption of calcium and phosphorus from food in the intestine and the reabsorption of calcium in the kidneys to maintain normal bone growth.³

Pseudovitamin D-deficiency rickets is common in French Canadians with a carrier rate of 1 in 26 in the Charlevoix-Seguenay-Lac Saint Jean area in Quebec.⁴ The incidence of the disease in Denmark is 0.4 per 100,000.⁵ The test includes three recurrent mutations that cause pseudovitamin D-deficiency rickets. The 958delG mutation was found in 12 French Canadian individuals and genetic analysis showed that these patients were descended from a single founder.^{1,2,6} The 3398-3406insCCCACCC mutation was found in 13 patients from different ethnic groups including Koreans, Filipinos, Chinese, Polish, African Americans, Caucasian Americans and Hispanic Americans.^{1,2,6,7} The IVS3+1G>A mutation was found in five Koreans.^{1,8}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes four mutations in the CYP27B1 gene.

CYP27B1 [958delG, 3398dupCCCACCC, R389H, IVS3+1G>A]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with pseudovitamin D-deficiency rickets, it is possible to carry a mutation that is not on our test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
275.3 Disorders of phosphorus metabolism Applies to: • Familial hypophosphatemia • Hypophosphatasia • Vitamin D-resistant: ◦ osteomalacia ◦ rickets	V82.71 Screening for genetic disease carrier status

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Sandhoff disease

Report Type: Carrier Status

About: Sandhoff disease is an inherited disorder that is characterized by a gradual deterioration of the central nervous system. There are three clinical forms of the disease: infantile, juvenile and adult. The infantile form is the most severe with disease onset occurring during the first 5 to 6 months of life. Manifestations include developmental delay, seizures, amaurosis and appearance of cherry-red spots on the retina. A child in terminal stages of Sandhoff disease regresses to an unresponsive, vegetative state, and death, usually caused by respiratory infections, occurs by 3 to 4 years of age^{1,2,3}. The juvenile and the adult forms have milder clinical symptoms, such as progressive muscular atrophy, ataxia and mental illness^{1,2}.

Genetics: Sandhoff disease is caused by mutations in the HEXB gene, which encodes the beta subunit of beta-hexosaminidase. This protein is a lysosomal enzyme that is involved in the degradation of GM2-gangliosides in the brain and other organs of the body.⁴ Loss of the beta-hexosaminidase function leads to the accumulation of GM2-gangliosides in the lysosomes of nerve cells, which leads to the eventual death of these cells.

Sandhoff disease can be described as a severe form of Tay-Sachs disease, except that, in Tay-Sachs, the genetic defect is in the alpha subunit of the beta-hexosaminidase encoded by the HEXA gene. Unlike Tay-Sachs disease, which is highly prevalent among Ashkenazi Jews, Sandhoff disease is not limited to any ethnic group (PGID 113). However, a high incidence of Sandhoff disease is found in some geographically isolated populations in northern Saskatchewan (Metis Indians), in the Argentinean province of La Roija⁵ and in the Maronite community in Cyprus.⁶ In the U. S., the carrier rate of Sandhoff disease has been estimated to be 1 in 278 in the non-Jewish population and to be 1 in 500 in the Jewish population.⁷

The IVS2+1G>A mutation is the most frequent mutation identified in Argentinean families,⁸ and the 76delA mutation is a highly recurrent mutation found among carriers of Sandhoff disease in the Christian Maronite community on Cyprus.⁶

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes three mutations in the HEXB gene.

HEXB [S62L, 76delA, IVS2+1G>A]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with Sandhoff disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
330.1 Cerebral lipidoses Applies to: • Amaurotic (familial) idiocy • Disease: ◦ Batten ◦ Jansky-Bielschowsky ◦ Kufs' ◦ Spielmeyer-Vogt ◦ Tay-Sachs ◦ Gangliosidosis	V82.71 Screening for genetic disease carrier status

References

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Short-chain acyl-CoA dehydrogenase deficiency

Report Type: Carrier Status

About: Short-chain acyl-CoA dehydrogenase (SCAD) deficiency is a rare, inherited fatty acid oxidation disorder.¹ Clinical symptoms may appear during infancy or early childhood, including failure to thrive, lack of energy, poor muscle tone, seizures, developmental delay and acute acidosis. Individuals with SCAD deficiency exhibit elevated levels of ethylmalonic acid in the urine. In some patients, the symptoms do not appear until adulthood while other patients may never develop any symptoms.¹

Genetics: Short-chain acyl-CoA dehydrogenase (SCAD) deficiency is caused by mutations in the ACADS gene, which encodes the SCAD enzyme.¹ This enzyme breaks down short-chain fatty acids, and defects in the enzyme can lead to a shortage of energy and a buildup of short-chain fatty acids in the blood.²

The incidence of SCAD deficiency is approximately 1 in 40,000 to 100,000 newborns.¹

The test includes eleven mutations in the ACADS gene that cause SCAD deficiency.² These mutations are found in Caucasian, African American, Spanish and Jewish populations. R107C is found in 1 in 15 individuals of Ashkenazi Jewish ethnicity, and may be a founder mutation for this population.³ S353L is considered a founder mutation for patients of Dutch origin.²

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics recommends newborn screening for short-chain acyl-CoA dehydrogenase deficiency.⁴

If a patient has a SCAD deficiency mutation, please check the ethylmalonic aciduria report for two common variants that may increase susceptibility for the development of symptoms of SCAD deficiency.

Mutations Tested: The test includes 11 mutations in the ACADS gene.

ACADS [S353L, R380W, R139C, Q365H, I390M, T169P, M370V, A199V, R46W, R107C, W177R]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
ACADS	Ashkenazi Jewish	65%	1 in 15	1 in 41

^aPercentage of affected patients carrying mutations detected by this test.³

^bCarrier risk before testing.³

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with short-chain acyl-CoA deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.85 Disorders of fatty acid oxidation Applies to: • Carnitine palmitoyltransferase deficiencies (CPT1, CPT2) • Glutaric aciduria type II (type IIA, IIB, IIC) • Long chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHAD) • Long chain/very long chain acyl CoA dehydrogenase deficiency (LCAD, VLCAD) • Medium chain acyl CoA dehydrogenase deficiency (MCAD) • Short chain acyl CoA dehydrogenase deficiency (SCAD)	V82.71 Screening for genetic disease carrier status

References

1. Jethva R, Bennett MJ, Vockley J. Short-chain acyl-coenzyme A dehydrogenase deficiency. *Molecular genetics and metabolism*. 2008;95:195-200.
2. Pedersen CB, Kølvrå S, Kølvrå A, et al. The ACADS gene variation spectrum in 114 patients with short-chain acyl-CoA dehydrogenase (SCAD) deficiency is dominated by missense variations leading to protein misfolding at the cellular level. *Human genetics*. 2008;124:43-56.
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Sick sinus syndrome

Report Type: Carrier Status

About: Sick sinus syndrome (SSS) is an inherited condition that is characterized by pathological sinus bradycardia, sinus arrest and/or chronotropic incompetence (attenuated heart rate response to exercise). Although SSS incidence increases in an exponential-like manner with age, it can occur at all ages, including in the newborn. The mean age of patients with the syndrome is 68 years. The syndrome occurs in 1 of every 600 cardiac patients older than 65 years and accounts for approximately half of implantations of pacemakers in the United States.^{1,2} When the genetic causes are known, SSS is often associated with other heart conditions, such as Brugada syndrome, cardiac conduction defect and long QT syndrome.³ However, SSS is also found as a congenital form in children who do not have other underlying heart problems.

Genetics: Most mutations that cause sick sinus syndrome (SSS) have been found in the SCN5A gene, which encodes a subunit of a sodium ion channel found in the heart. Mutations that disrupt channel function can impact the sodium current across the membrane of the cell and, thus, the electrophysiology of the heart.

The test includes four mutations in SCN5A (T220I, P1298L, G1408R and R1632H) that are known to cause congenital sick sinus syndrome.⁴ Notably, G1408R has also been reported as a dominant mutation that causes Brugada syndrome and cardiac conduction disease.⁵ Mutations in SCN5A are also found in other diseases in the heart.⁶

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes four mutations in the SCN5A gene.

SCN5A [G1408R, T220I, P1298L and R1632H]

Ethnic Prevalence and Frequency of Mutations Tested: The prevalence of SSS is about 3 per 10,000 in the general population and is higher with advanced age. Men and women are equally affected.

Limitations and Warnings: Since there are other mutations that are associated with sick sinus syndrome, it is possible to carry a mutation that is not on our test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

427.81 Sinoatrial node dysfunction	V82.71 Screening for genetic disease carrier status
Applies to: • Sinus bradycardia: ◦ persistent ◦ severe • Syndrome: ◦ sick sinus ◦ tachycardia-bradycardia	

References

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Sickle cell anemia

Report Type: Carrier Status

About: Sickle cell anemia (also known as homozygous sickle cell disease or HbSS) is the most common inherited blood disorder in the U.S., accounting for 60% to 70% of all sickle cell disease in the country. The condition is a chronic, lifelong, inherited disorder that is associated with a decreased lifespan and characterized by the clumping of red blood cells, which can cause painful episodes and permanent damage to the eyes, brain, heart, lungs, kidneys, liver, bones and spleen. Infections and lung disease are the leading causes of death for people with sickle cell anemia.^{1,2,3}

Genetics: Sickle cell anemia is caused by a mutation in the HBB gene, which encodes the beta subunit of hemoglobin. Individuals with two copies of the HbS mutation have sickle cell anemia, whereas individuals with one copy of the HbS mutation have sickle cell trait and can pass this mutation to their children.^{1,4} Most people with sickle cell trait lead normal lives, but they are at increased risk for exertional rhabdomyolysis, a condition that may lead to exercise-induced sudden cardiac death.^{5,6,7}

Sickle cell anemia is a hemoglobinopathy and other mutations in the HBB gene cause other hemoglobinopathies, including hemoglobin C disease (HbC), hemoglobin E disease (HbE) and beta-thalassemia.¹

Sickle cell anemia occurs in 1 in 600 to 700 African American births and in 1 in 19,000 to 46,000 Hispanic American births.⁸

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: The American College of Obstetricians and Gynecologists (ACOG) recommends offering carrier screening for hemoglobinopathies to people of African, Southeast Asian and Mediterranean ancestry.⁹ The American College of Medical Genetics identified sickle cell anemia as one of 29 diseases for which newborn screening should be mandated.¹⁰

The NCAA requires that all Division I athletes undergo testing for sickle cell trait.¹¹ Individuals with sickle cell trait can compete and play sports at all levels as long as they are aware of the trait and take proper precautions.¹²

Mutations Tested: The test includes one mutation in the HBB gene.

HBB [hemoglobin S]

Ethnic Prevalence and Frequency of Mutation Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
HBB	African American	100%	1 in 15	0

HBB	Native American	100%	1 in 150	0
HBB	Hispanic American	100%	1 in 203	0
HBB	Middle Eastern	100%	1 in 478	0
HBB	Caucasian	100%	1 in 642	0
HBB	Asian Indian	100%	1 in 652	0
HBB	Filipino	100%	1 in 879	0
HBB	Asian	100%	1 in 1,315	0
HBB	Southeast Asian	100%	1 in 2,365	0

^aPercentage of affected patients carrying mutations detected by this test.

^bCarrier risk before testing.¹³

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Sickle cell anemia carriers may have misleading results in the hemoglobin A1C test (also known as glycated hemoglobin, glycosylated hemoglobin, and HbA1c) that is used to diagnose diabetes and to monitor blood glucose levels in diabetics. False A1C test results can lead to false diagnosis, over-treatment or under-treatment of diabetes in people with hemoglobin variants.¹⁴

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
282.60 Sickle-cell disease, unspecified	V78.2 Screening for sickle cell disease/trait
Applies to:	
• Sickle-cell anemia NOS	

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2. Fixler J, Styles L. Sickle cell disease. *Pediatric clinics of North America*. 2002;49:1193-210, vi.
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14. Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. *Clinical chemistry*. 2001;47:153-63.

Sickle cell disease

Report Type: Carrier Status

About: Sickle cell disease (SCD) is a chronic, lifelong, inherited disorder that is associated with a decreased lifespan.^{1,2,3} In SCD, red blood cells clump together and stick to blood vessel walls, which can cause painful episodes and permanent damage to the eyes, brain, heart, lungs, kidneys, liver, bones and spleen. Infections and lung disease are the leading causes of death for people with sickle cell disease. The severity of anemia that is characteristic of SCD depends on an individual's genotype.¹

The broader term sickle cell disease includes sickle cell anemia but also includes individuals with one copy of the HbS mutation and one copy of another HBB gene mutation such as hemoglobin C (HbC) or various beta-thalassemia variants.^{1,4} The high prevalence of the Hemoglobin S (HbS) variant in areas of the world where malaria occurs is due to the protection against malarial infection conferred by the presence of just one HbS variant.⁵

Genetics: SCD is associated with the hemoglobin S (HbS) mutation in the HBB gene, which encodes the beta subunit of hemoglobin. Individuals with two copies of the HbS mutation have sickle cell anemia, whereas individuals with one copy of the HbS mutation have sickle cell trait and can pass this mutation to their children.^{1,4} Most people with sickle cell trait lead normal lives, but they are at increased risk for exertional rhabdomyolysis, a condition that may lead to exercise-induced sudden cardiac death.^{6,7,8}

SCD is the most common inherited blood disorder in the U.S., occurring in 1 in 350 African American births and in 1 in 16,000 Hispanic American births. Sickle cell anemia occurs in 1 in 600 to 700 African American births and in 1 in 19,000 to 46,000 Hispanic American births. HbS/HbC disease occurs in 1 in 1,200 African American births and in 1 in 58,000 to 360,000 Hispanic American births. HbS/beta-thalassemia disease occurs in 1 in 4,000 African American births and in 1 in 175,000 to 730,000 Hispanic American births.⁹

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: The American College of Obstetricians and Gynecologists (ACOG) recommends offering carrier screening for hemoglobinopathies to people of African, Southeast Asian and Mediterranean ancestry.¹⁰ The American College of Medical Genetics identified sickle cell anemia as one of 29 diseases for which newborn screening should be mandated.¹¹

The NCAA requires that all Division I athletes undergo testing for sickle cell trait.¹² Individuals with sickle cell trait can compete and play sports at all levels as long as they are aware of the trait and take proper precautions.¹³

Mutations Tested: HBB [hemoglobin S]

Ethnic Prevalence and Frequency of Mutation Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
HBB	African American	100%	1 in 15	0
HBB	Native American	100%	1 in 150	0
HBB	Hispanic American	100%	1 in 203	0
HBB	Middle Eastern	100%	1 in 478	0
HBB	Caucasian	100%	1 in 642	0
HBB	Asian Indian	100%	1 in 652	0
HBB	Filipino	100%	1 in 879	0
HBB	Asian	100%	1 in 1,315	0
HBB	Southeast Asian	100%	1 in 2,365	0

^aPercentage of affected patients carrying mutations detected by this test.

^bCarrier risk before testing.¹⁴

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: SCD carriers may have misleading results in the hemoglobin A1C test (also known as glycated hemoglobin, glycosylated hemoglobin, and HbA1c) that is used to diagnose diabetes and to monitor blood glucose levels in diabetics. False A1C test results can lead to false diagnosis, over-treatment or under-treatment of diabetes in people with hemoglobin variants.¹⁵

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
282.63 Sickle-cell/Hb-C disease without crisis	V78.2 Screening for sickle-cell disease or trait
Applies to:	
• Hb-S/Hb-C disease without crisis	

References

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3. Yardumian A, Crawley C. Sickle cell disease. *Clinical medicine (London, England)*. 2001;1:441-6.
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6. Kark JA, Ward FT. Exercise and hemoglobin S. *Seminars in hematology*. 1994;31:181-225.
7. Harrelson GL, Fincher AL, Robinson JB. Acute exertional rhabdomyolysis and its relationship to sickle cell trait. *Journal of athletic training*. 1995;30:309-12.
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9. Hassell KL. Population estimates of sickle cell disease in the U.S. *American journal of preventive medicine*. 2010;38:S512-21.
10. ACOG Practice Bulletin No. 78: hemoglobinopathies in pregnancy. *Obstetrics and gynecology*. 2007;109:229-37.
11. Newborn screening: toward a uniform screening panel and system. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2006;8 Suppl 1:1S-252S.
12. Bonham VL, Dover GJ, Brody LC. Screening student athletes for sickle cell trait--a social and clinical experiment. *The New England journal of medicine*. 2010;363:997-9.
13. Sickle cell trait. National Collegiate Athletic Association web site. <http://www.ncaa.org/wps/wcm/connect/public/NCAA/Health+and+Safety/Sickle+Cell/Sickle+Cell+Landing+Page>. Updated March 2012. Accessed June 29, 2012.
14. Information for providers on the California hemoglobin trait follow-up program. California Department of Public Health web site. <http://www.cdph.ca.gov/programs/NBS/Documents/NBS-HbTraitFactSheetJuly04.pdf>. Accessed June 28, 2012.
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Simvastatin-induced myopathy

(DC:TB-0229.001 06DEC2012)

Report Type: Pharmacogenetics

About: Simvastatin is a member of the statins, a class of cholesterol-lowering drugs whose major adverse effect is skeletal muscle toxicity. Approximately 5% to 10% of patients taking statins experience muscle pain (myalgia).¹ A small portion of patients, (1.5% to 5.0%) may develop more severe symptoms indicating muscle degradation (myopathy).¹ In rare cases (0.1 to 0.2 cases per 1,000 person-years), severe muscle damage leads to acute, potentially lethal kidney failure (rhabdomyolysis).^{1,2}

Genetics: Simvastatin-induced myopathy has been shown to be influenced by variation in the *SLCO1B1* gene.³ Approximately 60% of myopathy cases in a simvastatin (80 mg/day) clinical trial were attributed to the C allele of the rs4149056 marker in the *SLCO1B1* gene.³ *SLCO1B1* encodes the organic anion-transporting polypeptide 1B1 (OATP1B1, also known as OATP-C or OATP2), which regulates the hepatic uptake of statins and other drugs. The C allele at rs4149056 reduces the activity of the OATP1B1 transporter,⁴ leading to increased blood simvastatin levels and the potential for increased toxicity to the muscles. However, available clinical data are insufficient to show whether the *SLCO1B1* variant also alters myopathy risk associated with the use of statins other than simvastatin.⁵

The risk of myopathy varies with the type of statin and is dose-related. Some statins are associated with lower risk of myopathy compared with others,¹ and the pharmacokinetic effects of variants of rs4149056 are not uniform for different statins.^{6,7} The incidences of myopathy and rhabdomyolysis while taking 80 mg simvastatin daily are disproportionately higher than those with lower doses.⁸

Genetic variation in *SLCO1B1* also affects pharmacokinetics of other drugs, such as methotrexate and HIV protease inhibitors.⁹

Recommendations: The NIH Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines for *SLCO1B1* genotyping and simvastatin-induced myopathy, recommending reduced dose or alternative statins for patients with the C allele at rs4149056. The CPIC also recommends routine surveillance of serum creatine kinase levels for those patients.⁵

Possible Outcomes: Increased Risk, Typical Risk

Markers and Alleles Tested: *SLCO1B1* [rs4149056]

Ethnic Distribution of Tested Allele

Frequency of C allele of the rs4149056 marker in major ethnic groups.⁵

Ethnicity	C allele frequency (rs4149056)
Caucasian	15%
African	3%
Middle Eastern	20%
Asian	13%

Limitations and Warnings: Although the tested SLCO1B1 variant has the most significant genetic effect on the risk of simvastatin-induced myopathy in clinical studies, rarer mutations in SLCO1B1 that may also affect the function of the encoded protein are not screened in this test. Current knowledge is limited on the involvement of other genes in the metabolism and clinical effects of simvastatin. In addition to genetic effects, the risk of simvastatin-induced myopathy varies with the patient's age, gender, body mass index, ethnicity and other clinical factors.⁵

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
359.4 Toxic myopathy	N/A

References

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Spherocytosis, hereditary

Report Type: Carrier Status

About: Hereditary spherocytosis (HS) is an inherited disease with symptoms that range from mild to very severe and life-threatening.^{1,2} Symptoms include anemia, spleen enlargement, jaundice, reticulocytosis and gallstone formation. Although HS may develop at any age, most cases are diagnosed in infancy or childhood and are mild to moderate. About 10% of HS patients require occasional blood transfusions and only 3% to 4% of patients have a life-threatening anemia that requires regular transfusions.³ Removal of the spleen can cure HS because the spherical RBCs have a nearly normal lifespan when there is no spleen to remove them.³

Genetics: HS is caused by mutations in the ANK1 and EPB42 genes, which encode the ankyrin 1 and EPB42 (erythrocyte membrane protein band 4.2) proteins, respectively. These proteins help maintain the biconcave shape of red blood cells (RBCs).^{1,2} Defects in either of these proteins destabilize the membrane structure, leading to a loss of membrane surface area that produces the characteristic spherical shape of RBCs in spherocytosis. Spherical RBCs are destroyed in the spleen, which leads to anemia, spleen enlargement and the release of bilirubin, which causes jaundice and may precipitate to form gallstones. In response to anemia, more immature RBCs appear (reticulocytosis).³

HS is found in all ethnic groups, but is the most common inherited anemia in individuals of northern European descent with a frequency of about 1:5000.¹ About 1% of the population in the U.S. is estimated to be a silent carrier of a mutation for recessive HS.³

Approximately 15% to 20% of ANK1 mutations are de novo, but recurrent mutations in ANK1 have been found.

Approximately 40% to 65% of HS cases in northern European populations are due to defects in the ANK1 gene.¹ Less than 5% of HS cases are caused by defects in the EPB42 gene in northern European populations. In contrast, in Japan, only 5% to 10% of HS cases result from defects in the ANK1 gene, while 45% to 50% of HS cases are caused by defects in the EPB42 gene.¹

The test includes mutations in the ANK1 and EPB42 genes that cause recessive hereditary spherocytosis. Most mutations in the ANK1 gene that cause HS are inherited in an autosomal dominant fashion, but this test only includes mutations that are inherited in an autosomal recessive fashion. Mutations in the EPB42 gene that cause hereditary spherocytosis are inherited in an autosomal recessive fashion.

Mode of Inheritance: Autosomal recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes eight mutations in two genes.

EPB42 [A142T, W119X, D175Y, R310Q, R317C, IVS6+1G>A]; ANK1 [5703(+16C>T), V463I]

Ethnic Prevalence and Frequency of Mutations Tested: The test includes six mutations in EBP42, including A142T (also known as protein 4.2 Nippon), the most common mutation in Japanese families with hereditary spherocytosis.^{4,5,6}

Limitations and Warnings: Since there are other mutations associated with hereditary spherocytosis, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
282.1 Hereditary spherocytosis Applies to: • Acholuric (familial) jaundice • Congenital hemolytic anemia (spherocytic) • Congenital spherocytosis • Minkowski-Chauffard syndrome • Spherocytosis (familial)	V82.71 Screening for genetic disease carrier status

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Systemic lupus erythematosus

Report Type: Health Conditions

About: Systemic lupus erythematosus (SLE) is the most common form of lupus.¹ This chronic autoimmune disease is characterized by the production of autoantibodies that can cause renal failure, arthritis, thrombosis, vasculitis and seizures.² Risk factors for SLE include exposure to silica dust, hormonal and reproductive factors and cigarette smoke.^{2,3} Research indicates that genetic factors are also associated with the disease^{4,5,6}

Genetics: Systemic lupus erythematosus (SLE or lupus) can occur either sporadically or be recurrent in families. Genes connected to the immune system are associated with the development of SLE, including the HLA Class II molecules of the major histocompatibility complex (MHC) and genes involved in the complement system.

The rs2187668 marker is located in the HLA Class II region and is linked to a high-risk set of alleles in three tightly linked genes in Caucasians.⁴ The high risk alleles are HLA-DRB1*0301-HLA-DQA1*0501-DQB1*0201. This combination of alleles is very common, but it is the pairing of these alleles with others that can initiate SLE as well as other autoimmune diseases. The minor allele, "A", of rs2187668 has been associated with increased SLE risk in Caucasians.

Other genes included in the test are also involved in the immune system. Among these, the FCGR2A gene encodes a receptor that is expressed on immune cells and interacts with antibody complexes. The T allele of the rs1801274 marker causes an altered interaction with IgG and is thought to perpetuate autoimmune responses in SLE in Caucasians and Asians.^{5,6}

In another example, the IRF5 gene encodes a transcription factor that regulates other genes that respond to interferon-alpha (IFN alpha). IFN alpha is normally produced in response to viral infections, but its levels are abnormally high in SLE patients. Increased IFN alpha levels result in increased IRF5 levels. The T allele of the rs2004640 marker encodes an alternative form of IRF5 and is associated with increased risk for SLE in individuals of Caucasian, Asian, African and Hispanic descent.⁷ IRF5 has also been shown to have additive effects with STAT4 for increased risk for SLE.

The STAT4 gene encodes a transcription factor that regulates inflammatory gene expression. The T allele of the rs7574865 marker is associated with increased STAT4 expression and is thought to contribute to earlier onset and more severe disease in Caucasians, Asians and people of Hispanic ancestry.^{8,9,10}

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h

ITGAM	rs1143679	A	1.55	African	11.0%	Validated	18204448
ITGAM	rs1143679	A	1.78	Caucasian	10.0%	Validated	18204448
ITGAM	rs1143679	A	2.26	Hispanic	9.0%	Validated	19129174
TNFSF4	rs1234314	G	1.26	Caucasian	42.5%	Validated	19092840
BLK	rs13277113	A	1.30	Asian	75.0%	Validated	19225526
BLK	rs13277113	A	1.39	Caucasian	23.5%	Validated	18204098
BANK1	rs17266594	T	1.64	Asian	84.5%	Validated	19357697
BANK1	rs17266594	T	1.42	Caucasian	73.9%	Validated	18204447
MECP2	rs1734787	C	1.55	Asian	88.5%	Validated	18320046
MECP2	rs1734787	C	1.35	Caucasian	18.5%	Validated	19333917
FCGR2A	rs1801274	C	1.87	African	45.3%	Validated	12115187
FCGR2A	rs1801274	C	1.61	Asian	31.5%	Validated	12867584
FCGR2A	rs1801274	C	1.24	Caucasian	50.9%	Validated	12115187
HLA	rs2187668	A	1.76	Caucasian	8.0%	Validated	19493061
CTLA4	rs231775	G	1.25	Asian	69.6%	Validated	15688186
PTPN22	rs2476601	A	1.35	Caucasian	11.7%	Validated	19493061
PTPN22	rs2476601	A	2.06	Hispanic	5.2%	Validated	16868974
CTLA4	rs3087243	G	1.32	Caucasian	54.0%	Validated	15248219
TNFAIP3	rs5029939	G	2.09	Caucasian	2.7%	Validated	19387456
STAT4	rs7574865	T	1.71	Asian	35.2%	Validated	19225526
STAT4	rs7574865	T	1.56	Caucasian	23.4%	Validated	18516230
STAT4	rs7574865	T	1.62	Hispanic	40.0%	Validated	18432273
CRP	rs3093062	G	1.45	African	79.9%	Preliminary	18182444

^aGene or locus containing the tested marker.

^bMarker tested.

^cAllele associated with disease risk.

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

^eEthnicity of the population in the corresponding study.

^fPercentage of people who have the associated allele in the population studied.

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
710.1 Systemic lupus erythematosus Applies to: - Disseminated lupus erythematosus - Libman-Sacks disease	V82.9 Screening for unspecified condition

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Tay-Sachs disease

Report Type: Carrier Status

About: Tay-Sachs disease (TSD), also known as GM2 gangliosidosis, is a severe genetic disease that causes degeneration of nerves and can result in the loss of motor function, mental retardation, and ultimately death, depending on the classification of the disease. The infantile onset form is the most serious, and the severity and onset of the disease are related to the amount of beta-hexosaminidase enzyme activity present in the body. Juvenile, chronic and adult-onset forms of the disease exist, have variable ages of onset and neurological findings, and slower progression. There is currently no cure or treatment for Tay-Sachs disease.¹ Since screening began for Tay-Sachs enzyme levels and known Tay-Sachs mutations, the incidence of the disease has been drastically reduced in populations with increased carrier rates.^{2,3}

Genetics: TSD is caused by mutations in the HEXA gene, which encodes the alpha subunit of beta-hexosaminidase. This enzyme is necessary for the breakdown of the fatty acid called GM2-ganglioside. A defective enzyme leads to the accumulation of these fatty acids and damage to the cell. Neurons are most severely affected due to GM2-gangliosides being most prevalent in neurons.^{1,4,5}

The incidence of TSD is higher in people of Ashkenazi Jewish descent. In the U.S. population, the incidence is approximately 1 in 320,000 live births, but it is 1 in 3,600 for Ashkenazi Jews.^{1,6} One in 31 people of Ashkenazi Jewish descent carries a mutation that causes TSD.⁷ Screening programs for this condition are a model for the success of genetic screening.^{2,3} The incidence of TSD in the Jewish population of North America has been reduced by more than 90% since the introduction of carrier screening in 1970.³

The American College of Medical Genetics recommends carrier screening for TSD in individuals of Ashkenazi Jewish descent. Three mutations are recommended for testing. Of these mutations, the 1278insTATC mutation is present in 80% of Ashkenazi Jews with TSD, IVS12+1G>C is present in 12% and G269S is present in 6%.^{1,8}

Mode of Inheritance: Autosomal Recessive¹

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) recommend offering prenatal and preconception Tay-Sachs disease carrier screening to individuals with Ashkenazi Jewish ancestry or a positive family history.^{7,9}

Please also see the genetic test for the related condition, Tay-Sachs pseudodeficiency, which includes alleles that cause a false positive result in the biochemical diagnostic test for Tay-Sachs disease.¹

Mutations Tested: The test includes 19 mutations in the HEXA gene. ACMG recommends carrier screening in Ashkenazi Jews for three mutations, which are underlined below.⁸

HEXA [IVS9-1G>T, deltaTTC910-912, 613delC, 1278insTATC, R178H/L, G269S, S210F, R499H, R504C, R170Q, R170W, V192L, W329X, I335F, C458Y, IVS12+1G>C, IVS2+1G>C, IVS9+1G>A, IVS5-1G>T]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
HEXA	Ashkenazi Jew	99%	1 in 31	1 in 3,001
HEXA	non-Jewish	46%	1 in 250	1 in 462

^aPercentage of affected patients carrying the three mutations recommended by ACMG plus the IVS2+1G>C mutation;^{7,8} the actual detection rate may be higher.

^bCarrier risk before testing.^{1,8}

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other rare mutations associated with Tay-Sachs disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
330.1 Cerebral lipidoses Applies to: • Amaurotic (familial) idiocy • Disease: ◦ Batten ◦ Jansky-Bielschowsky ◦ Kufs' ◦ Spielmeyer-Vogt ◦ Tay-Sachs ◦ Gangliosidosis	V82.71 Screening for genetic disease carrier status

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Tay-Sachs pseudodeficiency

Report Type: Carrier Status

About: Tay-Sachs pseudodeficiency is not a disease. Tay-Sachs enzyme screening programs (as opposed to DNA testing) detect carriers by testing the activity of the HEXA enzyme. A deficiency in HEXA enzyme activity most often means that a person is a carrier for Tay-Sachs disease.¹ However, there are known changes in the HEXA gene that do not cause the disease but can cause positive results in the enzyme screening test because the test uses a synthetic substrate. The synthetic substrate does not react with the HEXA protein that has these gene changes, leading to a false-positive enzyme test result.¹

Genetics: A patient with Tay-Sachs pseudodeficiency carries a nondisease-causing mutation of the HEXA gene that gives a false diagnosis of Tay-Sachs disease in biochemical testing.¹ The HEXA gene encodes the alpha subunit of the beta-hexosaminidase A enzyme that is necessary for the breakdown and metabolism of GM2-ganglioside.

Up to 35% of non-Ashkenazi people who test positive for Tay-Sachs carrier status in the enzyme test actually have a pseudodeficiency allele and are not at risk of passing a disease-causing variation to offspring.¹ In contrast, about 2% of people of Ashkenazi Jewish descent who test positive for Tay-Sachs carrier status in the enzyme test are found to carry a pseudodeficiency allele.

The test includes two known pseudodeficiency alleles that may clarify enzyme test results for individuals with positive HEXA findings.^{1,2}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: Please also see the genetic test for the related condition Tay-Sachs disease.

Mutations Tested: The test includes two mutations in the HEXA gene.

HEXA [R247W, R249W]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
N/A	V82.71 Screening for genetic disease carrier status

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Thrombocytopenia, congenital amegakaryocytic

Report Type: Carrier Status

About: Congenital amegakaryocytic thrombocytopenia (CAMT) is an extremely rare, inherited bone marrow failure disease.^{1,2} Patients have a severe thrombocytopenia at birth, but no physical anomalies. CAMT is classified into two types based on the course and outcome of the disease. CAMT type I is characterized by the early onset of severe pancytopenia (shortage of red and white blood cells as well as platelets), very low platelet counts and decreased bone marrow activity. CAMT type II is characterized by transient increases of platelet count to nearly normal levels during the first year of life and an onset of bone marrow failure at age 3 or later. Platelet transfusion is an effective treatment for CAMT patients but the only curative therapy to date is hematopoietic stem cell transplantation.³

Genetics: CAMT is caused by mutations in the MPL gene.^{4,5} The MPL gene encodes the receptor for thrombopoietin (TPO), a factor that stimulates the development of megakaryocytes from which the platelets that help form blood clots are derived.⁶ TPO is also involved in the regulation of hematopoietic stem cells.⁶

The test includes the most recurrent mutations in the MPL gene that cause CAMT. The most frequent mutation, R102P, was detected in about 35% of CAMT patients from Western Europe.⁵ R43X is a recurrent mutation found in patients of Bedouin, Kurdish and Italian origins.^{4,7}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes two mutations in the MPL gene.

MPL [R102P, R43X]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with congenital amegakaryocytic thrombocytopenia, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)

287.5 Thrombocytopenia, unspecified	V82.71 Screening for genetic disease carrier status

References

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Tyrosinemia

Report Type: Carrier Status

About: Tyrosinemia is an inherited disorder that disrupts the breakdown of the amino acid tyrosine. Infants with tyrosinemia type I typically show symptoms within the first year of life, although the age at onset of the initial symptoms, the organs involved and the progression of the disease vary significantly among affected individuals. Common symptoms of tyrosinemia type I include liver failure, liver cancer, kidney dysfunction, delayed growth, rickets, and recurrent crises of the nervous system. Untreated children usually die before 10 years of age.¹

Genetics: Tyrosinemia type 1 is caused by mutations in the FAH gene, which encodes the enzyme fumarylacetoacetate hydrolase.^{1,2} The FAH enzyme is responsible for the last reaction in a process that breaks tyrosine into smaller molecules. In people with tyrosinemia type 1, tyrosine, intermediate products and byproducts accumulate and are toxic to many cells, which leads to a variety of clinical manifestations.¹

The test includes common disease-causing FAH mutations found in various ethnic groups.^{1,2} The P261L mutation accounts for more than 99% of disease-causing mutations in the Ashkenazi Jewish population. The G337S, W262X and Q64H mutations are common in the Scandinavian, Finnish, Turkish and Pakistani populations, respectively.¹

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified tyrosinemia as one of 29 diseases for which newborn screening should be mandated.³

Mutations Tested: The test includes four mutations in the FAH gene.

FAH [W262X, G337S, Q64H, P261L]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
FAH	Ashkenazi Jew	99%	1 in 100	1 in 9,901
FAH	European	8%	1 in 100	1 in 108

^aPercentage of affected patients carrying mutations detected by this test.^{1,4}

^bCarrier risk before testing.¹

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with tyrosinemia type 1, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
270.2 Other disturbances of aromatic amino-acid metabolism Applies to: • Albinism • Alkaptonuria • Alkaptonuric ochronosis • Disturbances of metabolism of tyrosine and tryptophan • Homogentisic acid defects • Hydroxykynureninuria • Hypertyrosinemia • Indicanuria • Kynureninase defects • Oasthouse urine disease • Ochronosis • Tyrosinosis • Tyrosinuria • Waardenburg syndrome	V82.71 Screening for genetic disease carrier status

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Ulcerative colitis

Report Type: Health Conditions

About: Ulcerative colitis (UC) has been on the rise for the past 50 years, but incidence rates seem to be plateauing.¹ This chronic, idiopathic condition is characterized by ulcers in the rectum and colon that can cause pain and bloody diarrhea.² Risk factors include a family history of the disease and smoking.^{3,4} Research indicates that genetic factors are also associated with UC.^{5,6,7}

Genetics: Both genetics and environmental factors are known to contribute to the risk of developing UC. A role for genetics is shown by the observation that people with a family history of UC have an increased risk of developing the disease. Up to 20% of UC cases occur in families, with a higher incidence in those of northern European and Jewish ancestry.⁸ The genetic contribution to ulcerative colitis (UC) can be divided into two groups: HLA (human leukocyte antigen) and non-HLA susceptibility loci.

Like other autoimmune conditions, there is a strong association between susceptibility to UC and variants of the HLA region on Chromosome 6.⁵ The involvement of HLA genes in UC has long been known, but the exact mechanisms are not well understood. The HLA-associated UC susceptibility loci in the test include the rs2395185 marker in the HLA Class II region⁹ and the rs1800629 marker in the TNFA gene, which encodes the immune stimulatory TNF-alpha protein.¹⁰ The genetic association to TNFA alleles has only been reliably demonstrated in Asians. TNF-alpha is a target of antibody drugs used to treat ulcerative colitis.¹¹

Non-HLA UC susceptibility genes in the test include IL10 (interleukin 10)⁶ and IL23R (interleukin 23 receptor),⁷ among others. Several pro-inflammatory interleukin proteins, including IL10 and IL23, are targets for ulcerative colitis drug therapies that are either available or in clinical development.¹¹

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus ^a	Marker ^b	Associated Allele ^c	Odds Ratio ^d	Ethnicity ^e	Population Frequency ^f	Scientific Strength ^g	PMID ^h
NKX2-3	rs10883365	G	1.20	Caucasian	45.6%	Validated	18438406
IL23R	rs11209026	G	1.81	Caucasian	95.9%	Validated	19122664
IFNG	rs1558744	A	1.35	Caucasian	40.3%	Validated	19122664
HLA	rs2395185	G	1.77	Caucasian	56.7%	Validated	19122664

IL10	rs3024505	T	1.46	Caucasian	18.1%	Validated	18836448
MST1	rs3197999	T	1.20	Caucasian	26.1%	Validated	18438406
RNF186	rs3806308	G	1.37	Caucasian	60.2%	Validated	19122664
Intergenic_1p36	rs6426833	A	1.45	Caucasian	50.9%	Validated	19122664
BSN	rs9858542	A	1.31	Caucasian	25.7%	Validated	18438406
TNFa	rs1800629	A	2.27	Asian	8.9%	Preliminary	18827481

^aGene or locus containing the tested marker

^bMarker tested

^cAllele associated with disease risk

^dMeasure of the likelihood that an individual will get the disease if carrying a specific allele

^eEthnicity of the population in the corresponding study

^fPercentage of people who have the associated allele in the population studied

^gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

^hPubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
556.6 Universal ulcerative (chronic) colitis	N/A
Applies to:	
• Pancolitis	

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Venous thrombosis

Report Type: Health Condition

About: Venous thrombosis is the formation of a blood clot in the veins that can potentially lead to thromboembolism. The individual risk of venous thromboembolism (VTE) is determined by a complex interaction of genetic, circumstantial and environmental factors. Risk factors include immobility, surgery, trauma, cancer, hormonal therapy, pregnancy, advanced age and family history.^{1,2} Genetic factors are also associated with the risk of VTE development.

Genetics: Factor V Leiden, a mutation in the F5 gene, is the most common and most studied genetic prothrombotic defect, with an overall prevalence in Caucasians of approximately 5%. It is found in 20% of all patients with venous thrombosis, and in up to 50% of patients with thrombophilia.³ The F5 gene encodes coagulation factor V, an important cofactor that accelerates the activation of prothrombin to thrombin in the blood coagulation cascade. The Factor V Leiden mutation impairs down-regulation of coagulation factor V, resulting in increased risk of clotting.

Individuals who are heterozygous for the Factor V Leiden mutation have a 3.5-fold increase in risk of VTE.^{1,4,5,6} Homozygous patients are at a higher risk than heterozygous patients.^{1,4}

After Factor V Leiden, the most common mutation associated with heritable thrombophilia is prothrombin G20210A,⁷ which is located in the 3'-untranslated region of the gene and is associated with increased levels of prothrombin.³ Increased levels of prothrombin are a risk factor for thrombosis.⁸ Individuals with the mutation are at increased risk of VTE,^{1,4,5,6} and risk further increases in individuals who have the Factor V Leiden mutation.^{9,10} Individuals who are heterozygous for both mutations have a 20-fold increase in risk, whereas individuals who are heterozygous for either mutation only have a four- to five-fold increase in VTE risk.¹¹

Among women with history of VTE, the Factor V Leiden and prothrombin G20210A mutations are independently associated with increased risk of VTE during pregnancy and puerperium.¹⁰ Risk of thrombosis increases more than 100-fold in pregnant women who have both mutations compared to women without the mutations.^{10,12}

MTHFR is an important enzyme in folate metabolism and DNA synthesis. The homozygous MTHFR C677T genotype has been associated with an increased risk of elevated plasma homocysteine levels¹³ and hyperhomocysteinemia, an independent risk factor for VTE.^{14,15,16} The homozygous C677T genotype has also been associated with risk of VTE in Chinese and Korean populations.^{5,14,17,18} A meta-analysis found that, in studies of non-Americans, the homozygous C677T genotype was associated with a 20% higher risk of VTE compared to the homozygous wild-type genotype.¹⁶ In contrast, the homozygous C677T genotype had no effect on VTE in North America, possibly due to the higher intake rates of folate and riboflavin. In support of this hypothesis, one study found that homocysteine levels in homozygous C677T individuals were significantly higher than in homozygous wild-type individuals only if folate levels were below 15.4 nmol/L.^{5,19} Thus, individuals who are homozygous for C677T may require more dietary folate than individuals who are wild-type.

Recommendations: The American College of Medical Genetics, the American College of Obstetricians and Gynecologists and the European International Thrombophilia Guidelines recommend Factor V Leiden and/or G20210A testing in populations that are likely to have a mutation.^{7,20,21}

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers and Alleles Tested: F5 [Factor V Leiden/R506Q]; F2 [G20210A]; MTHFR [C677T]

Ethnic Distribution of Tested Alleles: The Factor V Leiden and prothrombin G20210A mutations are common in Caucasians but extremely rare in Asians and Africans.²² The allele frequency of Factor V Leiden in the U.S. population is 5% in Caucasians, 2.2% in Hispanics and 1.2% in blacks.^{1,23} Prothrombin G20210A has a prevalence of approximately 2% in the US population and occurs primarily in Caucasians.¹ Double heterozygosity for Factor V Leiden and prothrombin G20210A is estimated to affect 1 in 1,000 individuals in the general population.

There is significant ethnic and geographic variation in the frequency of C677T. The prevalence of the homozygous C677T genotype ranges from around 1% in Black populations in the US, sub-Saharan Africa, and South America to more than 20% in US Hispanics, Colombians and Amerindians in Brazil. The homozygous C677T genotype occurs at a frequency of 8-20% in Caucasians in Europe, North America, and Australia and at 12% in Japanese.²⁴

Limitations and Warnings: Genetic variants in other proteins, such as protein S, protein C and antithrombin are known to increase the risk of venous thrombosis, but are not part of this test. Non-genetic factors known to increase the risk of venous thrombosis include age, obesity, trauma/surgery, smoking, pregnancy and airplane travel.²⁵

According to the American College of Medical Genetics (ACMG) Consensus Statement on Factor V Leiden Mutation Testing, the MTHFR C677T only accounts for a third of hyperhomocysteinemia cases, and plasma measurements of homocysteine may be more informative than molecular methods.⁷

Dietary factors, such as folic acid intake, may influence the association between MTHFR and VTE.¹⁹

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
453.9 Other venous embolism and thrombosis of unspecified site • Embolism of vein • Thrombosis (vein)	N/A

References

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Verapamil and QTc interval

(DC:TB-0235.001 06DEC2012)

Report Type: Pharmacogenetics

About: Verapamil is an L-type calcium-channel blocker that is used to treat hypertension and angina. Its interaction with calcium channels reduces the force and rate of muscle contraction, leading to decreased blood pressure and heart rate.¹

Genetics: The nitric oxide synthase 1 (neuronal) adaptor protein, which is encoded by the NOS1AP gene, regulates the synthesis of nitric oxide, a known regulator of intracellular calcium.^{2,3} Variants in the NOS1AP gene are associated with the prolongation of QTc interval in patients taking verapamil.⁴

When treated with verapamil, patients who were homozygous for the G allele at the tested marker in NOS1AP were more likely to display verapamil-induced QTc interval prolongation, compared to individuals who were not.⁴ Individuals of any genotype on other calcium-channel blocker medications did not show this potentiation effect.⁴ The association of this NOS1AP marker with verapamil-induced QTc interval prolongation has not yet been independently replicated. In some studies, a prolonged QTc has been shown to increase the risk for developing certain tachyarrhythmias that increase the risk of sudden cardiac death.^{5,6} However, QTc interval length depends on many factors, including age, gender and other genes. In addition, QTc interval prolongation has been associated with certain medications and specific disease pathologies.^{7,8}

Recommendations: NA

Possible Outcomes: Increased Risk of Prolongation, Typical Risk of Prolongation

Markers or Alleles Tested: NOS1AP [rs10494366]

Ethnic Distribution of Tested Alleles: NA

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A

Applies to:

- Unspecified adverse effect of medicinal substance NEC properly administered

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Verapamil vs. atenolol

(DC:TB-0232.001 06DEC2012)

Report Type: Pharmacogenetics

About: Verapamil is an L-type calcium-channel blocker that is used to treat hypertension and angina. Its interaction with calcium channels reduces the force and rate of muscle contraction, leading to decreased blood pressure and heart rate.¹

Atenolol is a cardioselective beta(1)-adrenergic antagonist that is used to manage hypertension and chest pain caused by coronary heart disease. By inhibiting beta(1)-adrenergic receptors in the heart and smooth muscle of the vasculature, atenolol decreases resting heart rate, cardiac output and blood pressure.²

Genetics: Calcium-channel blockers, such as verapamil, bind to L-type calcium channels via the alpha1c-subunit, which is a major component of the channel pore and is encoded by the CACNA1C gene. Variants in CACNA1C are associated with a patient's response to different treatment strategies (beta-blockers versus calcium-channel blockers), but the mechanism is unknown.³ Variants in CACNA1C have also been shown to be associated with blood pressure⁴ and a reduction in blood pressure in response to calcium-channel blockers.^{5,6}

Based on a study that included patients with hypertension and stable coronary artery disease, those individuals who were homozygous for the A allele at the tested marker in CACNA1C and were treated with verapamil were more likely to have decreased incidence of death, myocardial infarction or stroke compared to individuals with the same genotype who were treated with the beta-blocker atenolol. On the other hand, patients who were homozygous for the G allele and were treated with atenolol were more likely to have decreased incidence of death, myocardial infarction or stroke compared to individuals with the same genotype who were treated with verapamil. For heterozygous patients, no association of increased benefits with atenolol versus verapamil was found. It is important to note that all patients in this study had their blood pressure under control regardless of medication taken. Consequently, the mechanism that explains how different genotypes lead to the different outcomes in response to calcium-channel blockers and beta-blockers is not understood.³ The association of this CACNA1C marker with benefits on verapamil or atenolol has not yet been independently replicated.

Recommendations: NA

Possible Outcomes: Likely Increased Benefit on Atenolol, Likely Increased Benefit on Verapamil, Likely Similar Benefit on Verapamil or Atenolol

Markers or Alleles Tested: CACNA1C [rs1051375]

Ethnic Distribution of Tested Alleles: NA

Limitations and Warnings: The results of this test are based on a study of patients with hypertension and stable coronary artery disease. Thus, they may not apply to patients being treated with verapamil or atenolol for other conditions.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance	N/A
Applies to:	
Unspecified adverse effect of medicinal substance NEC properly administered	

References

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Very long-chain acyl-CoA dehydrogenase deficiency

Report Type: Carrier Status

About: Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a genetic disease that disrupts the breakdown of very long-chain fatty acids. Affected infants often have severe cardiac defects. Approximately 50% of people with VLCAD deficiency have severe symptoms within the first year of life. Symptoms begin with vomiting, drowsiness and hypoglycemia, and can quickly worsen, leading to a life-threatening crisis with seizures and coma. Such crises usually occur after the infant goes without food for a long period of time or has a common infection that causes fever and reduced appetite. Approximately one third of VLCAD deficiency patients have their first crises of hypoglycemia between 1 to 13 years of age, but these cases usually do not involve heart problems. Some people with VLCAD deficiency first develop symptoms as adolescents or adult with typical symptoms being recurrent muscle pain and breakdown of muscles, usually triggered by strenuous exercise or a long period of fasting.^{1,2}

Genetics: VLCAD deficiency is caused by mutations in the ACADVL gene, which encodes an enzyme called very long-chain acyl-coenzyme A dehydrogenase.³ The enzyme is required for the first reaction in a stepwise process that breaks very long-chain fatty acids into smaller molecules.^{1,2} In individuals with VLCAD deficiency, energy cannot be generated from very long-chain fatty acids. Consequently, when other energy sources are depleted, individuals with the disease may experience an episode of “energy crisis” in which they cannot rely on certain fats stored in their own bodies.^{1,2}

Most mutations in the ACADVL gene are private,¹ but this test screens for V283A, a recurring mutation that was found in Germany during newborn screening.^{3,4}

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: The American College of Medical Genetics identified very long-chain acyl-CoA dehydrogenase deficiency as one of 29 diseases for which newborn screening should be mandated.⁵

Mutations Tested: The test includes one mutation in the ACADVL gene.

ACADVL [V283A]

Ethnic Prevalence and Frequency of Mutations Tested: NA

Limitations and Warnings: Since there are other mutations associated with VLCAD deficiency, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing

laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
277.85 Disorders of fatty acid oxidation Applies to: • Carnitine palmitoyltransferase deficiencies (CPT1, CPT2) • Glutaric aciduria type II (type IIA, IIB, IIC) • Long chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHAD) • Long chain/very long chain acyl CoA dehydrogenase deficiency (LCAD, VLCAD) • Medium chain acyl CoA dehydrogenase deficiency (MCAD) • Short chain acyl CoA dehydrogenase deficiency (SCAD)	V82.71 Screening for genetic disease carrier status

References

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Von Willebrand disease, type 2 Normandy

Report Type: Carrier Status

About: Von Willebrand disease is a congenital bleeding disorder that presents with the following possible symptoms: a propensity for easy bruising, routine nosebleeds, excessive bleeding after trauma or surgery, or severe joint and internal bleeding. The disease is classified into three general types based on the functionality of the VWF protein.¹ Type 2 von Willebrand disease is uncommon and seen in 15% to 20% of von Willebrand disease cases. It typically results in a mild to moderate phenotype. Subtype 2 Normandy (2N) differs from the other type 2 diseases in that it is autosomal recessive and shows symptoms that include mild to moderate mucocutaneous bleeding, prolonged bleeding occurrences, and excessive bleeding after surgery or trauma.^{2,3,4}

Genetics: Von Willebrand disease is caused by mutations in the VWF gene, which encodes a large glycoprotein found in the blood, called von Willebrand factor that normally participates in platelet adhesion. Mutations in the VWF gene that alter the VWF protein can cause abnormal bleeding due to lack of proper, timely clotting and platelet activity.^{5,6,7,8} Typically, disease severity is inversely correlated with the level of functional VWF protein and is used to divide von Willebrand disease into three general types.⁹ Type 1 von Willebrand disease is a partial quantitative deficiency of normal VWF protein, VWD type 2 is a qualitative deficiency of defective VWF protein and type 3 von Willebrand disease is a complete quantitative deficiency of VWF protein.

The test includes three mutations in the VWF gene that account for more than 96% of the type 2 Normandy von Willebrand disease cases as well as many less common mutations associated with the disease.¹⁰

Please see the related carrier status test for type 3 von Willebrand disease.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes 20 mutations in the VWF gene.

VWF [C788R, C804F, E1078K, M771V, R763G, P812L, T791M, R816W, R854Q, C1225G, Y795C, R816Q, Q1053H, R782W, H817Q, E787K, G785E, C788Y, D879N, C1060R]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
VWF	World-wide	75%	1 in 500	1 in 1,997

^aPercentage of affected patients carrying mutations detected by this test.¹¹

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.¹² The actual carrier rate and the post-test residual risk are likely to be lower.

^cCarrier risk after a "not a carrier" test result.

Limitations and Warnings: Since there are other mutations associated with type 2 Normandy von Willebrand disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
286.4 Von Willebrand disease	V82.71 Screening for genetic disease carrier status
Applies to:	
• Angiohemophilia (A) (B) • Constitutional thrombopathy • Factor VIII deficiency with vascular defect • Pseudohemophilia type B • Vascular hemophilia • von Willebrand's (-Jürgens') disease	

References

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Von Willebrand disease, type 3

Report Type: Carrier Status

About: Von Willebrand disease is a congenital bleeding disorder that presents with the following possible symptoms: a propensity for easy bruising, routine nosebleeds, excessive bleeding after trauma or surgery, or severe joint and internal bleeding. The disease is classified into three general types based on the functionality of the VWF protein.¹ Type 3 von Willebrand disease is very rare, results in complete loss of VWF protein function and shows the most severe clinical symptoms with excessive and prolonged bleeding episodes. Type 3 von Willebrand disease is typically diagnosed in childhood.²

Genetics: Von Willebrand disease is caused by mutations in the VWF gene, which encodes a large glycoprotein found in the blood, called von Willebrand factor that normally participates in platelet adhesion. Mutations in the VWF gene that alter the VWF protein can cause abnormal bleeding due to lack of proper, timely clotting and platelet activity.^{3,4,5,6} Typically, disease severity is inversely correlated with the level of functional VWF protein.

The test includes many mutations in the VWF gene that cause type 3 VWD, including the R2535X mutation. This mutation is associated with von Willebrand disease in several Dutch, Swedish, German, Italian and Turkish families.⁷

Please also see the related carrier test for von Willebrand disease, type 2 Normandy.

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote, Compound Heterozygote

Recommendations: NA

Mutations Tested: The test includes 67 mutations in the VWF gene.

VWF [191delG, 6182delT, 276delT, 2016_2019delCTCT, 2157delA, 2269_2270delCT, 4092_4093delAC, 7683delT, 374del14, 3940delG, 1384delG, 7674dupC7139dupT, 892dupG, 3258_3259insT, 3736_3737dupCC, 7172_7173insT, 1657dupT, R273W, Q218X, W222X, R373X, Q1346X, Y1542X, C2174G, C2804Y, C2754W, Y357X, D47H, Y610X, C1071F, R2434X, Q2544X, Y1456X, Q565X, L1267X, R324X, W377C, E620X, R1315C, R1853X, C2739Y, C2362F, C2671Y, S71X, IVS9-1G>A, IVS29+10C>T, IVS40-1G>C, IVS28+1G>A, IVS45+7C>T, IVS7+1G>A, IVS50+3G>T, 4324dupAGTGTGGA, R365X, R2535X]

Ethnic Prevalence and Frequency of Mutations Tested

Gene	Population	Detection Rate ^a	Pre-Test Carrier Rate ^b	Post-Test Residual Risk ^c
VWF	Swedish, Finnish	10%	1 in 500	1 in 555

^aPercentage of affected patients carrying mutations detected by this test.⁸

^bCarrier risk before testing. The true carrier rate is unknown for this extremely rare disease. The carrier rate of 1 in 500 is calculated based on an estimated disease prevalence of 1 in 1,000,000.⁹ The actual carrier rate and the post-test residual risk are likely to be lower.

^cCarrier risk after a “not a carrier” test result.

Limitations and Warnings: Since there are other mutations associated with type 3 von Willebrand disease, it is possible to carry a mutation that is not on the test.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
286.4 von Willebrand Disease	V82.71 Screening for genetic disease carrier status
Applies to: • Angiohemophilia (A) (B) • Constitutional thrombopathy • Factor VIII deficiency with vascular defect • Pseudohemophilia type B • Vascular hemophilia • von Willebrand's (-Jürgens') disease	

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Voriconazole metabolism

(DC:TB-0220.002 29JAN2013)

Report Type: Pharmacogenetics

About: Voriconazole is a triazole antifungal drug that is used to treat a wide variety of fungal infections, such as *Candida*, *Cryptococcus*, *Aspergillus*, most dimorphic fungi and other yeasts and hyaline molds.¹ Therapeutic drug monitoring is recommended for optimizing voriconazole therapy and preventing toxicity due to the drug's high interpatient variability and nonlinear pharmacokinetic properties in adults.^{1,1,2,3} Voriconazole serum concentrations less than 1 mg/L are associated with therapeutic failure, whereas levels greater than 5.5 mg/L have been linked to encephalopathy without improvement of therapeutic efficacy.⁴

Though the metabolic pathways of voriconazole are not completely understood, voriconazole is mainly metabolized to N-oxide,⁵ which has low antifungal activity.³ Metabolism to N-oxide is primarily mediated by enzymes encoded by CYP2C19 and CYP3A4, and to a lesser extent by CYP2C9,^{6,7} though voriconazole has the highest affinity for CYP2C19.⁸

Genetics: Variants in the CYP2C19 gene have been associated with variability in voriconazole metabolism and exposure.³ Individuals can be classified based on their CYP2C19 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).⁹

Variants of the CYP2C19 gene account for approximately half of the variability in oral clearance.^{10,11} UMs have decreased plasma concentrations of voriconazole with exposure reduced by up to approximately 50% compared to EMs.^{10,12,13} CYP2C19 PMs display decreased metabolism of voriconazole, increased plasma concentrations and approximately four-fold higher voriconazole exposure than EMs. Pharmacokinetic effects in IMs are between those of PMs and EMs.^{3,5,10,11,13,14,15}

There is not yet sufficient evidence for an association of CYP2C19 genotype and pharmacodynamic effects such as treatment efficacy or adverse events in patients treated with voriconazole.^{16,17} However, there are data linking VOR plasma concentrations to treatment failure or risk of adverse events. Low plasma concentrations of voriconazole, as found in some UMs, are associated with an increased risk of treatment failure and mortality in some non-genetic studies.^{18,19,20,21} In a 2011 study, the UM genotype was found to be more prevalent in patients with extremely low plasma concentrations of voriconazole (0.03 mg/mL).¹² In another study, 5 patients with persistently low VOR concentrations (<0.35 mg/mL) died from invasive fungal infection.¹⁸ In another study, 1 patient who had low plasma concentrations of voriconazole experienced therapeutic failure, which was reversed with a higher dose.¹⁹

In addition, high plasma concentrations of voriconazole have been shown to be associated with liver toxicity,^{18,21,22,23} although a recent study indicates no association of plasma VOR levels with liver toxicity.²⁴

Recommendations: The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenomics Working Group recommends therapeutic drug monitoring (TDM) for voriconazole treatment of CYP2C19 PMs and IMs.²⁵

The FDA-approved label indicates that when CYP2C19 is inhibited, dose adjustment or monitoring for adverse events or lack of efficacy may be needed.

Co-administration of inhibitors of CYP2C19, CYP2C9 and CYP3A4 may increase the voriconazole plasma concentrations.³ According to one study, the administration of ritonavir, a potent CYP3A4 inhibitor, resulted in a higher exposure with voriconazole, which might increase the risk of adverse reactions, particularly in CYP2C19 PMs.¹⁵

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers Tested: CYP2C19 [CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*8, CYP2C19*17]

Ethnic Distribution of Tested Alleles:

CYP2C19	Allele	Caucasian	African	East Asian	Middle Eastern	Enzyme activity
Wild-type	*1	63%	68%	60%	87%	Normal
rs4244285	*2	15%	15%	29%	12%	None
rs4986893	*3	0.42%	0.52%	8.9%	1.1%	None
rs28399504	*4	0.25%	0.093%	0.049%	ND ^a	None
rs56337013	*5	0.0073%	ND	0.062%	ND	Reduced
rs72552267	*6	0.017%	0%	0%	ND	None
rs41291556	*8	0.35%	0%	0%	ND	Reduced
rs12248560	*17	21%	16%	2.7%	ND	Increased

^aNot Determined

Predicted CYP2C19 Metabolizer Status⁹

CYP2C19 Diplotype	Predicted Metabolizer Status
*2-*8/*2-*8	Poor Metabolizer
*1/*2-*8, *17/*2-*8	Intermediate Metabolizer
*1/*1	Extensive Metabolizer
*1/*17, *17/*17	Ultrarapid Metabolizer

Limitations and Warnings: Many rare CYP2C19 variants have been identified, but are not part of this test. It is possible, but unlikely, that the patient may have a variant that is not included in this test.

CYP2C19 genotype and metabolizer status may also affect responses to other drugs.²⁶

Known CYP2C19 Substrates ²⁷	Known CYP2C19 Inhibitors ²⁷
Proton-pump Inhibitors lansoprazole omeprazole pantoprazole rabeprazole	Proton-pump Inhibitors lansoprazole omeprazole pantoprazole rabeprazole
Anti-epileptics diazepam phenytoin S-mephenytoin phenobarbitone	Other chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oxcarbazepine probenicid ticlopidine topiramate
Other amitriptyline carisoprodol citalopram chloramphenicol clomipramine clopidogrel cyclophosphamide hexobarbital imipramine N-deME indomethacin R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin	

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Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
N/A	V58.83 Encounter for therapeutic drug monitoring

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Warfarin

(DC:TB-0230.001 06DEC2012)

Report Type: Pharmacogenetics

About: Warfarin is the most frequently used oral anticoagulant worldwide, prescribed for prophylaxis and treatment of thrombotic disorders and thromboembolic events. Such indications include venous thrombosis, pulmonary embolism, atrial fibrillation and cardiac valve replacement. Warfarin is highly efficacious, but its narrow therapeutic index and large interindividual dosing variability lead to a high incidence of adverse events. Improper warfarin dosing is the second leading cause of drug-related emergency room visitation¹ and the number one cited reason for drug-related mortality.²

Warfarin acts as an anticoagulant through its ability to inhibit reduction of vitamin K by the VKORC1 enzyme complex. Reduced vitamin K is an essential cofactor of gamma-glutamyl carboxylase, the enzyme that activates coagulation factors II, VII, IX and X. By decreasing the amount of reduced vitamin K available, warfarin depresses the activation of factors II, VII, IX and X into functional, coagulant proteins, and, therefore, decreases the ability of blood to clot. The primary metabolizing enzyme of warfarin is CYP2C9.³

In 2010, the United States Food and Drug Administration (FDA) released a table of dosing recommendations for initiation of warfarin therapy based on vitamin K epoxide reductase complex subunit 1 (VKORC1) and cytochrome P450 2C9 (CYP2C9) genotypes. This pharmacogenetics-based dosing table significantly improved accuracy of therapeutic dose prediction compared to the traditional strategy of empirically determined dose.⁴

Genetics: The A allele of the -1639G>A mutation in the VKORC1 gene has been shown to decrease hepatic expression of VKORC1 and, therefore, increase patient sensitivity to warfarin.^{5,6,7} Research studies have shown that the therapeutic dose of warfarin in patients with two copies of the A allele was less than the dose of patients with two copies of the G allele, with a difference up to 2.0 to 4.5-fold.^{7,8,9}

Individuals carrying *2 or *3 genetic variants of CYP2C9 clear warfarin at a 30% to 50% or 80% to 90% slower rate, respectively, and exhibit increased serum levels of warfarin compared to carriers of only the reference wild-type variant *1.^{10,11} CYP2C9*2 and CYP2C9*3 variants may decrease the dose required for effective anticoagulation and may increase the time necessary to achieve stable, therapeutic effect.^{9,12} The CYP2C9*6 variant may also reduce metabolic activity and the dose required for effective anticoagulation.^{11,13}

Customizing initial warfarin dose to VKORC1 and CYP2C9 genotypes may decrease patient risk of bleeding complications and may reduce the time required to achieve a stable, therapeutic effect.^{12,14,15}

Recommendations: The FDA-approved label for warfarin recommends initial dosing based on VKORC1 and CYP2C9 genotypes in addition to clinical factors.¹⁶ The National Institutes of Health (NIH) Clinical Pharmacogenetics Implementation Consortium guidelines recommend initial dosing based on VKORC1 and CYP2C9 genotypes.¹¹

Standard doses of warfarin may cause bleeding complications in patients whose genotypes indicate increased or substantially increased sensitivity to warfarin. These patients may require lower initial doses of warfarin. Increased laboratory monitoring may be appropriate.

Classes of drugs that potentially interact with warfarin include the following:¹⁶ inhibitors or inducers of CYP2C9, CYP1A2 and/or CYP3A4, anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory agents, serotonin reuptake inhibitors, antibiotics, antifungals, and botanical (herbal) products and foods. This list is not complete. Consult the warfarin drug label¹⁶ and the labels of all concurrently used drugs for more specifics about warfarin drug interactions.

Possible Outcomes: Substantially Increased Sensitivity, Increased Sensitivity, Typical Sensitivity

Markers or Alleles Tested: VKORC1 -1639G>A [rs9923231]; CYP2C9 [CYP2C9*2/rs1799853, CYP2C9*3/rs1057910, CYP2C9*6/rs9332131]

Ethnic Distribution of Tested Alleles

Frequency of VKORC1 and CYP2C9 alleles differs significantly between racial and ethnic groups.¹⁷

Gene	Allele	Caucasian	African American	Asian	Hispanic
VKORC1	-1639: G	59.4%	89.2%	33.3%	56.4%
VKORC1	-1639: A	40.6%	10.8%	66.7%	43.6%
CYP2C9	*1	78.8%	86.7%	92.2%	82.2%
CYP2C9	*2	15.1%	2.8%	2.9%	6.9%
CYP2C9	*3	5.7%	2.0%	3.9%	6.4%
CYP2C9	*6	0.0%	1.0%	0.0%	0.5%

Predicted Warfarin Sensitivity Status

	VKORC1 -1639G>A genotype		
CYP2C9 genotype (below)	G/G	G/A	A/A
*1/*1	Typical sensitivity	Typical sensitivity	Increased sensitivity
*1/*2	Typical sensitivity	Increased sensitivity	Increased sensitivity
*1/*3	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*1/*6	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity

*2/*2	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*2/*3	Increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*2/*6	Increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*3/*3	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*3/*6	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*6/*6	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity

Limitations and Warnings: Warfarin can cause major or fatal bleeding. Additional genetic variants within VKORC1, CYP2C9, and other genes not included in this test are known to affect warfarin sensitivity. Not all genetic factors influencing warfarin sensitivity have been identified. Regular monitoring of INR (international normalized ratio) should be performed on all treated patients.

Not all factors influencing warfarin response are known. Important non-genetic factors include age, sex, weight, height, race, ethnicity, comorbidities, warfarin indication, target INR, and use of tobacco and interacting medications.¹¹

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
E934.2 Anticoagulants causing adverse effects in therapeutic use	N/A

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