Name of Policy:  
Genetic Testing for Non-Cancerous Inheritable Diseases

Policy #: 136  
Category: Laboratory  
Latest Review Date: February 2013  
Policy Grade: D

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
A genetic disorder is a disease caused in whole or in part by a mutation of a gene. Genetic disorders can be passed on to family members who inherit the genetic abnormality. A number of disorders are caused by a mistake in a single gene. Genetic testing can be diagnostic, prenatal, presymptomatic, predispositional, and pharmacogenetic.

Genetic tests attempt to identify abnormalities in an individual’s genes, which include the presence or absence of key proteins whose production is directed by specific noncoding RNAs. These abnormalities in either the presence or absence of proteins could indicate an inherited disposition for a disorder.

Genetic testing includes gene, DNA or RNA testing and biochemical or protein testing. Gene tests are performed on DNA taken from blood, body fluids or tissues and examined for the abnormality. Abnormalities may be large or small involving either a piece of a chromosome or an entire chromosome may be missing or added. Genes may be amplified, over-expressed, inactivated or lost. In some instances, genes may become switched, transposed or discovered in the wrong location. Biochemical testing evaluates the presence or absence of key proteins and metabolites that may indicate abnormal or malfunctioning genes.

**Policy:**
Genetic testing meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used to establish a molecular diagnosis of an inheritable disease when all of the following criteria are met:

- The individual displays clinical features or is at direct risk of inheriting the mutation in question based on family history or ethnic background (e.g. Ashkenazi Jews)
- **The result of the test will directly impact the treatment or management of the individual or other family members**
- After history, physical examination, pedigree analysis, genetic counseling, completion of appropriate conventional diagnostic studies, and a definitive diagnosis remains uncertain, genetic testing is medically necessary for the following diagnoses (this list is not all inclusive):

  - Albinism
  - Alpha thalassemia*
  - Angelman Syndrome
  - Beta thalassemia*
  - Canavan Disease
  - Charcot-Marie-Tooth (PMP22)
  - Classical Lissencephaly
  - Congenital Adrenal Hyperplasia
  - Dentatorubral-pallidoluysian atrophy
  - Duchenne Muscular Dystrophy
  - Dystonias (i.e., Sandifer syndrome, stiff person syndrome, Isaac syndrome)
  - Hereditary Deafness [(Connexin 26 Gene) (GJB2)]
  - Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)
  - Huntington’s disease
  - Kennedy Disease (SBMA)
  - Lowe Syndrome/Oculocerebrorenal dystrophy (OCRL)
  - MTHFR mutation (effective 01/01/13)
  - Myotonic Dystrophy
  - Niemann-Pick Disease
  - Neurofibromatosis Type I
Factor V Leiden mutation  Prader-Willi Syndrome
Fascioscapulohumeral Dystrophy (FSHD)  Prothrombin 20210A mutation
Fragile X Syndrome  Sickle Cell Anemia
Friedreich’s ataxia  Spinal Muscular Atrophy
Gaucher Disease  Tay-Sachs disease
Hemoglobin E thalassemia*  Thanatophoric dysplasia (FGFR3)
Hemoglobin S and/or C*  Von Hippel-Lindau Syndrome

*Electrophoresis is the appropriate initial laboratory test for individuals judged to be at-risk for a hemoglobin disorder.

In the absence of specific information regarding advances in the knowledge of mutation characteristics for a particular disorder, the current literature indicates that genetic tests for each mutation need only be conducted once per lifetime of the patient.

Testing should be performed in a setting that has adequately trained health care providers who can give appropriate pre-and post-test counseling and that has a qualified laboratory (See Key Points).

Medical Criteria for Disease Specific Genetic Testing

Genetic testing meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used to establish a molecular diagnosis of an inheritable disease when all of the following criteria are met:

- The individual displays clinical features or is at direct risk of inheriting the mutation in question based on family history or ethnic background (e.g. Ashkenazi Jews); and
- The result of the test will directly impact the treatment or management of the individual or other family members; and
- After history, physical examination, pedigree analysis, genetic counseling, completion of appropriate conventional diagnostic studies, and a definitive diagnosis remains uncertain; and
- Follows individual criteria for specific disease/diagnosis listed below

**CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy**

Genetic testing for CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when one or more of the following criteria are met:

- Patients with symptoms of CADASIL, i.e., history of migraines with aura, multiple subcortical ischemic events in the absence of hypertension and other vascular risk factors, progressive dementia, diffuse subcortical lesion in white matter on magnetic resonance imaging, and mood disorders, with or without a family history of the condition; or
- Pre-symptomatic individuals where there is a known mutation in an affected family member.
**Cystic Fibrosis**

**Genetic testing for the cystic fibrosis gene meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when one or more of the following criteria are met:
- The baby has significantly elevated immuno-reactive trypsinogen (IRT); **or**
- The baby is considered to have a positive screen for CF (one or two gene mutations are identified) and may be an asymptomatic carrier of the CF gene; **or**
- Parents of a baby with a positive CF gene, to determine if they are CF gene carriers; **or**
- Adults with a family history of CF; **or**
- Partners of people with CF; **or**
- Individuals with a family history of congenital bilateral absence of the vas deferens.

**Genetic testing for the cystic fibrosis gene for couples currently planning a pregnancy without any of the criteria listed above does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage unless there is a contract benefit specific for cystic fibrosis routine screening.

**Hereditary Pancreatitis**

**Effective for dates of service on or after March 3, 2011:**

**Genetic testing for hereditary pancreatitis using serine protease 1 gene (PRSS1) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in patients with pancreatitis when one or more of the following criteria are met:
- Relatives known to carry mutations associated with hereditary pancreatitis; **or**
- Idiopathic chronic pancreatitis or recurrent acute attacks of pancreatitis for which there is not identifiable cause when the onset of pancreatitis occurs before age 25; **or**
- An unexplained documented episode of pancreatitis as a child.

**Long QT Syndrome (LQTS)**

**Genetic testing for long QT syndrome (LQTS) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when one of the following criteria are met:
- Individuals have a prolonged QTc interval (corrected QT interval) on resting electrocardiogram of ≥ 450 msec in males and ≥ 470 msec in females and do not have an identifiable external cause for QTc prolongation, such as heart failure, bradycardia, electrolyte imbalance, certain medications, or other medical conditions; or a Schwartz score of 2-3; **OR**
- Individuals with a 1st degree relative (i.e., parents, full siblings, children) who have long QT syndrome or a defined LQT mutation; or whose genetic status is not known or unavailable

AND

- Testing is done for the following genes known to be associated with this condition: KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6); **OR**
- Testing for Brugada Syndrome (SCN5A, LQT3) has been expanded to include 6 additional genes for a total of 7 tested genes (GPD1L, CACNA1C, CACNB2, SCN1B, KCNE3, and SCN3B).
**Polycystic Kidney Disease**

Genetic testing for polycystic kidney disease meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for patients younger than 30 years of age when one or more of the following criteria are met:

- there are equivocal imaging results; or
- a definitive diagnosis is required (such as a potential living related donor).

**Non-Coverage Indications**

Genetic testing does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for the following, including but not limited to:

- **ACE gene polymorphisms** for the purpose of managing or treating diseases, including but not limited to cardiovascular disease, pulmonary disease, renal disease, diabetes mellitus and sarcoidosis.
- **Amyotrophic lateral sclerosis (ALS)**, also known as Lou Gehrig’s disease
- **Autism**
- **Glaucoma**
- **Hypertrophic cardiomyopathy (HCM)**
- **In-home or at-home genetics tests**
- **Lactose intolerance**
- **Pierson syndrome, congenital nephrotic syndrome**, for evaluating glomerular disease
- **Preimplantation genetic testing**, including screening (PGS) and diagnosis (PGD)

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

In August 2003, there were 579 laboratories testing for 998 genetic diseases, 643 of those are clinical and 355 are research only according to the GeneTests Web site that is funded by the National Institutes of Health, the Health Resources and Services Administration and the US Department of Energy. Genetic testing can only provide information about an inherited condition and also for many conditions there is the lack of treatment for many genetic disorders once diagnosed. Physical risks for testing are small, except in prenatal testing.
Genetic disorders are grouped by geneticists into three categories:

1. Single gene disorders caused by a mistake in a single gene such as sickle cell disease, cystic fibrosis and Tay-Sachs disease.
2. Chromosome disorders caused by an excess or deficiency of the genes such as Down syndrome.
3. Multifactorial inheritance disorders caused by a combination of small variations in genes, sometimes combines with environmental factors such as heart disease, most cancers and Alzheimer’s disease.

There are also numerous types of genetic testing. These include: carrier identification as in sickle-cell and cystic fibrosis; prenatal diagnosis as in Down syndrome; newborn screening as in phenylketonuria; late-onset disorder as in cancer, heart disease and Huntington’s disease; and identification as in unique identification of an individual.

Many of the non-cancerous genetic disorders are autosomal recessive mutations. There must be two copies of the gene present for the disorder to occur. The genetic status of both parents and/or spouse of an affected individual needs to be evaluated before information regarding potential risks to siblings or offspring can be provided. Retinoblastoma, for example, may occur without a family history or sporadically or it can be inherited with a family history.

Competence for ordering genetic testing should be required before permitting providers from ordering predictive tests as needing stringent scrutiny or to counsel about them. Laboratories performing genetic testing should be certified under CLIA, the Clinical Laboratory Improvement Amendments of 1988.

Genetic testing is contract dependent.

The following are critical issues should be addressed when genetic testing is to be performed responsibly and effectively in the care of patients with a possible inherited genetical disorder predisposition:

1. Counseling should be integrated into the role of the clinical medical geneticist.
   - During the evaluation and management or consultation of these patients, the following services should occur:
     ▪ Documentation of a family history for the possible inherited disorder;
     ▪ Counseling regarding familial disorder and options for prevention and early detection;
     ▪ Recognition of those families for which genetic testing may serve as an aid in appropriate counseling.

2. Counseling should be performed by a specialist who is appropriately sanctioned by a genetics credentialing organization (e.g. American Board of Genetic Counseling, Inc.) and who has been trained in the following:
   - Quantitative risk assessment;
   - Genetic testing;
   - Pre and post-test genetic counseling.

3. Proper informed consent must be obtained. Basic elements for informed consent include the following:
Information on the specific test being performed.
Implication of a positive or negative test result.
Possibility that the test will not be informative.
Options for risk estimation without genetic testing.
Risk of passing a mutation or predisposition to children.
Technical accuracy of the test.
Fees involved in testing and counseling.
Risks of psychological distress.
Risks of insurance or employer discrimination.
Confidentiality issues.
Options and limitations of medical surveillance and screening following the testing.

4. Indications for counseling and testing:
- The patient has a strong family history of disorder (specific criteria is required for each genetic test to satisfy this requirement),
- The test can be adequately interpreted.
- Result will influence medical management of the patient and/or family member.

5. Proper medical management, post-testing and counseling:
- Discuss possible risks and benefits of early detection and treatment modalities that are presumed but unproven efficacy for individuals at the highest hereditary risk.
- Encourage long-term research of outcome studies and/or cooperative studies or registries.

Amyotrophic lateral sclerosis (ALS)
Amyotrophic lateral sclerosis (ALS) sometimes called Lou Gehrig’s disease, is a rapidly progressive, invariably fatal neurological disease that attacks the nerve cells. This disease belongs to a group of disorders known as motor neuron disease, which are characterized by the gradual degeneration and death of motor neurons. As many as 20,000 Americans have ALS, and an estimated 5,000 people in the United States are diagnosed with the disease each year. ALS is one of the most common neuromuscular diseases worldwide, and people of all races and ethnic backgrounds are affected. In 90 to 95 percent of all ALS cases, the disease occurs apparently at random with no clearly associated risk factors. Patients do not have a family history of the disease, and their family members are not considered to be at increased risk for developing ALS. About 5 to 10 percent of all ALS cases are inherited. The familial form of ALS usually results from a pattern of inheritance that requires only one parent to carry the gene responsible for the disease. About 20 percent of all familial cases result from a specific genetic defect that leads to mutation of the enzyme known as superoxide dismutase 1 (SOD1). Research on this mutation is providing clues about the possible causes of motor neuron death in ALS. Not all familial ALS cases are due to the SOD1 mutation; therefore other unidentified genetic causes clearly exist.

Validation of the clinical use of any diagnostic test focuses on 3 main principles: 1) the technical feasibility of the test; 2) the diagnostic performance of the test, such as the sensitivity, specificity, PPV, and NPV in different populations and compared to the gold standard; 3) the clinical utility of the test, or how the results will be used to manage the patient.
The diagnostic performance is related to the interpretation of the results of the genetic analysis. The absence of an identified mutation does not imply absence of disease, since other mutations on different genes could potentially be involved. Also, the clinical significance of an identified mutation must be determined. The cardiac ion channel genes are quite large, and there may be numerous mutations discovered along the length. The discovered mutation can be compared to a growing database of known mutations, and if it is similar to one already identified in an affected patient, it is presumed that there is an increased risk that the mutation is pathogenic. However, there is varying penetrance of mutations and there is not necessarily a strong correlation between the genotype and the phenotype.

**Angiotensin Converting Enzyme (ACE) Gene Polymorphism**

The Angiotensin Converting Enzyme (ACE) insertion/deletion (I/D) polymorphism is one of the most widely studied genetic variants. It involves a 287-base pair insertion or deletion within intron 16 of the ACE gene. Although the clinical significance of this polymorphism remains controversial, the association with ACE enzymatic activity has consistently been demonstrated. Studies have shown that persons with the DD genotype have the highest ACE activity, heterozygotes (I/D) have intermediate levels and II genotype have the lowest levels of ACE activity. The relationship of the ACE gene I/D polymorphism has been explored in relation to numerous conditions including cardiovascular disease, (e.g., atherosclerosis, MI, CHF, HTN), stroke, pulmonary disease (e.g., pneumonia, ARDS), renal disease, sarcoidosis, diabetes, pancreatitis, ovarian disease, pediatric disease and others. The literature is replete with articles about the ACE gene polymorphisms and their relation to diseases and treatments.

Angiotensin-converting enzyme (ACE) inhibitors are widely used drugs for the treatment of hypertension, heart failure, and prevention of diabetic nephropathy. There is interest in these drugs because of a common polymorphism known to cause variations in serum ACE levels. The insertion/deletion (I/D) polymorphism has been noted to account for 47% of the variability in serum ACE levels. The DD genotype is seen in approximately one-third of the population. The I’D polymorphism has been studied as a risk factor for coronary artery disease; DD genotype may be a risk factor for myocardial infarction. The I/D polymorphism appears to be a strong predictor of ACE levels, which may be a predictor of cardiovascular outcomes, so interaction with ACE inhibitor treatment seems plausible. It is hypothesized that those with the DD genotype may be more responsive to ACE inhibitors. The ACE I/D polymorphism has also been studied in relation to other cardiovascular treatments, such as statins and beta blockers, with conflicting findings.

There are several published studies in the literature that investigate the interaction of ACE gene polymorphisms and pharmacogenomics interactions.

There are two recent reviews on the interaction of ACE gene polymorphisms and ACE inhibitor treatment. Scharplatz, et al (2005), reviewed 11 studies that examined the I/D polymorphism in relation to ACE inhibitor treatment. These studies had a wide variety of clinical indications and analyzed a variety of clinical endpoints and outcomes. The authors noted a trend toward better response to ACE inhibitors in Caucasian DD carriers. However, they noted the small number of studies and the lack of sufficient genetic data precluded drawing any convincing conclusions. Studies in Asian populations showed the opposite results, with DD carriers having worse outcomes with ACE inhibitor treatment.
Tsikouris and Peters (2007) published another review article that looked at ACE gene polymorphisms and ACE inhibitor therapy in patients with coronary artery disease. The authors evaluated 11 studies and reported the findings to be inconclusive and conflicting.

Arnett, et al (2005), reported on the GenHAT study that looked at ACE gene I/D polymorphism and pharmacogenomics interaction in 37,000 persons randomized to different classifications of hypertension medication. It was hypothesized those with the DD genotype randomized to ACE inhibitors would achieve superior outcomes compared to those assigned to other medications. They found that the ACE I/D polymorphism was not a predictor of any outcome, nor was there any interaction with the ACE inhibitor treatment. For one outcome, BP control, patients with the DD phenotype were less responsive to ACE inhibitors than other medications. The study cast doubts on the association between genotype and cardiovascular risk in general, and whether variations in serum ACE are associated with cardiovascular disease. The association between genotype and cardiovascular disease was inconsistent across studies, but a meta-analysis was consistent with a small effect.

Tascilar, et al (2009), reported on a study that looked at ACE I/D polymorphism in patients with large-vessel (n=97) and small-vessel (n=60) atherosclerotic stroke and in healthy subjects (n=85). The results showed a lack of association between stroke and ACE I/D polymorphism, and this did not change in the presence of traditional risk factors (hypertension, diabetes mellitus, smoking and dyslipidemia). The authors concluded that ACE I/D polymorphism did not predict the risk of stroke or hypertension in this population in Turkey.

The ACE gene polymorphism has also been studied in patients with sarcoidosis. The angiotensin-converting enzyme (ACE) is secreted by the epithelioid cells of sarcoid granulomas, and some patients with clinically active sarcoidosis exhibit elevated serum ACE levels. The serum ACE levels in normal and sarcoidosis patients are influenced by I/D polymorphism in the ACE gene. Average serum ACE levels are decreased in patients homozygous for the insertion (genotype II) and increased in patients without the insertion (genotype DD). This same pattern has been found in patients with sarcoidosis. An early report from Japan found an association of the D allele with the risk of sarcoidosis in females. However, most investigators could not confirm this finding. The ACE DD genotype has been found to be over-represented in African-American (AA) and in German patients with a family history of sarcoidosis.

Maliarik et al (1998), reported on the ACE gene polymorphism and sarcoidosis in African-Americans. They compared 183 AA cases and 111 control subjects. The results showed that in the risk for sarcoidosis was 1.3 for ID heterozygotes and 3.17 for DD homozygotes. The risk associated with DD homozygotes was even greater in AA with a positive family history. Further analyses of AA cases showed the ACE genotype was not associated with disease severity, extrathoracic involvement, or overall radiographic change two to four years after diagnosis. They concluded that the ACE genotype may play a more important role in sarcoidosis susceptibility and progression in AA than in Caucasians.

Pietinalho et al (1999), reported on the ACE genotype and prognosis in Finnish sarcoidosis patients. They looked at 59 Finnish sarcoidosis patients and 70 healthy control subjects and followed them for five years. The results showed that more patients with the DD genotype had a
poor prognosis compared with patients with II homozygotes and ID heterozygotes, and the result was statistically significant. The authors noted that larger studies are warranted.

Levels of serum ACE are used to determine disease activity in sarcoidosis. However, serum ACE levels are influenced by the D/I polymorphism, so the sensitivity and specificity of this test for disease monitoring are limited.

Schena, et al (2001), reported on the association of ACE gene polymorphism and IGA nephropathy in patients from Southern Italy. They evaluated 247 patients with IgAN and 205 healthy subjects and followed them for three years. The results showed no difference in the ACE I/D gene distribution between patients and controls and between patients with stable and those with deteriorating renal function.

van de Garde, et al (2008) reported on a study that examined whether the ACE I/D polymorphism affects the risk and outcome of community-acquired pneumonia (CAP) in a Dutch white population. There were 200 patients with pneumonia and 200 control subjects. All patients were genotyped, and pneumonia severity and clinical outcome were compared between patients with II, ID and DD genotypes of the ACE gene. Pneumonia severity was assessed using the acute physiology score (APS). The results showed that the APS scores were not different between the genotype groups on any of the days, and all clinical outcomes were comparable between the three genotype groups on any of the days, and all clinical outcomes were comparable between the three genotype groups. The ACE I/D genotype distribution was identical for patients and control subjects. The ACE I/D polymorphism was not associated with risk and outcome of CAP in this population.

**Autism**

At present there are no specific genetic tests for autism. Research is ongoing to correlate clinical phenotypes with specific genetic profiles. If such correlations can be made it is likely that in the future, there will be genomic screening panel for autism. The American Academy of Pediatrics (AAP) and the American Academy of Neurology (AAN) and Child Neurology Society have some general guidelines but have some slight differences:

1. The AAN guidelines recommend high resolution chromosome studies (karyotype) and DNA analysis for Fragile X for individuals with autism and mental retardation, in those in whom mental retardation cannot be excluded, if there is a family history of Fragile X syndrome or undiagnosed mental retardation, or if dysmorphic features are present.
2. The AAP guidelines suggest that genetic testing (e.g., chromosomal analysis, subtelomeric FISH, and specific Fragile X testing) may be indicated in children with ASD and coexisting global developmental delay/mental retardation.

The National Guideline Clearinghouse also has the same information per the American Academy of Neurology and the Child Neurology Society regarding genetic testing in children with autism: High resolution chromosome studies (karyotype) and DNA analysis for Fragile X, should be performed in the presence of mental retardation (or if mental retardations cannot be excluded), if there is a family history of Fragile X or undiagnosed mental retardation, or if dysmorphic features are present. However there is little likelihood of positive karyotype or Fragile X testing in the presence of high-functioning autism.
An article by Lintas and Persico discusses autism and genetic testing including the MECP2 gene mutation. In females, the MECP2 gene mutation occurs in 80% of patients with Rett syndrome, whereas in males this mutation is generally lethal. These mutations are rare in the autistic population, accounting for 0.8-1.3% of cases in female autism spectrum disorder (ASD) patients. This test is usually performed in girls with ASD and mental retardation. Therefore with the low percentage found these tests would not be covered.

Miles and McCathren published an overview of autism. For individuals with secondary autism, genetic counseling is based on information relevant to the primary diagnosis. For idiopathic autism, the empiric aggregate risk to siblings is 4% for autism and an additional 4 to 6% risk for milder conditions, including language, social and psychiatric disorder. For families with two or more affected children, the recurrence risk approaches 35%. Male siblings of a proband (clinically affected individual through whom a family is found that can be used to study the genetics of a particular disorder) with essential autism have a 7% risk for autism and additional 7% risk for milder ASD. Female siblings of a proband with essential autism have a 1% risk for autism. The risk for a milder ASD spectrum disorder is unknown. The recurrence risk of ASD to siblings of a proband with complex autism is1% for autism and an additional 2% for a milder ASD. Only about 3% of individuals with autism have a maternally inherited chromosomal duplication in the Prader-Willi syndrome/Angelman syndrome region of 15q11-q13. Children with Down syndrome have autism more commonly than expected.

**Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)**

**June 2010 update**

CADASIL is characterized by a history of migraine headaches, mid-adult onset of cerebrovascular disease progressing to dementia, and diffuse white matter lesions and subcortical infarcts on neuroimaging. CADASIL is inherited in an autosomal dominant manner. The prevalence of CADASIL had been estimated to be 1.98 per 100,000 adults. The initial clinical manifestations of CADASIL are usually either migraine typically with aura or ischemic episodes. Deficits in cognition and demential are also observed in later stages. The clinical course of CADASIL is highly variable even in patients from the same family. The penetrance of sequence variants in the NOTCH3 gene is thought to be close to 100% in addition to genetic testing, diagnosis of CADASIL can be made through neuroimaging or skin biopsy.

There is no treatment for CADASIL. Supportive therapies aimed at symptom amelioration and decreasing stroke risk is appropriate for affected individuals. Aspirin is frequently used to treat CADASIL because of its low complication rate. Anticoagulants and angiography are contraindicated in these patients. Smoking has been noted to increase the risk of strokes in CADASIL patients and should be avoided.

Genetic testing for CADASIL is available in the United States through Athena Diagnostics Inc. and is called the Complete CADASIL Evaluation #421; it provides a complete analysis of all 23 exons in which sequence variants are known to cause CADASIL.
September 2011 Update
Mosca et al (2011) performed mutation analysis of the NOTCH3 gene through direct sequencing in 140 patients with clinical suspicion of CADASIL. Patients underwent genetic counselling pre and post testing. The two to 23 exons containing all EGF-like domains were screened. Fourteen familial forms of the disease have been identified with 14 different causative mutations in exons 2, 3, 4, 5, 7, 10, 14, 19, 20 and 22 of the NOTCH3 gene; no pathogenetic mutations have been identified in exons six and eight; several genetic variations both in coding as well as in intronic regions were identified too. Their data confirm the importance of screening the whole EGF-like domains region of NOTCH3 gene for the molecular diagnosis of CADASIL among the Italian population too. Moreover genetic variants different from loss or gain of a cysteine residue are identified and presented.

Summary for CADASIL
NOTCH3 mutations are found to be the cause of CADASIL in the majority of patients with the syndrome. The diagnostic accuracy of NOTCH3 cannot be determined with certainty due to the lack of a true gold standard for diagnosis of CADASIL. However, a high percentage of patients in whom CADASIL is diagnosed by clinical methods will have a NOTCH3 mutation on genetic testing. Conversely, NOTCH3 mutations are not commonly found in unaffected individuals.

Testing with NOTCH3 has uncertain clinical utility. The diagnosis of CADASIL can often be made by a combination of clinical presentation, MRI findings, and skin biopsy findings. In such cases, NOTCH3 testing is not necessary for diagnosis. In other cases, the diagnosis cannot be made on the basis of clinical presentation, MRI, and skin biopsy results. In these cases, NOTCH3 testing may be useful in confirming or excluding the diagnosis of CADASIL.

However, there is no effective treatment for CADASIL, so that establishing a definitive diagnosis of CADASIL will not change management. Knowledge of the presence of a NOTCH3 mutation may lead to changes in lifestyle decisions for the affected individual, for example in the areas of reproduction and employment. Therefore, testing of an index case for NOTCH3 can assist in predictive testing for family members, since it can then be determined if family members have inherited the same NOTCH3 mutation present in the index case.

Congenital Adrenal Hyperplasia (CAH)
Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by deficiency in one or more of the enzymes required for synthesis of cortisol, aldosterone, and sex steroids in the adrenal gland. There are at least five gene mutations associated with various forms of CAH. The most frequent form of CAH, 21-hydroxylase deficiency (21-OHD), is associated with gene mutations in CYP21A2 and accounts for 90% to 95% of all cases. Other gene mutations include CYP11B1, CYP17A1, HSD3B2 and STAR. Nimkarn and New (2009) reported that the most common form of CAH, 21-OHD, in its most severe form can cause genital ambiguity in females. Affected females experience virilization both physically and psychologically. Steroid 21-OHD can be diagnosed in utero through molecular genetic analysis of fetal DNA. Appropriate prenatal treatment by dexamethasone administration to the at-risk pregnant mother is effective in reducing genital virilization in the fetus, thus avoiding unnecessary genitoplasty in affected females. Current data from large human studies show that prenatal diagnosis and treatment are safe in the short term for both the fetus and the mother. Preliminary data from long-term studies support these results.
**Congenital Nephrotic Syndrome**

Pierson syndrome is a rare autosomal recessive condition defined by severe nephrosis presenting in early infancy accompanied by distinct ocular abnormalities. It is caused by mutations in the laminin B2 gene, LAMB2. Laminin B2 is part of a complex of glycoproteins in the renal glomerular basement membrane. Clinically, it is characterized by congenital nephrotic syndrome (CNS) that may progress to end-stage renal failure and ocular abnormalities including cataracts, anterior chamber and iris abnormalities, and progressive blindness due to retinal detachment.

Danderpani and Pollak (2006) published a review of the biologic and genetic complexity of the glomerular filtration barrier. They noted that there are several known congenital nephrotic syndrome genes and mutations in the same gene may lead to different phenotypes. The spectrum of genetic lesions underlying congenital nephrotic syndrome has yet to be fully defined. They noted that there is a large spectrum of inherited proteinuric disorders ranging from the relatively mild proteinuria and slowly progressive renal failure to severe congenital nephrosis. Further work is needed to define the precise downstream effects of these mutant or absent proteins to explain this variability. They noted that as our understanding of other genetic etiologies of nephrosis increased, so will our understanding of their prognostic and therapeutic implications. The authors noted that careful analysis of single gene disorders will continue to provide some informative insights into disease mechanisms. There is no current peer-reviewed literature that addresses changes in treatment options or outcomes for congenital nephrotic syndrome as a result of genetic testing.

**Cystic Fibrosis**

The Centers for Disease Control and Prevention (CDC) released recommendations for screening of newborns for cystic fibrosis (CF). The report also includes an evaluation of the benefits and risks of this type of screening program. Many states offer newborn screening for CF as part of the newborn testing programs.

Newborn screening for CF consists of multiple protocols and algorithms that all begin with measuring immunoreactive trypsinogen (IRT) in a dry blood heel-stick sample. Infants with elevated IRT values are referred for further testing. Depending on the state in which the testing is done, the next test following an elevated IRT may be a repeat IRT (IRT-repeat IRT protocol) or DNA analysis (IRT/DNA algorithm). Infants with an elevated repeat IRT or who have one or more cystic fibrosis transmembrane regulator (CFTR) mutations found on DNA analysis would then be referred for sweat testing.

In January 2008, the Alabama Department of Health will be adding CF to the Newborn Screening Panel for every child born Alabama.

**Glaucoma**

Alward, et al, discussed the prevalence of variations in the myocilin gene in patients with primary open-angle glaucoma (POAG) in a study that included 779 patients and 524 with POAG. 3.2% had a disease-causing sequence (DCV) in the POAG group and 6.4% in the juvenile-onset group. None of these values were statistically significant. They concluded that for a genetic test to be useful, it must be able to identify subjects at risk in a population of disease
carriers at a high rate. DCVs in the myocilin gene were found in only 3% of the glaucoma population with no differentiation between types. The authors concluded that screening for it would not help predict people at risk for glaucoma. More research on genetic testing for glaucoma is required before it can be an effective tool.

Cohen and Allingham in 2004 reviewed recent trends for patents with glaucoma. They stated some investigators have found that the myocilin gene may increase disease severity in patients with POAG, whereas others have not found this association. Genetic testing for glaucoma holds promise but currently available tests for disease related tests in patients with glaucoma or at risk for this disease remain controversial.

Mackey and Craig also wrote that to use DNA testing to identify individuals at high risk for glaucoma, it is necessary to have solid evidence with sensitivity and specificity parameters, genotype-phenotype correlations, and information on prevalence and penetrance. These data will have to be replicated in several studies using large, population-matched control groups.

There are complicated technical and ethical issues associated with preimplantation genetic diagnosis. Assisted reproductive techniques may be subject to specific contractual restriction.

**Hereditary Pancreatitis (HP)**
Autosomal dominant hereditary pancreatitis is most often associated with mutations in the serine protease 1 gene (PRSS1) on chromosome 7q35, which encodes cationic trypsinogen. Rarely is autosomal-dominant-appearing hereditary pancreatitis identified in a kindred that does not have an identifiable PRSS1 mutation. This disorder has high penetrance and causes chronic pancreatitis in both children and adults. Since PRSS1 mutations are inherited in an autosomal dominant manner, 50% of the offspring of carriers inherit the mutation. The onset of symptoms is early, with median age of onset being 13 years. More than 50% of families who have HP have PRSS1 mutations, and 70% to 80% of patients with R122H and N291 mutations develop pancreatitis. Genetic testing for nonsyndromic pancreatitis may significantly alter an individual’s choices and the medical management of their disease. Pretest and post-test counseling are essential for patients and families fully to benefits from genetic testing for a susceptibility to develop pancreatitis.

**Hypertrophic Cardiomyopathy (HCM)**
Hypertrophic cardiomyopathy is the most common identifiable cause of sudden death in the young. Cardiomyopathy is a condition in which the muscle of the heart is abnormal in the absence of an apparent cause. There are three types of cardiomyopathy: hypertrophic, dilated, and restrictive. The main feature of hypertrophic cardiomyopathy is an excessive thickening of the heart muscle. Diagnosis of HCM is most often established when two-dimensional echocardiography detects left ventricular hypertrophy (LVH) in a non-dilated ventricle or electrocardiography; it can also be established by pathognomonic histopathologic findings in cardiac tissue. HCM can occur without symptoms, but others may experience dyspnea, angina and palpitations. There is usually a gradual progression symptoms but can result in sudden death or severe heart failure may occur.

Genetic testing is now being considered by some an important part of diagnosis, particularly in familial HCM. The identification of gene mutations for HCM has led to the development of
DNA-based testing of patients with HCM to aid diagnosis and management of patients. Per a review by uptodate.com the use of genetic testing still has issues that result in a poor recommendation. This article cites that all genes responsible for HCM have not yet been identified. In addition, among some genes that have been identified, the spectrum of possible disease-causing mutations is still incomplete. There is also evidence that some patients are compound heterozygotes (inherit two different mutations within a single HCM gene), double heterozygotes, or homozygotes. It is also noted that even in a known heterogeneity with clinical manifestations of a given mutation that the clinical course cannot be predicted with any degree of certainty. Rapid gene tests for HCM are also available that are capable of identifying some but not all genetic causes of the disease. There has not yet been a clear role defined by genetic testing and screening for HCM and therefore this testing is not covered at this time.

**Long QT Syndrome**
Congenital long QT syndrome (LQTS) is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential, resulting in prolongation of the QT interval. This leads to an increased risk for arrhythmic events, such as torsades de pointes, which may in turn result in syncope and sudden cardiac death. Management has focused on the use of beta-blockers as first-line treatment, with pacemakers or implantation cardioverter defibrillators (ICD) as second-line therapy.

Genetic testing for LQTS is recognized as an important research tool, but there is still discussion on whether the results can be used to improve patient management. At present, the initial treatment for LQTS is typically beta-blocker therapy, although this strategy has never been tested in controlled trials, and several authors caution that there is still a high rate of cardiac events in patients on beta-blocker therapy. Other treatment options include left-sided cardiac sympathetic denervation, pacemakers, or implantable cardioverter defibrillator (ICD). The bulk of the published literature consists of retrospective studies and there are no articles in which genotypic analysis was used in the management of the patient. Genetic testing has been used in several different clinical situations. It has been used in symptomatic patients with clinically diagnosed LQTS to determine the subtype. It has also been used in an asymptomatic family member who has a relative with LQTS with known genotype.

Congenital LQTS usually manifests itself before the age of 40 years, and may be suspected when there is a history of seizure, syncope, or sudden death in a child or young adult; this history may prompt additional testing in family members. It is estimated that more than one half of the 8,000 sudden unexpected deaths in children may be related to LQTS. The mortality of untreated patients with LQTS is estimated at 1%-2% per year, although this may vary with genotypes. Frequently, syncope or sudden death occurs during physical exertion or emotional excitement, and there has been some discussion about LQTS with regard to evaluation of adolescents for participation in sports. Also, LQTS may be considered when a long QT interval is incidentally observed on an EKG. Diagnostic criteria for LQTS have been established, and focus on EKG findings and clinical and family history. The corrected QT interval (QTc) is LQTS is usually > 0.46 sec in men and > 0.47 sec in women, although 1/3 of affected individuals may have QTc intervals that fall within the normal or non-diagnostic range. Typical ST-T wave patterns are also suggestive of specific subtypes.
The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS. The most recent version of this scoring system is shown in the Table. A score of four or greater indicates a high probability that LQTS is present; a score of 2–3 an intermediate probability; and a score of one or less indicates a low probability of the disorder. Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; therefore, the accuracy of this scoring system is ill-defined.

<table>
<thead>
<tr>
<th>Table. Diagnostic Scoring System for LQTS (Adapted from reference 3) Criteria</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Electrocardiographic findings</td>
<td></td>
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<tr>
<td>*QTc &gt;480 msec</td>
<td>3</td>
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<td>*QTc 460-470 msec</td>
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<td>*QTc &lt;450 msec</td>
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<tr>
<td>History of torsades de pointes</td>
<td>2</td>
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<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T-waves in three leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
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<tr>
<td>*Syncope brought on by stress</td>
<td>2</td>
</tr>
<tr>
<td>*Syncope without stress</td>
<td>1</td>
</tr>
<tr>
<td>*Congenital deafness</td>
<td>0.5</td>
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<tr>
<td>Family history</td>
<td></td>
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<tr>
<td>*Family members with definite LQTS</td>
<td>1</td>
</tr>
<tr>
<td>*Unexplained sudden death in immediate family members younger than 30 years of age</td>
<td>0.5</td>
</tr>
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</table>

Currently, there are four recognized LQT syndromes: the Romano-Ward syndrome (RWS), Jervell and Lange-Nielsen syndrome (JLN), Andersen-Tarvil syndrome, and Timothy syndrome. The RWS, (i.e., familial occurrence with AD inheritance, QT prolongation, and ventricular tachyarrhythmias) is the most common form and accounts for 85% of all LQTS cases. It is not associated with extracardiac manifestations, and may be difficult to detect clinically. Three phenotypes have been described and mutations in at least five different genes have been identified. The JLN syndrome (i.e., familial occurrence with AR inheritance) is associated with congenital deafness, marked QT prolongation, and ventricular arrhythmias.

In recent years, advances in molecular genetics and basic research have established that LQTS is an inherited disorder of cardiac ion channels. Abnormalities in the sodium and potassium channels that control the excitability of the cardiac myocytes leads to delayed repolarization of cardiac muscles, and prolongation of the QT interval on EKG. A genetic basis for LQTS has also emerged, with at least eight genes being associated with LQTS. Also, several hundred unique mutations have been identified within these genes. Some of the genotypic designations are as follows: LQT1 is the most common form and is associated with mutations in the gene KCNQ1 located on chromosome 11. It is responsible for about 45% of genotyped patients. The most common trigger for a cardiac event in these patients is exercise (particularly swimming), followed by emotional stress (fear, anger, or startle response). More than 80% of patients have a
first cardiac event by age 20. Patients with LQT1 may be advised to minimize exercise. LQT2 is associated with mutations in the gene KCNH2 located on chromosome 7 and accounts for 40% of genotyped patients. Arrhythmic events appear to be precipitated by auditory stimuli, and these patients may be advised to avoid clock alarms, etc. LQT3 is associated with mutations in the SCN5A located on chromosome 3. This subtype is seen in 3%-4% of patients with LQTS. Most events in LQT3 patients occur during sleep or rest, suggesting they are at higher risk at slow heart rates. LQT3 variant is also known as the Brugada syndrome. LQT5 and 7 involve KCN genes located on chromosomes 21 and 17. These variants each account for <1% of LQTS. LQT4 involves ANK genes on chromosome 4. LQT8 involves LAC genes located on chromosome 12.

The Familion Test describes the analysis of the genes responsible for subtypes LQT 1-5. This test has been used in a variety of situations. If a person has been diagnosed with LQTS based on clinical characteristics, complete analysis of all five genes can be performed to identify the specific mutation and the subtype of LQTS. If a mutation is identified, then additional family members can undergo a focused genetic analysis for the identified mutation. If a specific type of LQTS is suspected based on the EKG abnormalities, and genetic testing can focus on the individual gene.

All of the LQTS genes are large, and genetic testing has revealed multiple different mutations along their length. The pathophysiologic significance of each of the discrete mutations is an important part of the interpretation of genetic analysis. Genaissance, the laboratory offering the Familion test, compares the results to the Genaissance Cardiac Ion Channel Variant Database, which includes data from over 750 individuals of diverse ethnic backgrounds. Therefore, the chance that a specific mutation is pathophysiologically significant is increased if it is the same mutation as that reported in several other cases of known LQTS. Some of the detected mutations may be of unknown significance. Also, the absence of a mutation does not imply the absence of LQTS. It is estimated that mutations are only identified in 60%-70% of patients with a clinical diagnosis. Another factor complicating interpretation of genetic analysis is the penetrance of a given mutation or the presence of multiple phenotypic expressions. For example, 50% of carriers of a mutation never have any symptoms.

PGxHealth Familion has published information that testing for Brugada syndrome (BrS) a member of the ion channel disease of LQTS. LQT3 is associated with mutations in the gene SCN5A located on chromosome 3. This subtype is seen in 3%-4% of patients with LQTS. In this subtype, the majority of cardiac events occur during sleep. LQT3 variant is also known as the Brugada syndrome. The gene previously analyzed by the current test is SCN5A. PGxHealth has recommended an expansion of the FAMILION BrS test to include an additional six genes bringing the total number of tested genes to seven. These genes are recommended for inclusion due to their ability to identify additional patients with a high index of clinical suspicion for BrS. This will result in an increased sensitivity of the FAMILION BrS test to detect a disease-causing mutation in 25%-40% of patients with a high index of clinical suspicion for BrS. In addition to the SCN5A gene, the expanded BrS tests will analyze the following genes: GPD1L, CACNA1C, CACNB2, SCN1B, KCNE3, and SCN3B. This expanded testing began on May 15, 2010.
There are many articles published in the peer-reviewed literature that discuss genetic testing for LQTS. Genetic testing has been used to establish a diagnosis of LQTS and to identify specific subtypes of LQTS and/or specific genetic mutations.

Zareda, et al (1998), looked at the genotypes of 246 patients with LQTS and determined the cumulative probability and lethality of cardiac events occurring from birth-age 40 years. The results showed the frequency of cardiac events was higher among subjects with mutations at the LQT1 locus (63%) or LQT2 locus (46%) than among subjects with mutations at the LQT3 locus (18%).

Schwartz, et al (2001), reported on the incidence of cardiac events in 670 LQTS patients with known genotype LQT 1-3. The results showed that patients with LQT1 had a lower cardiac event rate (28%) than LQT2 (40%) or LQT3 (49%).

Priori, et al (2003), looked at the risk of cardiac events based on genotype in 647 LQTS patients. The results showed that the incidence of a first cardiac event before age 40 and before therapy was lower in LQT1 patients (30%) than in LQT2 patients (46%) or LQT3 patients (42%).

Priori, et al (2004), reported on the incidence of cardiac events in 335 LQTS patients with known genotype, treated with beta-blockers. The results showed the incidence of cardiac events was lower in LQT1 patients (10%) than in LQT2 patients (23%) or LQT3 patients (32%).

Tester, et al (2006) looked at the sensitivity and specificity of genetic testing compared with clinical methods. They looked at 274 patients who had a LQTS mutation and compared the genetic diagnosis with the clinical diagnosis, defined as a Schwartz score of ≥ 4. They reported a sensitivity of 72% and specificity of 57% for the genetic testing.

Hofman, et al (2007), looked at the sensitivity and specificity of various clinical methods used to make the diagnosis of LQTS, as compared with genetic testing. They looked at 513 relatives of 77 probands with known disease-causing mutation. The results showed the Schwartz criteria, using a score ≥ 4, had 19% sensitivity and 99% specificity. The Keating criteria had a 36% sensitivity and 99% specificity. Analyzing the QTc duration alone, using a cutoff ≥ 430 msec, had 72% sensitivity and 86% specificity. They concluded that in genotyped families, genetic testing is the preferred diagnostic test.

**Summary for Long QT genetic testing**

A genetic mutation can be identified in approximately 70-75% of patients with LQTS. The majority of these are point mutations that are identified by gene sequencing analysis, however a small number are deletions/duplications that are best identified by chromosomal microarray analysis (CMA). The clinical validity of testing for point mutations by sequence analysis is high, while the clinical validity of testing for deletions/duplications by CMA is less certain.

The clinical utility of genetic testing for LQTS is high when there is a moderate to high pre-test probability of LQTS and when the diagnosis cannot be made with certainty by other methods. A definitive diagnosis of LQTS leads to treatment of LQTS with beta blockers in most cases, and sometimes to treatment with an ICD. As a result, confirming the diagnosis of LQTS will lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and sudden cardiac...
death. The clinical utility of testing is also high for close relatives of patients with known LQTS, since these individuals should also be treated if they are found to have a pathologic LQTS mutation. Therefore, genetic testing for the diagnosis of LQTS is medically necessary for the following individuals who do not have a clinical diagnosis of LQTS but who have: 1) a close relative (i.e., first-, second-, or third-degree relative) with a known LQTS mutation, 2) a close relative diagnosed with LQTS by clinical means whose genetic status is unavailable, or 3) signs and/or symptoms indicating a moderate-to-high pretest probability of LQTS. For all other indications, including prognosis and management of patients with known LQTS, genetic testing is considered investigational.

**Lowe Syndrome**

Wasserstein reports that in 1952, Lowe et al described an infant with congenital cataracts and mental retardation. When more patients were described, the phenotype was expanded to include the renal Fanconi syndrome, and the X-linked inheritance pattern was noted. The diagnostic triad of the oculocerebrorenal syndrome of Lowe (OCRL) includes congenital cataracts, neonatal or infantile hypotonia with subsequent mental impairment, and renal tubular dysfunction. OCRL is inherited in an X-linked fashion. Most patients are male, only a few females have been reported.

Dystonia refers to syndrome of involuntary sustained or spasmodic muscle contractions involving co-contraction of both the agonist and the antagonist. The movements are usually slow and sustained. They often occur in a repetitive and patterned manner, but they can be unpredictable and fluctuate. The frequent abnormal posturing and twisting can be painful and functionally disabling. Primary or idiopathic dystonia can manifest in a sporadic, autosomal dominant, autosomal recessive, or X-linked recessive manner. Heritable childhood-onset dystonia is particularly common among Ashkenazi Jewish people. Currently at least 12 types of dystonia can be distinguished on a genetic basis. Genetic screening for DYT gene abnormalities and genetic counseling is important for patients with an onset of primary dystonias at younger than 30 years or those who have an affected relative.

**Polycystic Kidney Disease**

Autosomal dominant polycystic kidney disease (ADPKD) is a common disorder, occurring in approximately one in every 400 to 1000 live births. Approximately 85% of families with ADPKD have an abnormality on chromosome 16 (PKD1 locus) that is tightly linked to the alpha-globin gene locus. The other patients have a different defect that involves a gene on chromosome 4 (the PKD2 locus).

Patients with PKD2 have a less severe phenotype than those with PKD1, but neither disorder is benign. Cysts occur later in PDK2 disease, as does end-stage renal disease. As a result, false negative results are more likely when screening young subjects with PKD2 disease.

The diagnosis of ADPKD relies principally upon imaging of the kidney. Ultrasonography is most commonly used as the imaging modality. Typical findings include large kidneys and extensive cysts scattered throughout both kidneys. Genetic testing may be needed in some cases for a definitive diagnosis.

The current methods used to perform genetic testing are linkage or sequence analysis of DNA:
Linkage analysis uses microsatellite markers that flank the PKD1 and PKD2 genes. The technique requires the accurate diagnosis in an adequate number of known family members (at least four) who are willing to be tested. Linkage analysis is therefore suitable in less than one-half of families.

Direct DNA analysis of the PKD1 and PKD2 genes is hampered by their immense size, complexity, and allelic heterogeneity. With both genes, mutation detection rates of approximately 65 to 70 percent have been reported with denaturing high-performance liquid chromatography (DHPLC). Direct sequencing is associated with rates of approximately 85 to 90 percent. However, whether a mutation is associated with pathogenicity is unclear since most changes are unique and missense changes in PKD1 constitute nearly one-third of all mutations.

A study by Zhao, et al, showed that a combined approach using both modalities may be most effective. Genetic linkage and direct DNA analysis was most effective among two prospective kidney donors with a positive family history and, the use of both linkage and DNA sequencing was required to definitively exclude the presence of ADPKD.

**Preimplantation genetic testing**

Preimplantation genetic diagnosis (PGD) describes a variety of adjuncts to an assisted reproductive productive procedure in which either maternal or embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect prior to implantation of the embryo into the uterus. The ability to identify preimplantation embryos with genetic defects before the initiation of pregnancy provides an attractive alternative to amniocentesis or chorionic villus sampling (CVS) with selective pregnancy termination of affected fetuses. Preimplantation genetic testing is generally categorized as either diagnostic (PGD) or screening (PGS). PGD is used to detect genetic evidence of a specific inherited disorder, in the oocyte or embryo, derived from mother or couple, respectively that has a high risk of transmission. PGS is not used to detect a specific abnormality but instead uses similar techniques to identify genetic abnormalities to identify embryos at risk. This terminology, however, is not used consistently e.g., some authors use the term preimplantation genetic diagnosis when testing for a number of possible abnormalities in the absence of a known disorder.

A number of trials related to preimplantation genetic screening (PGS) have been published and results of the studies have been summarized.

In 2007, Mastenbroek et al, in a randomized controlled trial, found that preimplantation genetic screening reduced the rates of ongoing pregnancies and live births after IVF in women of advanced (aged 35 through 41 years) maternal age. In this study, 408 women (206 assigned to PGD and 202 assigned to the control group) underwent 836 cycles of IVF (434 cycles with and 402 cycles without PGS). The ongoing pregnancy rate was significantly lower in the women assigned to PGS (52 of 206 women [25%]) than in those not assigned to PGS (74 of 202 women [37%]; rate ratio, 0.69; 95% confidence interval [CI]: 0.51–0.93). The women assigned to PGS also had a significantly lower live-birth rate (24% vs. 35%, respectively; rate ratio, 0.68; 95% CI: 0.50–0.92). In 2011, a follow-up study was published when surviving children were two years old. Forty-nine pregnancies in the PGS group and 71 in the control group resulted in live births of at least one child. Forty-five couples with 54 children (36 singletons and nine
twins) in the PGS group and 63 couples with 77 children (49 singletons and 14 twins) in the control group were available for follow-up. The groups of children did not differ significantly in scores on an infant development scale and child development checklist variables. For example, median scores on the total Child Behavior Checklist were 43.0 among children born after PGS and 46.0 in control children, p=0.44. However, the neurologic optimality score (NOS) was significantly lower in the PGS group than the control group, p=0.20. In the PGS group, there were four children (7%) classified as having simple minor neurologic dysfunction (MND), two (4%) with complex MND and one (2%) with cerebral palsy. In the control group, three (4%) children had simple MND, one (1%) had complex MND and there were no cases of cerebral palsy. Simple MND referred to the isolated presence of fine motor, gross motor of visuomotor dysfunction or mild dysregulation of muscle tone and complex MND to dysfunction in two or more of these domains.

In a 2008 editorial commentary, Fritz reviews five trials examining the impact of PGS on outcomes in women of advanced maternal age and four trials in patients having a generally good prognosis, and notes that all studies have failed to demonstrate any clear benefit for PGS. Fritz comments that while PGS should work, after a decade of experience there is no substantive evidence to indicate that it does work. Possible reasons for these findings include potential adverse effects of biopsy on implantation or developmental potential, transfer of presumed normal embryos that were aneuploid for one or more chromosomes that were not analyzed, and misdiagnoses due to interpretation errors or due to mosaicism. The commentary concludes that lack of technical prowess does not explain these findings.

In a second editorial commentary, Fauser notes that none of the reported randomized controlled trials (RCTs) demonstrate a benefit with PGS, whereas two studies suggest worse outcomes. He notes that well-designed studies failed to demonstrate a clinical benefit of PGS in IVF. Issues that need to be addressed, in the author’s view, include better understanding of mosaicism, improving PGS related to studying all chromosomes in a reliable manner, and determining the optimal timing for removal of one or more cells. Fauser does note that PGS may be useful as a marker for embryo quality in studies focusing on the biology of ovarian function related to IVF.

A randomized trial published in 2009 included “good prognosis” patients (similar to the general IVF population in the Checa meta-analysis) undergoing in vitro fertilization. This was defined as women with age younger then 39 years, normal ovarian reserve, body mass index less than 30 kg/m2, presence of ejaculated sperm, normal uterus and no more than two previous failed IVF cycles. Women were randomly assigned to receive PGS (n=23) or implantation without PGS on day three (n=24) after oocyte retrieval. There was no significant difference between groups in PGS and control groups in terms of clinical pregnancy rate (52.4% vs. 72.7%, respectively). However, there was a significantly lower rate of embryo implantation in the PGS group than the control group (31.7% vs. 62.3%, respectively, p=0.004). There was also a significantly lower live birth rate in the PGS group (28.6% vs. 68.2%, respectively, p=0.009). The investigators originally planned to enroll 100 women per group, but the study was terminated early because of results from a planned interim analysis.

Debrock et al in Belgium, published a trial in 2010 that included women of advanced (at least 35 years) maternal age who were undergoing in vitro fertilization to undergo preimplantation
genetic screening or implantation without PGS. Randomization was done by cycle; 52 cycles were randomized to the PGS group and 52 to the control group. Cycles were excluded if two or fewer fertilized oocytes were available on day one after retrieval or if two or fewer embryos of six or more cells were available on day three. Individuals could participate more than once and there was independent randomization for each cycle. More cycles were excluded postrandomization in the control group; outcome data were available for 37 cycles (71%) in the PGS group and 24 cycles (46%) in the control group. Study findings did not confirm the investigators’ hypothesis that the implantation rate would be higher in the group receiving PGS. The implantation rate was 15.1% in the PGS group and 14.9% in the control group; p=1. Moreover, the live-birth rate per embryo transferred did not differ significantly between groups; rates were 9.4% in the PGS group and 14.9% in the control group; p=0.76. An intention-to-treat (ITT) analysis of all randomized cycles (included and excluded) did not find any significant differences in outcomes including the implantation rate which was 11 of 76 (14.5%) in the PGS group and 16 of 88 (18.2%) in the control group, p=0.67. In the ITT, the live-birth rate per embryo transferred was 7 of 47 (14.9%) in the PGS group and 10 of 49 (20.4%) in the control group, p=0.60.

Summary for preimplantation genetic testing
Preimplantation genetic testing has been shown to be technically feasible in detecting single gene defects, structural chromosomal abnormalities, and aneuploid embryos using a variety of biopsy and molecular diagnostic techniques. In terms of health outcomes, small case series have suggested that preimplantation genetic diagnosis is associated with the birth of unaffected fetuses when performed for detection of single genetic defects and a decrease in spontaneous abortions for patients with structural chromosomal abnormalities. For couples with single genetic defects, these beneficial health outcomes are balanced against the probable overall decreased success rate of the PGD procedure compared to in vitro fertilization alone. However, the alternative for couples at risk for single genetic defects is prenatal genetic testing, i.e., amniocentesis or chorionic villus sampling, with pregnancy termination contemplated for affected fetuses. (It should be noted that many patients undergoing PGD will also undergo a subsequent amniocentesis or chorionic villus sampling to verify PGD accuracy.) Ultimately, the choice is one of the risks (both medical and psychologic) of undergoing IVF with PGD, compared to the option of normal fertilization and pregnancy with the possibility of a subsequent elective abortion. Thus, PGD is considered medically necessary, as noted in the policy statements, when the evaluation is focused on a known disease or disorder, and the decision to undergo PGD is made upon careful consideration of the risks and benefits. There is insufficient evidence that preimplantation genetic screening improves ongoing pregnancy and live birth rates; thus, PGS as an adjunct to IVF is considered investigational.

Practice Guidelines and Position Statements for preimplantation genetic testing
A 2007 practice committee opinion issued by the American Society for Reproductive Medicine concluded that available evidence did not support the use of PGS as currently performed to improve live birth rates in patients with advanced maternal age, previous implantation failure, or recurrent pregnancy loss, or to reduce miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy.
In 2009, the American College of Obstetricians and Gynecologists issued an opinion on preimplantation genetic screening for aneuploidy. They state that current data do not support the use of PGS to screen for aneuploidy due solely to maternal age.

**Thanatophoric dysplasia (TD)**

Thanatophoric dysplasia (TD) is a neonatal lethal short-limb dwarfism syndrome. TD is divided into Type I, characterized by micromelia with bowed face and, uncommonly the presence of cloverleaf skull deformity of varying severity; and Type II, characterized by micromelia with straight femurs and uniform presence of moderate-to-severe cloverleaf skull deformity. Other features common to the two subtypes of TD include short ribs, narrow thorax macrocephaly, distinctive facial features, brachydactyly, hypotonia, and redundant skin folds along the limbs. Most affected infants die of respiratory insufficiency shortly after birth. Diagnosis of TD is based on clinical examination and/or prenatal ultrasound examination and radiologic studies. Characteristic histopathology is also present. TD is considered an autosomal dominant disorder. FDFR3 is the only gene associated with TD. Approximately 99% of mutations causing TD can be identified through molecular genetic testing of FGFR3. TD I and TD II represent new mutations to normal parents. The recurrence risk is low. Because the mutated codons in TD are mutable for unknown reason and because of the theoretical risk of germ cell mosaicism, parents are offered prenatal diagnosis for subsequent pregnancies.

**Key Words:** Genetic test, Fragile X syndrome, Huntington’s disease, cystic fibrosis, Friedreich’s ataxia, Spinal Muscular Atrophy, Duchenne Muscular Dystrophy, Myotonic Dystrophy, Prader-Willi Syndrome, Angelman Syndrome, Neurofibromatosis Type I, Canavan Disease, Hemoglobin S and /or C, Kennedy disease, SBMA, Charcot-Marie-Tooth, Dentatorubral-pallidoluysian atrophy, Classical Lissencephaly, Niemann-Pick disease, Tay-Sachs, Von Hippel-Lindau syndrome, Gaucher Disease, Retinoblastoma, Hemoglobin E thalassemia, Beta thalassemia, Alpha thalassemia, Albinism, Factor V Leiden mutation, Prothrombin 20210A mutation, Hereditary Neuropathy with Liability to Pressure Palsies, HNPP, Sickle cell anemia, Hereditary Deafness Connexin 26 gene, GJB2, Fascioscapulohumeral dystrophy, FSHD, mutation, DNA, congenital long QT syndrome, LQTS, glaucoma, preimplantation genetic diagnosis, PGD, preimplantation genetic testing, preimplantation genetic screening, PGS, OCRL, Lowe Syndrome, LactoTYPE1 hypolactasia variant detection, lactase variant test, genetic testing for lactose intolerance, corrected QT interval (QTc), Romano Ward Syndrome (RWS), Jervell and Lange-Nielsen Syndrome (JLN), iron overload disorders, elevated transferrin-iron concentrations, elevated transferrin-iron levels, AmpliChip Cytochrome P450® Genotyping test, *Helicobacter pylori* (*H. pylori*), thanatophoric dysplasia, autism, MECP2, warfarin, Pierson Syndrome, Congenital Nephrotic Syndrome (CNS), angiotensin converting enzyme (ACE), gene polymorphisms, insertion (I), deletion (D), PMP22, CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, hereditary pancreatitis (HP), serine protease 1 gene (PRSS1), early onset myocardial infarction, congenital adrenal hyperplasia (CAH), NOTCH3
Approved by Governing Bodies:
Appropriate lab competency for testing:
  o State license, Clinical Laboratory Improvement Amendments (CLIA) certification, American College of Medical Genetics/College of American Pathologist (ACMG/CAP) certification
  o Director and staff credentialed by the American Board of Medical Genetics (ABMG).
  o Credentialed by the American Board of Bioanalysis (ABB) and American Board of Histocompatibility and Immunogenetics (ABHI).

Benefit Application:
Coverage is subject to member’s specific benefits. Some contracts exclude genetic testing. Some genetic screening may be routine and contract benefits should be verified for routine services as in cystic fibrosis. Group specific policy will supersede this policy when applicable. ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity. Special benefit consideration may apply. Refer to member’s benefit plan.

Current Coding:
CPT codes:

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<tr>
<th>Code</th>
<th>Description</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>81161</td>
<td>DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed</td>
<td>Effective 01/01/2013</td>
</tr>
<tr>
<td>81200</td>
<td>ASPA (aspartoacylase) (e.g. Canavan disease) gene analysis, common variants (e.g. E285A, Y231X)</td>
<td>Effective 01/01/2012</td>
</tr>
<tr>
<td>81205</td>
<td>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (e.g. Maple syrup urine disease) gene analysis, common variants (e.g. R183P, G278S, E422X)</td>
<td>Effective 01/01/2012</td>
</tr>
<tr>
<td>81209</td>
<td>BLM (Bloom syndrome, RecQ. helicase-like) (e.g. Bloom syndrome) gene analysis, 2281del6ins7 variant</td>
<td>Effective 01/01/2012</td>
</tr>
<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; common variants (e.g. ACMG/ACOG guidelines)</td>
<td>Effective 01/01/2012</td>
</tr>
<tr>
<td>81221</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; known familial variants</td>
<td>Effective 01/01/2012</td>
</tr>
<tr>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; duplication/deletion variants</td>
<td>Effective 01/01/2012</td>
</tr>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; full gene sequence</td>
<td>Effective 01/01/2012</td>
</tr>
<tr>
<td>81224</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g. male infertility)</td>
<td>Effective 01/01/2012</td>
</tr>
</tbody>
</table>
81240  F2 (prothrombin, coagulation factor II) (e.g. hereditary hypercoagulability) gene analysis, 20210G>A variant (Effective 01/01/2012)
81241  F5 (coagulation factor V) (e.g. hereditary hypercoagulability) gene analysis, Leiden variant (Effective 01/01/2012)
81242  FANCC (Fanconi anemia, complementation group C) (e.g. Fanconi anemia, type C) gene analysis, common variant (e.g. IVS4+4A>T) (Effective 01/01/2012)
81243  FMR1 (fragile X mental retardation 1) (e.g. fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g. expanded) alleles (Effective 01/01/2012)
81244  Fmr1 (fragile x mental retardation 1) (e.g., fragile x mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status) (Effective 01/01/2012)
81250  G6PC (glucose-6-phosphatase, catalytic subunit) (e.g., glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (e.g., R83C, Q347X) (Effective 01/01/2012)
81251  GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, l444P, IVS2+1G>A) (Effective 01/01/2012)
81252  GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence (Effective 01/01/2013)
81253  GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; known familial variants (Effective 01/01/2013)
81254  GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., nonsyndromic hearing loss) gene analysis, common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)]) (Effective 01/01/2013)
81255  HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G>C, G269S) (Effective 01/01/2012)
81257  HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring) (Effective 01/01/2012)
81260  IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T>C, R696P) (Effective 01/01/2012)
81280  Long QT Syndrome gene analyses (e.g., KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); full sequence analysis (Effective 01/01/2012)
81281  Long QT Syndrome gene analyses (e.g., KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP,
SNTA1, and ANK2); known familial sequence variant (Effective 01/01/2012)

81282 Long QT Syndrome gene analyses (e.g., KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); duplication/deletion variants (Effective 01/01/2012)

81290 MCOLN1 (mucolipid 1) (e.g., Mucolipidosis, Type IV) gene analysis, common variants (e.g., IVS3-2A>G, del6.4kb) (Effective 01/01/2012)

81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C) (Effective 01/01/2012)

81302 MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis (Effective 01/01/2012)

81303 MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant (Effective 01/01/2012)

81304 MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants (Effective 01/01/2012)

81324 PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis (Effective 01/01/2013)

81325 PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis (Effective 01/01/2013)

81326 PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant (Effective 01/01/2013)

81330 SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, type A) gene analysis, common variants (e.g., R496L, L302P, fsP330) (Effective 01/01/2012)

81331 SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome), methylation analysis (Effective 01/01/2012)

81404 Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)—includes PRSSI (protease, serine, I [trypsin 1]) (e.g., hereditary pancreatitis), full gene sequence (Effective 01/01/2013)

81479 Unlisted molecular pathology procedure (Effective 01/01/2013)

81599 Unlisted multianalyte assay with algorithmic analysis (Effective 01/01/2013)

HCPCS:

G9143 Warfarin response test
S3800 Genetic testing for amyotrophic lateral sclerosis (ALS)
S3842 Genetic testing for von Hippel-Lindau disease
S3844 DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
S3845 Genetic testing for alpha-thalassemia
S3846 Genetic testing for hemoglobin E beta-thalassemia
S3849 Genetic testing for Niemann-Pick disease
S3850 Genetic testing for sickle cell anemia
S3853 Genetic testing for myotonic muscular dystrophy
S3855 Genetic testing for detection of mutations in the presenilin – 1 gene
S3861 Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome
S3865 Comprehensive gene sequence analysis for hypertrophic cardiomyopathy analysis
S3866 Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

Previous Coding:
CPT codes:
There are no specific codes for this laboratory procedure. A series of molecular diagnostic codes (83890-83914) would likely be used. (Deleted 01/01/2013)

84999 Unlisted chemistry procedure
88299 Unlisted cytogenetic study
99199 Unlisted special service, procedure or report

HCPCS:
S3835 Complete gene sequence analysis for cystic fibrosis genetic testing (Deleted 04/01/2012)
S3843 DNA analysis of the F5 gene for susceptibility to Factor V Leiden thrombophilia (Deleted 04/01/2012)
S3847 Genetic testing for Tay-Sachs disease (Deleted 04/01/2012)
S3848 Genetic testing for Gaucher disease (Deleted 04/01/2012)
S3851 Genetic testing for Canavan disease (Deleted 04/01/2012)
S3860 Genetic testing, comprehensive cardiac ion channel analysis, for variants in 5 major cardiac ion channel genes for individuals with high index of suspicion for familial long QT syndrome (LQTS) or related syndromes (Deleted 04/01/2012)
S3862 Genetic testing, family-specific ion channel analysis, for blood-relatives of individuals (index case) who have previously tested positive for a genetic variant of a cardiac ion channel syndrome using either one of the above test configurations or confirmed results from another laboratory (Deleted 04/01/2012)
References:


27. Collins KK and Van Hare GF. Advances in congenital long QT syndrome. Current Opinions in Pediatrics, October 2006; 18(5); 497-502.
53. Genes and Disease from the National Center for Biotechnology Information. Von Hippel-Lindau syndrome.
54. Genes and Disease from the National Center for Biotechnology Information. Niemann-Pick disease.
76. Libby: Braunwald’s Heart Disease: A Textbook of Cardiovascular Medicine, 8th edition.


117. PGxHealth, New Haven, CT.


Policy History:
Medical Policy Group, September 2003 (1)
Medical Policy Group, March 2005 (1)
Medical Policy Group, July 2005 (1)
Medical Policy Group, August 2005 (1)
Medical Policy Group, January 2006 (1)
Medical Policy Group, April 2006 (1)
Medical Policy Group, May 2006
Medical Policy Group, August 2006 (1)
Medical Policy Group, August 2006
Medical Policy Group, December 2006 (3)
Medical Policy Group, January 2007
Medical Policy Group, May 2007 (1)
Medical Policy Group, July 2007 (1)
Medical Review Committee, July 2007
Medical Policy Administration Committee, June 2011
Available for comment June 8 – July 25, 2011
Medical Policy Group, July 2011 (1): Clarification of policy statement related to Preimplantation genetic testing, remains investigational; Update to Key points and References related to preimplantation genetic testing and Long QT syndrome
Medical Policy Administration Committee, August 2011
Medical Policy Group, September 2011 (1): Update to Key Points and References related to CADASIL
Medical Policy Group, December 2011: (1): Added 2012 Code updates
Medical Policy Group, February 2012: (3): 2012 Code Updates: Deleted ‘S’ codes effective 4/1/12
Medical Policy Group, December 2012 (3): 2013 Coding Updates: Added codes 81161, 81252, 81253, 81254, 81324, 81325, 81326, 81404, 81479 and 81599; Deleted Codes 83890-83914; and Moved codes 84999, 88299, and 99199 to Previous Codes effective 01/01/2013.
Medical Policy Group, February 2013 (1): Added MTHFR mutation to coverage criteria effective 01/01/2013
Medical Policy Group, January 2014 (1): Removed all aspects of 9p21 genotyping related to cardiovascular disease or aneurysm and created new policy #542; Removed all aspects of HLA-DQ testing related to celiac disease and created new policy #545; no other changes noted to policy
Medical Policy Group, February 2014 (1): Removed all aspects of genetic testing for hereditary hemochromatosis and created new policy #546; no other changes noted to policy
Medical Policy Group, April 2014 (1): Removed all aspects of genetic testing to predict coronary artery disease (Corus CAD) and created new policy #549; removed all aspects of genetic testing for adolescent idiopathic scoliosis (AIS) and created new policy #547; no other changes to policy

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.