



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Genetic Testing of Heritable Disorders**

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- Genetic Testing to Diagnose and Predict Susceptibility to Alzheimer's Disease
- Preimplantation Genetic Diagnosis

## INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

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## Coverage Policy

Coverage of genetic testing of heritable disorders is dependent upon benefit plan language and may be governed by federal and/or state mandates. Under some benefit plans, genetic testing may be entirely excluded from coverage or only covered when certain conditions apply. Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions and limitations of coverage.

If coverage for genetic testing is available, disease- or condition-specific criteria for genetic testing may be outlined in one of the related coverage policies listed. If a separate Coverage Policy does not exist and there is no benefit restriction, the following basic criteria apply:

**CIGNA covers genetic testing of heritable disorders as medically necessary when BOTH of the following are met:**

- The results will directly impact clinical decision-making and/or clinical outcome for the individual.
- The testing method is considered scientifically valid for identification of a genetically-linked heritable disease.

**AND EITHER of the following conditions is met:**

- The individual demonstrates signs/symptoms of a genetically-linked heritable disease.
- The individual or fetus has a direct risk factor (e.g., based on family history or pedigree analysis) for the development of a genetically-linked heritable disease.

**CIGNA covers predictive genetic testing for hypertrophic cardiomyopathy (HCM) as medically necessary in an at-risk family member when a known genetic mutation has been identified in a first- or second-degree relative.\***

**CIGNA covers genetic testing for the SMN1 gene deletion as medically necessary for ANY of the following indications:**

- confirmatory testing when clinical features are suggestive of spinal muscular atrophy (SMA).
- preconception or prenatal carrier testing for **EITHER** of the following indications:
  - at-risk family member (i.e., first or second-degree relative) when the SMN1 gene deletion has been identified in the proband and the individual has both the capacity and desire to reproduce.
  - reproductive partner of an individual with the SMN1 deletion and the couple has the capacity and intention to reproduce
- prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when the disease-causing mutation has been identified in a first- or second-degree relative\*

\*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

\*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

**An individual undergoing genetic testing for any reason should have both pre- and post- test genetic counseling with a physician or a licensed or certified genetic counselor.**

**CIGNA covers newborn screening for genetic disorders (e.g., screening for phenylketonuria) performed in accordance with state mandates.**

**CIGNA does not cover genetic testing for the screening, diagnosis or management of ANY of the following because it is considered experimental, investigational or unproven:**

- familial amyotrophic lateral sclerosis (FALS)
- Brugada syndrome

**CIGNA does not cover genetic testing or gene mapping in the general population because such screening is considered not medically necessary.**

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## **General Background**

The human genome is estimated to contain 100,000–140,000 genes consisting of 3–4 billion chemical bases, all of which reside on 23 pairs of chromosomes. Disease can result when an alteration in DNA sequence causes the cell to produce the wrong protein, or too much or too little of the correct protein. Genetic mutations are responsible for >3000 hereditary disorders. Some genetic disorders are caused by the mutation of a single gene, while chromosomal disorders are caused by an excess or deficiency of a number of genes or chromosomes. Other heritable conditions (e.g., heart disease and many cancers) are considered multifactorial inheritance disorders, arising from a combination of genetic and environmental factors. Mutations may increase an individual's risk of developing one of these conditions; however, it is the complex interplay of genetic and environmental factors that causes the disease to manifest itself.

The risk of inheriting a genetic mutation is usually calculated on the relationship to an affected individual that typically includes first- or second-degree relatives. A first-degree relative is defined as any relative who is one meiosis away from a particular individual in a family (e.g., parent, sibling, offspring), a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings and children. A second-degree relative is defined as any relative who is two meioses away from a particular individual in a pedigree; a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings (Gene Tests, 2004).

**Genetic Testing and Genetic Screening:** A genetic test is defined as “the analysis of human DNA, ribonucleic acid (RNA), chromosomes, proteins, and certain metabolites in order to detect alterations related to a heritable disorder. This can be accomplished by directly examining the DNA or RNA that makes up a gene (i.e., direct testing), looking at markers co-inherited with a disease-causing gene (i.e., linkage testing), assaying certain metabolites (i.e., biochemical testing), or examining the chromosomes (cytogenetic testing)” (Gene Tests, 2004).

Genetic tests are also used for the purpose of genetic screening of groups or populations. Although genetic screening typically uses the same assays as those used for genetic testing, it is distinguished from testing by its target population. The term “genetic screening” may be defined as a search in the population for persons possessing certain genotypes that are already associated with disease or predisposed to disease, may lead to disease in their descendants, or may produce other variations not known to be associated with disease. Under these definitions, testing an asymptomatic person in a family with several relatives affected with the disease constitutes not “screening” but “predictive” genetic testing (Holtzman, 2006).

In genetic screening, groups or populations may be offered testing because it is believed that they have a greater chance of carrying a gene that increases the risk of disease to them or to their children (Secretary's Advisory Committee on Genetic Testing [SACGT], 1999–2000). Some examples of screening include the testing of maternal serum markers to detect risk of Down syndrome, postnatal newborn testing for phenylketonuria (PKU), and cholesterol testing in children to identify those at risk for hyperlipidemias. It should be noted that some genetic screening tests are not DNA- or chromosome-based tests but rather utilize surrogate biochemical markers or phenotypic features.

**Criteria for Developing Genetic Tests:** The final report of the Task Force on Genetic Testing has recommended that the clinical use of a genetic test be based on evidence that the gene being examined is associated with the disease in question; that the test itself have analytical validity (i.e., analytical sensitivity and specificity) and clinical validity (i.e., clinical sensitivity and specificity) and both positive and negative predictive value, and that the test results be useful to the people tested. The report states that the genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of a disease, and the observations must be independently replicated and subject to peer review (Holtzman, 2006).

The term clinical validity refers to the accuracy with which a test predicts clinical outcome; it is affected by two features of genetic diseases: heterogeneity and penetrance. With heterogeneity, the same genetic disease might result from the presence (e.g., in the necessary gene dosage) of any of several different variants (i.e., alleles) of the same gene (i.e., allelic diversity) or of different genes (i.e., locus heterogeneity). The penetrance of the genotype is the probability that the disease will appear when a disease-related genotype is present. A test is considered clinically valid if it successfully detects a disease or predisposition.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing. Additionally, laboratories in the U.S. should follow the College of American Pathology Guidelines.

Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results, that is, the test must have clinical utility. Clinical utility refers to the usefulness of the test and the value of the information to the person being tested (SACGT, 1999-2000).

### **Purposes of Genetic Testing**

**Diagnostic/Confirmatory Testing in Symptomatic Individuals:** This testing is done to rule out, identify, or confirm a suspected genetic disorder in an affected individual. Diagnostic testing may be performed to help determine the course of a disease or choice of treatment.

**Preconception or Prenatal Carrier Testing:** This testing is performed to determine an individual's risk of passing on a particular genetic mutation in X-linked and autosomal-recessive conditions. The purpose of preconception or prenatal carrier testing is to identify family members who are themselves unaffected but are at risk for producing affected children. Because carriers of a particular inherited disorder do not actually have the disease, genetic testing to determine carrier status is generally only appropriate for those at risk for being carriers who are contemplating pregnancy to allow for informed reproductive choices.

**Predictive Testing:** Predictive testing is used to determine whether individuals who have a family history of a disease but no current symptoms have the gene alteration associated with the disease. Predictive genetic testing includes presymptomatic testing and predispositional testing. When a specific mutation is identified through presymptomatic testing, the individual will eventually develop symptoms of a disease (e.g., testing for Huntington's disease before symptoms are present). In predispositional testing, eventual development of symptoms is likely but not certain when the gene mutation is present (e.g., breast cancer) (Gene Tests, 2004).

**Prenatal Testing of the Fetus:** This testing is performed during pregnancy to determine if a developing fetus is at risk for inheriting identifiable genetic diseases or traits. Prenatal diagnostic tests are generally performed when there is an increased risk of having offspring with a genetic disorder due to advanced maternal age, family history, or other testing results (e.g., multiple screen markers, ultrasound) that are suggestive of a genetic disorder. Diagnosis is made through the testing of amniotic fluid, fetal cells and fetal and/or maternal blood cells via amniocentesis or chorionic villus sampling.

**Preimplantation Genetic Diagnosis:** Prenatal genetic testing performed as part of assisted reproductive techniques, such as in vitro fertilization, is described as preimplantation genetic diagnosis (PGD). This technique allows for determination of genotype of an embryo before implantation takes place, providing the opportunity to exclude embryos with genetic abnormalities before the initiation of pregnancy. Proponents of the technique contend that PGD provides an alternative to postconception diagnosis and pregnancy termination.

**Newborn Screening:** According to the American Academy of Pediatrics ([AAP], 2009), the purpose of newborn screening for genetic disorders is to limit the morbidity and mortality attributable to selected inherited diseases. Testing involves the analysis of blood or tissue samples, generally taken in early infancy, to detect conditions for which early intervention can avoid serious health issues or even death. Newborn screening programs are organized through state governments and are generally mandated. This testing typically involves the use of surrogate biochemical markers rather than molecular genetic testing. According to the March of Dimes (2008), screening is available for disorders in which accurate diagnosis and early treatment of the disorder can improve health outcomes. The disorders are grouped into five categories and include:

- Organic acid metabolism disorders (e.g., isovaleric academia, multiple carboxylase deficiency, beta-ketothiolase deficiency)
- Fatty acid oxidation disorders (e.g., medium chain acyl-CoA dehydrogenase deficiency, trifunctional protein deficiency, carnitine uptake defect)
- Amino acid metabolism disorders (e.g., phenylketonuria, maple syrup disease, homocystinuria due to CBS deficiency)
- Hemoglobinopathies (e.g., sickle cell anemia, hemoglobin S/beta-thalassemia, hemoglobin S/C disease)
- Others (e.g., cystic fibrosis, hearing loss, congenital hypothyroidism) (March of Dimes, 2008)

The AAP (2009) guidelines note genetic testing of children and adolescents to predict late-onset disorders is inappropriate when the genetic information has not been shown to reduce morbidity and mortality through interventions initiated in childhood.

**Genetic Counseling and Informed Consent**

Individuals who are contemplating genetic testing should be provided with detailed counseling from a qualified professional prior to and following testing so that they are able to make informed decisions. Patients should be advised that genetic testing is a multistep process that includes risk assessment, pre-testing education and follow-up counseling after the test results are known. While genetic counseling should provide sufficient information to allow the individual and family to make well-informed decisions about the benefits, risks, limitations, and implications of genetic testing, it should also be nondirective in nature. The American College of Medical Genetics (ACMG) (2001) states that genetic counselors are health care professionals who have completed training in an accredited Masters degree program and have passed the certification examination administered by the American Board of Genetic Counseling.

Specific gene mutations have been identified for a number of conditions, and are addressed in related Coverage Policies (please see related Coverage Policy section) including, but not limited to the following:

Condition	Mutation
Alzheimer disease	APOE4, APP, PSEN1, PSEN2
Susceptibility to breast and ovarian cancer	BRCA1, BRCA2
Canavan disease	ASPA
Cystic fibrosis	CFTR
Congenital profound deafness	GJB2, GJB6
Colorectal cancer: <ul style="list-style-type: none"> <li>• Familial adenomatous polyposis (FAP); includes Gardner syndrome, Turcot syndrome</li> <li>• Attenuated familial adenomatous polyposis (AFAP)</li> <li>• Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome; includes Muir-Torre syndrome</li> <li>• MYH-associated polyposis (MAP)</li> </ul>	APC, MLH1, MSH2, MSH6, PMS2, MYH
Factor V Leiden Thrombophilia	F5
Gaucher disease	GBA

Hemochromatosis	HFE
Hemoglobinopathies: <ul style="list-style-type: none"> <li>• Alpha-thalassemia</li> <li>• E beta-thalassemia</li> <li>• Sickle cell</li> </ul>	HBA1, HBA2, HBB
Long QT syndrome	CACNA1C, KCNE1, KCNE2, KCNJ2, KCNH2, KCNQ1, SCN5A
Mitochondrial disorders: <ul style="list-style-type: none"> <li>• Kearns-Sayre syndrome (KSS)</li> <li>• Pearsons syndrome</li> <li>• Progressive external ophthalmoplegia (PEO)</li> <li>• Neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP)</li> <li>• Leigh syndrome (LS)</li> <li>• Leber hereditary optic neuropathy (LHON)</li> <li>• Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)</li> <li>• Myoclonic epilepsy with ragged-red fibers (MERRF)</li> </ul>	MTATP, MTCO3, MTND1, MTND3, MTND4, MTND5, MTND6, MTTK, MTTV, MTTW
Myotonic dystrophy	DMPK, ZNF9
Neimann-Pick disease	NPC1, NPC2, SMPD1
Retinoblastoma	RB1
RET proto-oncogene germline testing for medullary thyroid carcinoma: <ul style="list-style-type: none"> <li>• Multiple endocrine neoplasia type 2A (MEN2A); includes Sipple syndrome</li> <li>• Multiple endocrine neoplasia type 2B (MEN2B); includes mucosal neuroma syndrome</li> <li>• Familial medullary thyroid carcinoma (FMTC)</li> </ul>	RET
Tay-Sachs disease and variants (e.g., Sandoff disease)	HEXA, HEXB
von Hippel-Lindau syndrome	VHL

Conditions for which a gene mutation has been identified but are not otherwise described in a separate Coverage Policy include the following:

Condition	Mutation
Amyotrophic lateral sclerosis	SOD1, TARP, TDP-43, FUS
Brugada syndrome	SCN5A, GPD1L, CACNA1C, CACNB2, SCN1B, SCN3B, KCNE3
Hypertrophic cardiomyopathy	MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC, MYL2, MYL3.
Spinal muscular atrophy	SMN1

**Amyotrophic Lateral Sclerosis:** Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease affecting upper and lower motor neurons, characterized initially by muscle weakness, with muscle atrophy as the disease progresses. There is no cure for amyotrophic lateral sclerosis (ALS); death generally occurs within three to five years due to compromise of the respiratory muscles (GeneReview, 2009).

ALS may be sporadic or non-inherited, accounting for about 90%–95% of individuals, or familial, caused by an inherited genetic mutation in 5%–10% of individuals with the disorder (National Institutes of Health [NIH], 2007). Penetrance is incomplete and phenotypic expression is variable in ALS depending on age, type of mutation, site of onset, and disease duration. Familial ALS can be categorized by mode of inheritance (i.e., autosomal dominant, autosomal recessive, or X-linked), and subcategorized by the specific gene or chromosomal locus. As with other heritable disorders, it is thought that there are many mutations that have not yet been identified.

A number of mutations, including those of the superoxide dismutase 1 (SOD1), TAR DNA binding protein (TARDP or TDP-43), and the FUS genes have been implicated in familial ALS, with various modes of inheritance noted. About 10%–20% of all familial cases result from a specific genetic mutation of SOD1, which is inherited in an autosomal dominant manner; >100 mutations have been identified. Additionally, about 1%–4% of individuals affected with familial ALS have TARDBP (TDP-43) mutations, and 4% have FUS mutations, which are also inherited in an autosomal dominant manner (GeneReviews, 2009). Although the specific mechanism of motor neuron degeneration is unknown at this time, it is thought to be a complex genetic-environmental interaction as the casual factor.

No one test can provide a definitive diagnosis of ALS (NIH, 2011). Diagnosis is made by the presence of characteristic clinical features, electrodiagnostic testing (e.g., electromyography, nerve conduction velocity), and histologic findings as well as the exclusion of other conditions with related symptoms. Although molecular genetic testing is available for several genes associated with familial ALS, including SOD1, the presence of these mutations may not provide prognostic information; interpretation of the significance of a mutation regarding disease severity and progression depends on the specific mutation because of the wide variability in genotype/phenotype correlations. Additionally, the absence of a mutation in a family where one has not been identified is not informative as it does not rule out familial ALS caused by other mutations (ALSA, 2010).

Several genome-wide association studies have been published in the peer-reviewed scientific literature. These studies indicate that there is no definitive or common highly penetrant allele that causes sporadic or familial ALS. Additionally, a number of gene mutations initially thought to be causative only for familial ALS, such as those for SOD1, TARDBP (TDP-43), and FUS have been identified in individuals diagnosed with sporadic ALS (Belzil, 2009; GeneReviews, 2009; Wijesekera, 2009; Paubel, 2008).

### **Professional Societies/Organizations**

The American Neurological Association and the American Academy of Neurology have not published guidelines regarding genetic testing for ALS.

**Summary for ALS:** There is insufficient evidence in the peer-reviewed scientific literature to support the clinical utility of genetic testing for the screening, diagnosis, or management of familial ALS. At this time the identification of a gene mutation does not diagnose familial ALS, and does not impact treatment, or health outcomes. Data are lacking in the published peer-reviewed scientific literature regarding the utility of genetic testing for prenatal or preconception carrier testing, prenatal testing of the fetus, or its use in preimplantation genetic diagnosis (PGD). These results suggest that the clinical utility of genetic testing for these mutations is not firmly established.

**Brugada Syndrome:** Brugada syndrome is a rare disorder with a prevalence of 5:10,000 worldwide, associated with a characteristically abnormal electrocardiogram (EKG) and a high risk of sudden cardiac death in individuals with a structurally normal heart (American College of Cardiology [ACC], 2006). It is considered to be a variant of the long QT syndrome type-3 (LQTS-3) disorder. As compared with the LQTS-3 disorder which is associated with a gain-in-function in sodium current, it is responsible for a loss-of-function resulting in reduced sodium current. Brugada syndrome is characterized by impaired cardiac conduction, unexplained ventricular fibrillation, unexplained syncopal episodes, and sudden cardiac death. Cardiac events in Brugada syndrome occur mostly at rest or during sleep, similar to events seen with LQTS-3. Priori et al. (2002) reported an 11% incidence of cardiac arrest and 17% incidence of syncope in a cohort of 200 patients with Brugada syndrome.

The disorder is transmitted by an autosomal dominant pattern of inheritance. At present, more than 100 mutations in seven genes have been associated with Brugada syndrome. The SCN5A gene mutation causes Brugada syndrome in 18%–30% of individuals identified as having the disorder (Antzelevitch, 2005). Other mutations, occurring less frequently are GPD1L, CACNA1C, CACNB2, SCN1B, SCN3B, and KCNE3. It is likely that other gene mutations exist but have not yet been identified.

Brugada syndrome exhibits variable expressivity, reduced penetrance, and mixed phenotypes (Hedley, 2009). Overlapping phenotypes between LQT3 and Brugada syndrome have been reported (Priori, 2007). Certain mutations may manifest different phenotypes in different individuals and families (NHLBI, 2008). Clinical manifestations (e.g., syncope or cardiac arrest) are rare during childhood but demonstrate increased severity in the third to fourth decades of life.

The diagnosis of Brugada syndrome may be challenging due to the heterogeneity of the disorder, although the surface electrocardiogram (EKG) recording usually suggests the diagnosis. The pattern of the right precordial leads resembles that seen in right bundle branch block with variable ST segment elevation and a 'coved' ST or type 1 EKG segment elevation is considered diagnostic in appearance (Priori, 2007). The typical arrhythmia is a rapid polymorphic ventricular tachycardia that frequently degenerates into ventricular fibrillation. Individuals with Brugada syndrome usually do not have ventricular extrasystoles or nonsustained runs of ventricular tachycardia on Holter monitor reading. EKG changes may not be apparent unless a pharmacologic agent inhibits the cardiac sodium channel.

The therapeutic approach for these individuals is the prevention of cardiac arrest (ACC, 2006). Risk stratification for sudden cardiac death is of great importance in individuals with Brugada syndrome. According to the ACC (2006), there are no data demonstrating that family history predicts cardiac events among family members; therefore it should not be assumed that asymptomatic individuals with the characteristic EKG but without family history are at low risk or that family members of an individual with sudden cardiac death are at increased risk.

A number of tests have been developed to detect the SCN5A mutation. Techniques include polymerase chain reaction (PCR), denaturing high-performance liquid chromatography, and DNA sequencing. The Familion<sup>®</sup> test (PGxHealth, a division of Clinical Data<sup>®</sup>, Inc., Newton, MA.), is a patented test that is intended to provide analysis of five major cardiac ion channel genes: KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. DNA amplification is by PCR. Regarding clinical specificity, analysis of all coding exons of the gene SCN5A is estimated to identify variants in only 15–25% of individuals with Brugada syndrome. Regarding clinical specificity, the technical specifications note that variants that would have been called possible or probable deleterious if seen in a patient have been found in apparently unaffected individuals in the genes included in the tests for LQTS, Brugada syndrome, and others. Analytical sensitivity and specificity of the tests are 100% according to the manufacturer. Comprehensive clinical evaluation is strongly recommended to direct treatment decisions, regardless of test results.

### **Professional Societies/Organizations**

**Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group (2008):** Genetic testing is not recommended as routine in known or suspected cases of Brugada syndrome, but may be considered in the setting of expert clinical and detailed family assessment.

**Summary for Brugada Syndrome:** There is insufficient evidence in the published, peer-reviewed literature to determine clinical utility of genetic testing for Brugada syndrome, including confirmatory/diagnostic testing, prenatal or preconception carrier testing, prenatal testing of the fetus, or PGM, given the low prevalence and identified variance in gene mutations with Brugada syndrome. Data are lacking regarding clinical sensitivity, specificity, and predictive value of these tests.

**Hypertrophic Cardiomyopathy (HCM):** HCM is the most common inherited cardiac disease in the U.S. and the most common cause of sudden cardiac death in adults <35 years (Blue Cross Blue Shield Association [BCBS] Technology Evaluation Center [TEC], 2010). Familial hypertrophic cardiomyopathy (HCM) occurs as an autosomal dominant inherited disease (Cirino, 2009). At least 12 susceptibility genes are associated with HCM, and > 900 mutations have been identified. These genes encode for contractile sarcomeric, calcium-handling, and mitochondrial proteins. No single mutation predominates in HCM, and the frequency of each causal mutation is low. A proband with familial HCM may have the disorder as the result of a new gene mutation. The proportion of cases caused by de novo mutations is unknown (Gene Reviews, 2009).

HCM is defined clinically by the presence of an enlarged left ventricle associated with a nondilated and hyperdynamic chamber in the absence of other cardiac symptoms. It is most easily and reliably diagnosed by 2-dimensional echocardiography demonstrating left ventricular hypertrophy  $\geq 15$ mm that is typically asymmetric in distribution, and virtually any diffuse or segmental pattern of left ventricular wall thickening (Baron, 2003). Both

cardiac and non-cardiac causes of increased cardiac mass or left ventricular hypertrophy must be excluded prior to a diagnosis of hypertrophic cardiomyopathy (HCM). HCM may have a genetic basis; however, some individuals with unexplained left ventricular hypertrophy may have no mutations in sarcomeric genes (Keren, 2008).

The availability of deoxyribonucleic acid -based diagnosis has led to the identification of increasing numbers of children and adults with a preclinical diagnosis of HCM, usually in the context of genetic testing in selected pedigrees. It appears likely that most such genotype-positive, phenotype-negative children will develop left ventricular hypertrophy while achieving full body growth and maturation (Maron, 1998).

HCM is characterized by clinical and genetic heterogeneity. Penetrance within families is variable; the clinical presentation within a given kindred may also vary between family members (Columbo, 2008). Not all individuals who harbor a genetic mutation demonstrate left ventricular hypertrophy. In children, the phenotypic expression of ventricular hypertrophy may occur secondary to other disorders which must be differentiated from HCM, including inborn errors of metabolism, malformation syndromes, and neuromuscular disorders (Cirino, 2009). Some individuals remain asymptomatic throughout life and others develop severe progressive symptoms of heart failure, or sudden death. In most individuals HCM results in normal life expectancy and little or no disability (Maron, 2002). Overall, HCM confers an annual mortality rate of about 1%.

Because of the reduced penetrance and variability in clinical expression of HCM mutations, the presence of a genetic mutation is not sufficient to predict if or when clinical manifestations of HCM will occur (BCBS TEC, 2010). In some cases a mutation may be a predisposing factor to disease in the presence of other genetic and environmental factors.

Clinical genetic testing is currently available for several sarcomeric genes including MYH7, MYBPC3, TNNT2, TNNI3, and TPM1, which account for 95%-99% of known mutations. Approximately 50-60% of individuals who are clinically diagnosed with hypertrophic cardiomyopathy and undergo testing have a positive result for at least one in 12 sarcomere genes tested. Genetic testing is offered by Correlagen Diagnostics (Waltham, MA), PGxHealth (Clinical Data, Inc., Newton, MA), and GeneDX (Gaithersburg, MD), among others.

To determine whether genetic testing for predisposition to inherited HCM improves health outcomes in individuals at risk for HCM (i.e., predispositional or predictive testing) the BCBS TEC (2010) reviewed seven studies that met inclusion criteria on testing for HCM. The authors noted that no studies met inclusion criteria for evaluating the impact of genetic testing on treatment decisions. Analysis of included studies indicated that clinical sensitivity of the genetic tests for finding HCM mutations in individuals with clinically defined HCM was 33%-63%. The authors note the less-than-perfect mutation detection rate is due, in part, to the published studies having investigated some, but not all, of the known genes that underlie HCM.

The authors noted that for individuals who are at-risk due to family history, the utility of genetic testing varies considerably depending on whether there is a known mutation in a family member. For at-risk individuals without a known mutation in the family there is little impact of genetic testing on clinical outcomes. Although the authors noted that there are limitations to the evidence, there are benefits if testing for an at-risk family member is negative and there is a known familial mutation. Inherited predisposition can be ruled out and further clinical surveillance is not required. Conversely, if testing for the at-risk individual is positive and there is a family member with a known familial mutation, clinical surveillance would continue. The authors noted that individuals who have a pathogenic mutation may alter reproductive decisions and/or avoid employment or participating in strenuous activities where vigorous exertion may trigger a catastrophic event. They note that there is no empiric evidence available to determine the impact of genetic testing on such decision making. It is difficult to determine the likelihood that an at-risk individual with a pathogenic mutation will develop clinical HCM.

**Clinical Utility:** For a patient with a known mutation in the family, targeted genetic testing for a familial mutation has high predictive value for both a positive and negative test result (BCBS TEC, 2010). If there is a known familial mutation, a negative test in an at-risk family member can rule out predisposition to HCM and there is no need for continued surveillance. Since HCM has no cure, early diagnosis of, or assessment of risk for, the condition may help physicians provide the most appropriate treatment as well as prevent possible complications (ECRI, 2010).

## Professional Societies/Organizations

**Blue Cross Blue Shield (BCBS) Technology Evaluation Center (TEC) (2010):** The technology assessment notes “The use of genetic testing for inherited hypertrophic cardiomyopathy (HCM) meets the TEC criteria for the following:

- Individuals who are at-risk for development of HCM, defined as having a close relative with established HCM, when there is a known pathogenic genetic mutation present in an affected relative”

“Genetic testing for inherited HCM does not meet the TEC criteria for predisposition testing in other situations, including the following:

- Individuals who are at-risk for development of HCM, defined as having a close relative with established HSC, when there is no known pathogenic gene mutation present in an affected relative. This includes:
  - Patients with a family history of HCM, with unknown genetic status of affected relatives.
  - Patients with a family history of HCM, when a pathogenic mutation has not been identified in affected relatives.”

**Heart Failure Society of America (HFSA):** On behalf of the HFSA, Hershberger et al. (2009) published a practice guideline for genetic evaluation of cardiomyopathy. Regarding hypertrophic cardiomyopathy, the guideline notes that genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management.

**Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group (2008):** Genetic testing is not recommended for diagnosis of hypertrophic cardiomyopathy outside the setting of expert clinical and detailed family assessment. Genetic testing should be considered for patients with a firm clinical diagnosis of hypertrophic cardiomyopathy as a means of cascade screening of relatives in the setting of expert clinical, and detailed family assessment.

**Summary for HCM:** The genetic heterogeneity and low frequency with which each casual mutation occurs in the general HCM population limits the application of genetic testing into routine clinical strategy (Baron, 2003). Although data are not robust, predictive testing of at-risk individuals when a known genetic mutation has been identified in a first- or second-degree relative can aid in risk stratification, and decisions regarding the need for continued surveillance.

**Spinal Muscular Atrophy (SMA):** SMA is a lethal autosomal recessive inherited neuromuscular disease characterized by the degeneration of spinal cord motor neurons, resulting in progressive skeletal muscular atrophy and weakness (ACOG, 2009; Wang, 2007). SMA is the most common genetic cause of infant mortality and occurs in 1:6,000–10,000 births. Carrier frequencies are estimated as 1:40 to 1:60 (ACOG, 2009). There is no effective treatment for this disorder and care is symptom-related and supportive.

SMA is divided into four clinical groupings or types according to age of onset and clinical presentation: SMA type 1 (i.e., infantile SMA, Wernig-Hoffman disease), SMA type 2 (intermediate SMA), SMA type 3 (i.e., juvenile SMA, Kugelberg-Welander disease), and SMA type 4 (adult-onset SMA, pseudomyopathic SMA). Phenotype varies depending on disease type and ranges from severe, generalized muscle weakness and hypotonia with onset in infancy seen in SMA type 1, to the ability to ambulate with minimal assistance and the presence of only minor muscular weakness which characterizes adult-onset SMA type 4. In SMA type 1, death from respiratory failure usually occurs before the age of two years.

Spinal muscular atrophy (SMA) is caused by a deletion of, or mutations in the survival motor neuron (SMN1) gene on chromosome 5q13. This gene is responsible for the production of a protein essential to motor neurons. More than 95%–98% of individuals with SMA have a loss of the SMN1 gene either through complete deletion or through a gene conversion event involving the adjacent, nearly identical SMN2 gene. The SMN2 gene does not produce much functional survival motor neuron protein; however, the primary genetic feature, which determines the severity of SMA, appears to be the number of gene copies of SMN2 in a given individual. A higher number of SMN2 copies correlates with generally milder clinical phenotypes; it is thought that this protein product can partially compensate for the absence of protein from the SMN1 alleles (ACOG, 2009).

**Genetic Testing for SMA:** Clinical uses of molecular genetic testing include confirmation of the diagnosis, carrier testing and prenatal diagnosis. Genetic testing is considered a standard of care for the diagnosis of SMA

(Wang, 2007). DNA analysis to detect the SMN1 deletion is considered sufficient to diagnose SMA; no further workup is necessary (ACOG, 2009; Murray, 2008). This test is approximately 95% sensitive and 100% specific for individuals with clinical features suspicious of SMA.

Preconception and prenatal carrier status allows individuals to make informed reproductive choices. Carrier testing requires quantitative polymerase chain reaction (PCR) assay which provides a measure of SMN1 copy number. There are limitations to the use of this assay. While detection of a single normal copy of SMN1 indicates the carrier state, approximately 3-4% of the general population has two SMN1 copies on one chromosome and no copies on the other. These individuals may be incorrectly identified as having a negative carrier status. Additionally, 2% of individuals have SMN1 mutations that are not detectable by PCR dosage analysis. Genetic counseling of individuals testing negative for carrier status must account for the residual risk; particularly in individuals from SMA-affected families (ACOG, 2009).

**Clinical Utility:** Although there is no curative treatment for SMA, confirmatory, preconception carrier status testing, and prenatal testing of the fetus and preimplantation genetic diagnosis allow affected individuals, parents and families to establish a supportive treatment plan and to make informed reproductive choices..

### **Professional Societies/Organizations**

**American College of Obstetricians and Gynecologists (ACOG):** In Committee Opinion No. 423 (2009) ACOG recommended that genetic counseling and carrier screening should be offered to individuals and couples with a family history of SMA or SMA-like disease. Discussion should include sensitivity, specificity, and limitations of testing. ACOG also notes "Prenatal and preconception screening for SMA is not recommended in the general population at this time."

**American College of Medical Genetics (ACMG):** On behalf of the Professional Practice and Guidelines Committee of the ACMG (2008), Prior et al. recommended the following:

- Carrier testing should be offered to all couples regardless of race or ethnicity.
- Formal genetic counseling services must be made available to anyone requesting this testing.

**Summary for SMA:** This disorder is an inherited autosomal recessive disorder characterized by varying degrees of disability. The primary goals of genetic testing for SMA are for confirmation of the diagnosis in order to establish a supportive treatment plan and for reproductive planning with carrier testing, prenatal diagnosis, and preimplantation genetic diagnosis (PGD).

### **Summary**

Genetic testing is appropriate for selected individuals when the results will directly impact clinical decision-making and clinical outcome for the individual, and the testing method is considered to be scientifically valid to identify the genetically-linked heritable condition. Newborn screening for genetic disorders (e.g., screening for phenylketonuria) performed in accordance with state mandates is considered medically necessary. Confirmatory, carrier, prenatal and preconception testing, and preimplantation genetic diagnosis are appropriate for selected individuals.

Predictive genetic testing for hypertrophic cardiomyopathy (HCM) gene mutation is appropriate for an at-risk individual when a known mutation has been identified in a first or second degree family member. Such testing may aid in determining the necessity of continued clinical surveillance.

The clinical utility of genetic testing for the SMN1 deletion is considered appropriate to confirm the diagnosis of spinal muscular atrophy in order to establish supportive treatment options. Genetic testing also assists in informed reproductive planning with prenatal and preconception carrier testing, and prenatal testing of the fetus and preimplantation genetic diagnosis.

The clinical utility of genetic testing for familial amyotrophic lateral sclerosis (ALS) and Brugada syndrome has not been established.

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## **Coding/Billing Information**

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

<b>CPT<sup>®</sup>* Codes</b>	<b>Description</b>
83890	Molecular diagnostics; molecular isolation or extraction
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83892	Molecular diagnostics; enzymatic digestion
83893	Molecular diagnostics; dot/slot blot production
83894	Molecular diagnostics; separation by gel electrophoresis (e.g., agarose, polyacrylamide)
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (e.g., Southern, Northern)
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first two nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83902	Molecular diagnostics; reverse transcription
83903	Molecular diagnostics; mutation scanning, by physical properties (e.g., single strand conformational polymorphisms (SSCP), heteroduplex, denaturing gradient gel electrophoresis (DGGE), RNA'ase A), single segment, each
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83905	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment
83906	Molecular diagnostics; mutation identification by allele specific translation, single segment, each segment
83907	Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue)
83908	Molecular diagnostics; amplification signal, each nucleic acid sequence
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis)
83912	Molecular diagnostics; interpretation and report
83914	Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay (OLA), single base chain extension (SBCE), or allele-specific primer extension (ASPE))
88245	Chromosome analysis for breakage syndromes; baseline Sister Chromatid Exchange (SCE), 20-25 cells
88248	Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, fragile X)
88249	Chromosome analysis for breakage syndromes; score 100 cells, clastogen stress (eg, diepoxybutane, mitomycin C, ionizing radiation, UV radiation)
88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
88263	Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding
88264	Chromosome analysis; analyze 20-25 cells
88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg,

	for derivatives and markers)
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
88280	Chromosome analysis; additional karyotypes, each study
88283	Chromosome analysis; additional specialized banding technique (eg, NOR, C-banding)
88285	Chromosome analysis; additional cells counted, each study
88289	Chromosome analysis; additional high resolution study
88291	Cytogenetics and molecular cytogenetics, interpretation and report

<b>HCPCS Codes</b>	<b>Description</b>
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known mutation in the family

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
335.0	Werdnig-Hoffmann disease
335.10	Spinal muscular atrophy, unspecified
335.11	Kugelberg-Welander disease
335.19	Spinal muscular atrophy, Other
425.1	Hypertrophic obstructive cardiomyopathy
V26.31	Testing of female for genetic disease carrier status
V26.34	Testing of male for genetic disease carrier status

**Experimental/Investigational/Unproven/Not Covered:**

<b>HCPCS Codes</b>	<b>Description</b>
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
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

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
335.20	Amyotrophic lateral sclerosis
746.89	Other specified anomaly of heart

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	4/15/2008	0052	Genetic Testing of Heritable Disorders
Great-West Healthcare	2/20/2007	05.271.02	Genetic Testing, Coverage Guidelines

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