Coverage Policy

Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions and limitations of coverage. 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, coverage for genetic screening and/or testing may be excluded or restricted.

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.

Covered

Cigna covers genetic testing of a heritable disorder as medically necessary when BOTH of the following are met:

- Results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
- Testing method is considered scientifically valid for identification of a genetically-linked heritable disease.

AND EITHER of the following conditions is met:
• Individual demonstrates signs/symptoms of a genetically-linked heritable disease.
• 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.

Any individual undergoing genetic testing for any indication should have both pre- and post-test genetic counseling completed by ONE of the following:

• an independent Board-Certified or Board-Eligible Medical Geneticist
• an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
• a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

**Hypertrophic Cardiomyopathy**

Cigna covers predictive genetic testing for hypertrophic cardiomyopathy (HCM) for the known familial mutation as medically necessary in an at-risk family member when there is an affected 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.

**CYP21A2**

Cigna covers genetic testing for CYP21A2 gene mutations as medically necessary when the associated criteria are met:

• confirmatory (diagnostic testing for a symptomatic individual with clinical features suggestive of 21-hydroxylase-deficient congenital adrenal hyperplasia (21-OHD) and abnormal biochemical findings, but for whom a definitive diagnosis remains uncertain following completion of conventional testing with ANY of the following tests:

  ➢ targeted mutation analysis for the known familial mutation (i.e., testing for the known familial variant) or for common variants (Current Procedural Terminology [CPT®] code 81402)
  ➢ deletion/duplication analysis
  ➢ full sequence analysis (CPT® code 81405) if results of targeted mutation analysis or deletion/duplication analysis are negative when there is an affected blood relative
  ➢ full sequence analysis (CPT® code 81405) as an initial test if no family history of 21-OHD
• carrier testing (prenatal or preconception) of a prospective biologic parent for a known familial mutation (i.e., testing for the known familial variant) with targeted mutation analysis when there is an affected blood relative with 21-OHD
• prenatal testing of a fetus or preimplantation genetic diagnosis (PGD) using targeted mutation analysis when two disease-causing mutations in the gene have been identified in both members of the reproductive couple

Cigna does not cover genetic testing for CYP21A2 gene mutations for any other indication because it is considered experimental, investigational or unproven.
Fragile X Syndrome (FMR1)

Cigna covers confirmatory (diagnostic) genetic testing for FMR1 gene mutations as medically necessary with targeted mutation analysis and methylation analysis when fragile X is suspected in the presence of intellectual disability, developmental delay, or autism.

Cigna covers genetic testing for a known familial mutation (i.e., testing for the known familial variant) for FMR1 gene mutations as medically necessary for EITHER of the following indications:

- preconception or prenatal carrier status of a prospective biologic parent when there is an identified mutation in a blood relative 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) testing when the mother is a known carrier of a disease-causing mutation in the FMR1 gene

Cigna covers genetic testing of FMR1 gene mutations as medically necessary with ANY of the following genetic testing methods when targeted mutation analysis and methylation analysis is negative and the clinical suspicion of fragile X syndrome remains high:

- deletion/duplication analysis
- sequence analysis

Preconception and Prenatal Carrier Panel Testing

Cigna covers preconception or prenatal carrier testing with a genetic testing panel for a prospective biologic parent of Ashkenazi Jewish descent as medically necessary for the following disorders as recommended by the American College of Medical Genetics and the American College of Obstetricians and Gynecologists:

- Tay Sachs disease
- Canavan disease
- Cystic fibrosis
- Familial dysautonomia
- Bloom syndrome
- Fanconi anemia
- Niemann-Pick disease
- Gaucher disease
- Mucolipidosis IV

Newborn Screening

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

Not Covered

Cigna does not cover genetic testing for the screening, diagnosis or management of ANY of the following indications because it is considered experimental, investigational or unproven:
• familial amyotrophic lateral sclerosis (FALS)
• Brugada syndrome
• alpha1-antitrypsin disease
• products of conception in the absence of recurrent pregnancy loss
• gene mutations:
  ➢ MTHFR
  ➢ ACE
  ➢ AGTR1
  ➢ CDKN2A

Cigna does not cover genetic disease carrier panel testing for heritable disorders in the general population, because such screening for multiple conditions is considered not medically necessary.

Cigna does not cover whole genome sequencing because it is experimental, investigational or unproven.

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

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-, and second-degree relatives and may include third-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. A third-degree relative is defined as a blood relative with whom an individual shares approximately 12.5% of his/her genes, including the individual’s great-grandparents, great-aunts/uncles, and first cousins (National Health Service, 2011; 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 deoxyribonucleic acid (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], 2013), 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 (2011), 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, 2011)

AAP (2013) guidelines note the AAP and American College of Medical genetics (ACMG) do not support the routine carrier testing in minors when such testing does not provide health benefits in childhood.

Genetic Counseling and Informed Consent

Individuals who are contemplating genetic testing should be provided with detailed counseling from a qualified board-certified or board-eligible medical geneticist, or licensed or certified genetic counselor 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.

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:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>APOE4; APP; PSEN1; PSEN2</td>
</tr>
<tr>
<td>Susceptibility to breast and ovarian cancer</td>
<td>BRCA1; BRCA2</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>ASPA</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>CFTR</td>
</tr>
<tr>
<td>Congenital profound deafness</td>
<td>GJB2; GJB6</td>
</tr>
<tr>
<td>Colorectal cancer:</td>
<td></td>
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<tr>
<td>- Familial adenomatous polyposis (FAP); includes Gardner</td>
<td>APC; MLH1; MSH2; MSH6; PMS2; MYH;</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Gene(s)</td>
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<td>---------------------------</td>
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<tr>
<td>Turcot syndrome</td>
<td>EPCAM/TACSTD1</td>
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<tr>
<td>Attenuated familial adenomatous polyposis (AFAP)</td>
<td>EPCAM/TACSTD1</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome; includes Muir-Torre syndrome</td>
<td>EPCAM/TACSTD1</td>
</tr>
<tr>
<td>MYH-associated polyposis (MAP)</td>
<td>EPCAM/TACSTD1</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>GBA</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>HFE</td>
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<tr>
<td>Hemoglobinopathies:</td>
<td>HBA1; HBA2; HBB</td>
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<tr>
<td>Alpha-thalassemia</td>
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<td>E beta-thalassemia</td>
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<tr>
<td>Sickle cell</td>
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<tr>
<td>Hereditary hypercoagulability disorders (e.g, factor V Leiden thrombophilia)</td>
<td>F5 Leiden; Coagulation factor II (i.e., 20210G&gt;A variant); F2 (coagulation factor II), 1199G&gt;A variant; F5 (coagulation factor V) HR2 variant; F7 (coagulation factor VII [serum prothrombin conversion accelerator] R353Q variant); F13B (factor XIII, B polypeptide), V34L variant</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>CACNA1C; KCNE1; KCNE2; KCNJ2; KCNH2; KCNQ1; SCN5A</td>
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<tr>
<td>Mitochondrial disorders:</td>
<td>MTATP6; MTCO3; MTND1; MTND3; MTND4; MTND5; MTND6; MTTK; MTTV; MTTW; MTTL1</td>
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<tr>
<td>Kearns-Sayre syndrome (KSS)</td>
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<td>Pearsons syndrome</td>
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<tr>
<td>Progressive external ophthalmoplegia (PEO)</td>
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<tr>
<td>Neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP)</td>
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<tr>
<td>Leigh syndrome (LS)</td>
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<tr>
<td>Leber hereditary optic neuropathy (LHON)</td>
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<tr>
<td>Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)</td>
<td></td>
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<tr>
<td>Myoclonic epilepsy with ragged-red fibers (MERRF)</td>
<td></td>
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<tr>
<td>Muscular dystrophy (i.e., Duchenne Muscular dystrophy (DMD), Becker Muscular dystrophy (BMD), Emery-Dreifuss muscular dystrophy (EDMD), Facioscapulohumeral muscular dystrophy (FSHD), Limb-Girdle muscular dystrophy, myotonic dystrophy)</td>
<td>CNBP; DMD; DMPK; LMNA; EMD; FLH1; ZNF9</td>
</tr>
<tr>
<td>Neimann-Pick disease</td>
<td>NPC1; NPC2; SMPD1</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB1</td>
</tr>
<tr>
<td>RET proto-oncogene germline testing for medullary thyroid carcinoma:</td>
<td>RET</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2A (MEN2A); includes Sipple syndrome</td>
<td>RET</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2B (MEN2B); includes mucosal neuroma syndrome</td>
<td>RET</td>
</tr>
<tr>
<td>Familial medullary thyroid carcinoma (FMTC)</td>
<td>RET</td>
</tr>
<tr>
<td>Spinal muscle atrophy</td>
<td>SMN1</td>
</tr>
<tr>
<td>Tay-Sachs disease and variants (e.g., Sandoff disease)</td>
<td>HEXA; HEXB</td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 antitrypsin disease</td>
<td>SERPINA1</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>SOD1; TARP; TDP-43; FUS; VCP, C9orf72</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>SCN5A; GPD1L; CACNA1C; CACNB2; SCN1B; SCN3B; KCNE3; HCN4</td>
</tr>
<tr>
<td>21-hydroxylase-deficient congenital adrenal hyperplasia (21-OHD)</td>
<td>CYP21A2</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>MYH7; MYBPC3; TNNT2; TNNI3; TPM1; ACTC; MYL2; MYL3; TNNC1; MYH6; PRKAG2; MYBPC3</td>
</tr>
<tr>
<td>Homocystinuria, hereditary hypercoagulability, neural tube defects</td>
<td>MTHFR</td>
</tr>
<tr>
<td>Melanoma/pancreatic cancer (increased risk/susceptibility)</td>
<td>CDKN2A</td>
</tr>
<tr>
<td>Renal tubular dysgenesis, nephropathy, essential hypertension, heart disease</td>
<td>ACE, AGTR1</td>
</tr>
</tbody>
</table>

**Genetic Testing for Amyotrophic Lateral Sclerosis:** Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurogenerative disease affecting upper and lower motor neurons, characterized initially by muscle weakness, with muscle atrophy as the disease progresses. There is no cure for ALS; death generally occurs within three to five years due to compromise of the respiratory muscles (GeneReview, 2012).

Amyotrophic lateral sclerosis (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], 2012). 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 reliable biological marker for ALS, a biochemical abnormality shared by all patients with the disease has not been identified (NIH, 2012). A number of mutations, including those of the superoxide dismutase 1 (SOD1), TAR DNA binding protein (TARDBP or TDP-43), FUS, and C9orf72 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, 2012). 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 causal factor.

No one test can provide a definitive diagnosis of ALS (NIH, 2012). 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.
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, 2012; Wijeseker, 2009; Paubel, 2008).

Use Outside of the US
European Federation of Neurological Societies (EFNS): Regarding amyotrophic lateral sclerosis (ALS), on behalf of the EFNS, Bergunder et al. (2011) noted that “Despite the rather low prevalence sequencing of the small SOD1 gene should be considered in patients with ALS with dominant inheritance to offer presymptomatic or prenatal diagnosis, if this is requested by the family.

Summary for ALS: ALS may be sporadic (i.e., non-inherited) or familial (i.e., autosomal dominant, autosomal recessive, or X-linked). Although several genes have been implicated in familial 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. 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.

Genetic Testing for 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). Considered to be a variant of the long QT syndrome type-3 (LQTS-3) disorder, it is responsible for a loss-of-function resulting in reduced sodium current, compared to a gain-in-function for LQTS.

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, KCNE3, and HCN4. 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). Additionally, certain mutations may manifest different phenotypes in different individuals and families. Clinical manifestations (e.g., syncope or cardiac arrest) are rare during childhood but demonstrate increased severity in the third to fourth decades of life.

Diagnosis is based on clinical findings (GeneReviews, 2012). It may be challenging due to the heterogeneity of the disorder, but the surface electrocardiogram (EKG) recording usually suggests the diagnosis. The therapeutic approach is the prevention of cardiac arrest (American College of Cardiology [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 deoxyribonucleic acid (DNA) sequencing. The Familion™ test (Transgenomic® Inc., New Haven, CT formerly manufactured by PGx Health™ a division of Clinical Data Inc, Newton, MA), is a patented test that is intended to provide analysis of nine cardiac ion channel genes: CACNA1C, CACNB2, GPD1L, KCNDO3, KCNE3, KCNJ8, SCN1B, SCN3B, and SCN5A. DNA amplification is by polymerase chain reaction (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 Society and European Heart Rhythm Association (HRS/EHRA):** On behalf of the HRS/EHRA, Ackerman et al. (2011) published joint consensus Guidelines regarding genetic testing for channelopathies and the cardiomyopathies. Regarding Brugada syndrome the Guideline notes the following: “Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the Brugada syndrome-causative mutation in an index case; comprehensive or Brugada syndrome 1 (i.e., SCN5A) targeted genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion based on examination of the patient’s clinical history, family history, and expressed electrocardiographic phenotype; genetic testing is not recommended in the setting of an isolated type 2 Brugada electrocardiogram pattern.”

**Use Outside of the US**

**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:** Although DNA testing is clinically available to detect nine of the more common genes associated with Brugada syndrome, diagnosis is based on the results of clinical assessment; including EKG findings. 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 preimplantation genetic diagnosis (PGD), given the low prevalence and identified variance in gene mutations. Data are lacking regarding clinical sensitivity, specificity, and predictive value of these tests.

**Genetic Testing for 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, 2014).

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 ≥15mm 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 (DNA)-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, hypertrophic cardiomyopathy (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 ACTC, GLA, LAMP2, MYBP3, MYL2, MYL3, PRKAG2, TNNT2, TNN13, TNNC1, TPM1 and MYH7 which is estimated to identify variants in 50-60% of individuals with HCM (Transgenomic, 2012). Genetic testing is offered by Correlagen Diagnostics (Waltham, MA), Transgenomic Inc. (New Haven, CT), 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.

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. 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. However, 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).

**Clinical Utility:** Since there is no cure for HCM, early diagnosis of, or assessment of risk for, the condition may help provide the most appropriate treatment as well as prevent possible complications (ECRI, 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 (BCBS TEC, 2010).

**Professional Societies/Organizations**

American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): On behalf of the ACCF/AHA, Gersh et al. (2011) published Guidelines regarding the diagnosis and treatment of hypertrophic cardiomyopathy. The Guidelines included the following recommendations for genetic testing:

- "Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM.
- Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient.
- Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with atypical presentation of HCM or when another genetic condition is suspected.
- Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM.
- The usefulness of genetic testing in the assessment of risk of sudden cardiac death in HCM is uncertain.
- Genetic testing is not indicated in relatives when the index patient does not have a definite pathogenic mutation.
• Ongoing clinical screening is not indicated in genotype negative relatives in families with HCM."

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 HCM, 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 (HFS) and European Heart Rhythm Association (EHRA): On behalf of the HFS/EHRA, Ackerman et al. (2011) published joint consensus Guidelines regarding genetic testing for hypertrophic cardiomyopathy. "Comprehensive or targeted (i.e., MYBPC3, MYH7, TNN13, TNNT2, TPM1) genetic testing is recommended for any patient in whom a cardiology has established a clinical diagnosis of HCM based on examination of the patient's clinical history, family history, and electrocardiographic phenotype. Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case."

Use Outside of the US

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 for this indication (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.

Genetic Testing for Methylenetetrahydrofolate Reductase (NAD(P)H) (MTHFR) Gene Mutations: The MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase which is important for a chemical reaction involving forms of the B-vitamin folate (i.e., folic acid, vitamin B9). Polymorphisms in the gene have been associated with an increased risk of homocystinuria and neural tube defects, and studied as a possible risk factor for a number of other conditions such as heart disease, stroke, preeclampsia, glaucoma, cleft palate, and certain psychiatric conditions.

At least 40 mutations in the MTHFR gene have been identified in individuals with homocystinuria. Some mutations cause the enzyme to be inactivated, while others lead to the production of an abnormally small, nonfunctional version of the enzyme (Genetic Home Reference [GHR], 2011a). Other gene mutations associated with homocystinuria, include CBS, MTR, MTRR, and MMADHC (GHR, 2011b). In the case of MTHFR mutations, homocysteine builds up in the bloodstream, and the amount of methionine is reduced. Researchers have not determined how altered levels of homocysteine and methionine lead to the health problems associated with homocystinuria. Increased levels of homocysteine have been associated with an increased risk of thromboembolism (GHR, 2011). Although MTHFR polymorphisms have been associated with increased risk of homocystinuria; genetic testing is not indicated because these variants are not associated with thromboembolism (Raffini, 2011; Dichter, 2009).
MTHFR mutations have been associated with an increased risk of neural tube defects, such as anencephaly or spinal bifida. The 677C>T variant is the most commonly studied polymorphism (GHR, 2011a). This involves a change in a single deoxyribonucleic acid (DNA) nucleotide in the MTHFR gene, which produces a form of MTHFR that has reduced activity at higher temperatures (i.e., thermolabile). Individuals with the thermolabile form of the enzyme have increased blood levels of homocysteine (GHR, 2011).

Genotyping for MTHFR mutations, including targeted mutation analysis, carrier testing, prenatal testing, and full sequence analysis is available in clinical laboratories for MTHFR deficiency (i.e., homocystinuria) and MTHFR thermolabile variant (e.g., cardiovascular disease risk factor, hyperhomocystinemia risk factor, neural tube defect risk factor, preeclampsia risk factor).

Clinical Utility: Although mutations of the MTHFR gene have been associated with increased risk of developing a number of conditions, its role in these conditions has not been established (Genetics Home Reference [GHR], 2011a). The impact of genetic testing on the diagnosis and management of any of these conditions has not been established.

Literature Review
Although there are a number of observational studies in the published peer-reviewed scientific literature regarding the association of MTHFR mutations and increased risk of homocystinuria, neural tube defects and other conditions, randomized control data are limited. Evidence to demonstrate the impact of genotyping on improved health outcomes, including disease management, is also limited.

Tsai et al. (2009) reported results of a longitudinal cohort analysis of participants (n=1434) of the CARDIA study. DNA was extracted from the peripheral leukocytes of blood collected from each participant. MTHFR 677C.T genotype was determined using selective amplification. The mean of serum B vitamins and tHcy concentrations and the prevalence of folate deficiency and moderate hyperhomocysteinemia were compared in 844 Caucasian and 587 African American participants before folic acid fortification (year 0 and year 7) and after fortification (year 15). Mandatory folic acid fortification as initiated by the U.S. government in 1998 improved the nutritional status of folate in both Caucasians and African Americans, with an approximate three-fold increase in folate concentrations at year 15 compared with year 0. The authors used the sensitivity and specificity of MTHFR 677C.T genotyping to predict elevated tHcy concentrations using various tHcy cutoffs to define hyperhomocysteinemia. The authors concluded that after folic acid fortification in the US, measurement of tHcy rather than genotyping of MTHFR 677TT should be used as the primary assay for the diagnosis and monitoring of moderate hyperhomocysteinemia.

Professional Societies/Organizations
American College of Medical Genetics (ACMG, 2013): The ACMG notes:

- MTHFR polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss
- MTHFR polymorphism genotyping should not be ordered for at-risk family members

Use Outside of the US
No relevant information.

Summary for MTHFR Gene Mutations
Although mutations of the MTHFR gene have been associated with increased risk of developing a number of conditions, its role in these conditions has not been established (Genetics Home Reference [GHR], 2011a, Raffini, 2011; Dietcher, 2009). There is insufficient evidence in the published peer-reviewed scientific literature to determine the clinical utility of genetic testing and its impact on net health outcomes. Professional society consensus support for MTHFR genotyping is limited. At this time the role of genetic testing for MTHFR has not been established.

Genetic Testing for Alpha1- Antitrypsin Deficiency (A1AT, AATD): Alpha1-antitrypsin deficiency (A1AT, AATD) is an autosomal recessive disorder resulting from a mutation of the serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin) member 1) (SERPINA1) gene. SERPINA1, encoding alpha-1 antitrypsin is the only gene in which mutations have been known to cause A1AT (GeneReviews, 2008). SERPINA1 provides instructions for making alpha-1 antitrypsin, which is a type of serine protease inhibitor that helps inhibit the
digestive enzyme trypsin. Alpha1-antitrypsin also blocks other enzymes which are released from leukocytes to fight infection (Genetics Home Reference [GHR], 2009). PI*Z is the most common deficiency allele. Ninety-five percent of A1AT results from the presence of two Z alleles.

Clinical disease is infrequent in heterozygotes. Mutations in the SERPINA1 gene may be characterized by chronic obstructive pulmonary disease in adults and liver disease in adults and children. COPD, primarily emphysema is the most common manifestation of A1AT. Non-smokers often have a normal life-span (GeneReviews, 2013, 2008). A1AT-associated liver disease in children is characterized by obstructive jaundice and raised serum aminotransferase levels; in adults, A1AT liver disease is characterized by cirrhosis and fibrosis. It is thought that additional genetic and environmental variables play a role in A1AT as phenotypes are variable.

Neither management nor diagnosis is dependent on genotyping results. Diagnosis of A1AT is made by the demonstration of low plasma levels of alpha1-antitrypsin (AAT) and observation of a deficient variant of ATT by protease inhibitor (PI) typing or molecular genetic testing. Carrier testing in asymptomatic individuals is available by PI typing (isoelectric focusing) or mutation analysis for siblings and offspring of affected individuals. Prenatal diagnosis by genetic testing is also available when the diagnosis of A1AT has been confirmed in an affected family member (GeneReview, 2008). Intravenous therapy with infusion of purified human AAT is recommended for affected individuals who meet certain thresholds for forced expiratory volume (FEV1) and continue to deteriorate despite smoking cessation. Avoidance of environmental factors such as passive smoking, and exposure to pollutants is also recommended. Liver transplantation is the preferred surgical treatment for individuals with advanced liver as a result of A1AT (GHR, 2013, 2009).

Professional Societies/Organizations
American Thoracic Society/European Respiratory: In a joint Society statement regarding standards for the diagnosis and management of individuals with Alpha-1 Antitrypsin Deficiency (2003), genetic testing was recommended for the following:
- Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators.
- Siblings of an individual with AAT deficiency

Use Outside of the US
Canadian Thoracic Society (CTS): On behalf of the CTS, Marciniok et al. (2012) published a clinical practice guideline which suggests that targeted testing be considered in individuals with COPD diagnosed before 65 years of age or with a smoking history of <20 pack years. A recommendation was also made that targeted testing not be undertaken in individuals with bronchiectasis or asthma.

Summary for Alpha-1 Antitrypsin Disease: Current treatment of A1AT, in the form of A1AT replacement therapy relies on measurements of the protein deficiency and functional impairment. A1ATD has been associated with mutations of the SERPINA gene; however the clinical utility of genetic testing has not been established. Although there is some consensus support for genetic testing, randomized data are limited in published peer-reviewed scientific literature to demonstrate improved health outcomes with genetic testing compared with empiric-based therapy. At this time the role of genetic testing is unknown.

Genetic Testing for Products of Conception: Genetic testing on products of conception (e.g., chorionic villus, fetal membranes, fetal tissues) generally involves karyotyping, which displays the arrangement of chromosome pairs, or molecular techniques for studying chromosomes, such as fluorescence in situ hybridization (FISH) or comparative array genomic hybridization (CGH) studies. Evidence in the peer-reviewed published scientific literature supports there is clinical utility for karyotype testing and/or FISH testing of products of conception when there is a history of recurrent miscarriage (i.e., two or more consecutive pregnancy losses) and there is ongoing therapy for recurrent pregnancy loss. Genetic testing for products of conception has also been recommended for other conditions, for example when there is evidence of fetal abnormalities on prenatal ultrasound or following miscarriage post in-vitro fertilization when there is a fetal abnormality demonstrated on prenatal ultrasound; however, evidence in the medical literature is limited and does not support clinical utility for these conditions. For information regarding testing of products of conception for recurrent pregnancy loss please refer to the related Cigna Coverage Policy Recurrent Pregnancy Loss.

Genetic Testing for CYP21A2 Gene Mutations: The CYP21A2 gene (i.e., cytochrome P450, family 21, subfamily A, polypeptide 2) provides instructions for making an enzyme called 21-hydroxylase, which is part of
the cytochrome P450 family of enzymes (Genetics Home Reference [GHR], 2010). The genotype-phenotype correlation in CAH due to 21-hydroxylase deficiency is well established (Stewart, 2011). More than 100 mutations in the CYP21A2 gene have been found to cause 21-hydroxylase deficiency (21-OHD). Common gene variants include IVS2-13G, P30L, I172N, exon 6 mutation cluster [I235N, V236E, M238K], V281L, L307FfsX6, Q318X, R356W, P453S, G110VfsX21, and 30-kb deletion variant.

21-OHD is one of the most common autosomal recessive disorders with a carrier frequency of 1:25 to 1:10 (Parjes, 2008). This disorder involves impaired synthesis of cortisol from cholesterol by the adrenal cortex. Several forms of 21-OHD have been identified. A classic form with severe enzyme deficiency and prenatal onset of virilization is distinguished from a non-classic form with mild enzyme deficiency and postnatal onset. The classic form is further divided into the simple virilizing form, (approximately 25% of affected individuals), and the salt-wasting form, in which aldosterone production is inadequate (≥75% of individuals). The salt-wasting form includes hyponatremia, hyperkalemia, acidosis, hypotension, cardiovascular collapse, and possibly death (Stewart, 2011). Individuals with the non-classic form of 21-OHD CAH present postnatally with signs of hyperandrogenism (GeneReviews, 2010).

Testing Strategy: Conventional biochemical testing to confirm a diagnosis of 21-OHD includes measurement of 17-hydroxyprogesterone (17-OHP), and other adrenal steroids, electrolytes, plasma renin, and ACTH stimulation testing. If conventional testing is inconclusive and suspicion remains high genetic testing is appropriate to facilitate early diagnosis and treatment; including prevention of primary manifestations. Molecular genetic testing (i.e., targeted mutation analysis, deletion/duplication analysis) of CYP21A2 for nine common mutations and gene deletions detects approximately 80%-98% of disease-causing alleles in affected individuals and carriers. Full gene sequencing may detect rarer alleles in affected individuals if targeted mutation analysis and gene deletion/duplication analysis does not yield conclusive results. It may also be appropriate as an initial genetic test if an individual is symptomatic and there is no family history of 21-OHD. Carrier testing (prenatal and preconception) is appropriate for a known familial mutation (i.e., testing for the known familial variant) with targeted mutation analysis when there is an affected blood relative with 21-OHD. Likewise, prenatal testing of a fetus or preimplantation genetic diagnosis (PGD) may be appropriate when two disease-causing mutations in the gene have been identified in both members of the reproductive couple.

Clinical Utility: If conventional testing is inconclusive and suspicion remains high genetic testing is appropriate to facilitate early diagnosis and treatment. This includes prevention of primary manifestations, and avoidance of life-threatening events, such as salt-wasting crises in newborns. Prenatal diagnosis may allow suppressive treatment with steroids to avoid the development of virilization of the female fetus. Diagnosis is made by measuring the level of 17-OHP in amniotic fluid or by genotyping cells obtained by chorionic villous sampling (Guber, 2011).

Literature Review: The role of CYP21A2 in 21-OHD is well established in the peer-reviewed published scientific literature. Although randomized controlled trial data are lacking to inform on the ability of genetic testing to improve health outcomes there is support for such testing in textbooks (Maita, 2010; Guber, 2011) and expert opinion (GeneReview, 2010; Genetic Home Reference [GHR], 2010).

Use Outside of the US
No relevant information.

Summary for Genetic Testing for CYP21A2: Mutations in the CYP21A2 gene have been identified as causative for 21-OHD. Confirmatory (diagnostic) testing, preconception and prenatal carrier testing, using targeted mutation analysis, deletion/duplication analysis, and full gene sequencing, and preimplantation genetic diagnosis (PGD) may be appropriate in selected individuals to aid in the diagnosis and management of individuals with 21-OHD.

Genetic Testing for ACE and AGTR1 Gene Mutations: The ACE gene (i.e., angiotensin I converting enzyme [peptidyl-dipeptidase A] 1) is part of the rennin-angiotensin system (Genetics Home Reference [GHR], 2013). ACE is a relatively nonspecific peptidase and one of the most polymorphic genes, thought to affect a number of physiologic processes including blood pressure control, hematopoiesis, reproduction, renal development, renal function, and immune response. Specifically, mutations in the ACE gene have been identified as the most common cause of renal tubular dysgenesis; at least 33 mutations have been found in affected individuals. A variation in the ACE gene, called the ACE I (insertion)/D (deletion) type, is a focus of ongoing research.
Individuals may have two I alleles (II), two D alleles (DD), or one of each (ID). The DD type has been associated with increased levels of angiotensin-converting enzyme compared to the other types. Researchers propose that individuals with the DD type have an increased risk of stroke. It is also thought that individuals with this type who have diabetes mellitus have an increased risk of nephropathy. However, the contribution of other genetic and environmental influences on these risk factors is unknown (GeneReviews, 2013).

The AGTR1 gene (i.e., angiotensin II receptor type 1 [AT1 receptor]) is also part of the rennin-angiotensin system (GHR, 2013). Like mutations associated with the ACE gene, AGTR1 gene variations have also been linked to renal tubular dysgenesis. Other mutations, including the 1166A>C variant have been associated with several conditions including an increased risk for the development of essential hypertension, heart disease, and nephropathy (GHR, 2013).

Clinical Utility: The clinical utility of genetic testing for ACE and AGTR1 gene mutations has not been established in the published peer-reviewed scientific literature. Although the presence of ACE gene mutations, especially insertion/deletion types have been associated with an increased risk or susceptibility for several conditions, the influence of other variables is unknown. Similarly, variations in the AGTR1 gene have been associated with increased risk and susceptibility for essential hypertension, heart disease, complications of diabetes, including nephropathy; however, the role of environmental factors and other genetic influences on the development of these conditions is unclear. The improvement in net health outcomes achieved as a result of genotyping for mutations in these genes has not been established.

Literature Review: Randomized controlled trial data to inform on the ability of genetic testing to improve health outcomes is lacking. Evidence in the published peer-reviewed scientific literature regarding genetic testing for ACE and AGTR1 gene mutations is primarily limited to association studies and uncontrolled trials related to conditions for which increased risk has been proposed. There are scarce data regarding testing strategies and the outcomes of genetic testing on the diagnosis and management of these conditions.

Summary of Genetic Testing for ACE and AGTR1 Gene Mutations: Although it has been suggested that ACE and AGTR1 gene mutations increase risk and susceptibility for a number of conditions, there are limited data in the published peer-reviewed scientific literature to inform improved health outcomes by such testing. Similarly, established strategies for genetic testing of this gene are lacking. Although a continued focus of research, the role of genetic testing for ACE and AGTR1 gene mutations has not yet been established.

Genetic Testing for CDKN2A Gene Mutations: The CDKN2A gene (i.e., cyclin-dependent kinase inhibitor 2A) normally inhibits cell proliferation by binding to cyclin-dependent kinase. Mutations in this gene lead to uninhibited cell cycle activation and proliferation (Jensen, 2012). The incidence of CDKN2A in the general population is low; however, incidence increases with a positive family history of melanoma. CDKN2A variances have also been associated with an increased risk of pancreatic ductal adenocarcinoma and other cancers. Genetic testing for CDKN2A mutations has been proposed as a means to identify those individuals with an increased risk of certain types of cancer, specifically cutaneous melanoma, and familial atypical mole-malignant melanoma syndrome.

Genetic Testing Strategy: Published guidance regarding genetic testing strategy was lacking in the peer-reviewed literature. Although risk for disorders associated with CDKN2A mutations is reduced if results of testing are negative, the individual may have a risk greater than the general population if there are family members with melanoma; likely due to other shared genetic and environmental influences.

Clinical Utility: At present the clinical utility of genetic testing for CDKN2A mutations is unknown. Although CDKN2A mutations have been associated with an increased risk for melanoma, a number of other genes have also been implicated, including CDK4, MCIR, and numerous others (Watson, 2012). Penetrance is variable. Reduction of sun exposure, sunscreen use, strict surveillance, and biopsy of suspect lesions are considered standard of care for patient management. At this time no well-established treatment strategy has been developed as a result of genetic testing of any gene. There is insufficient evidence to demonstrate that there are improved outcomes with the use of genetic testing.

Literature Review: In a review of the literature regarding familial melanoma, Ward, et al. (2012), note several reasons against routine genetic testing for CDKN2A for melanoma: most families with hereditary cutaneous malignant melanoma have no detected mutations, understanding regarding the risk to carriers is limited, other
factors (i.e., UV irradiation) appear to affect penetrance, and negative testing may provide false assurance, as up to 9% of noncarriers in CDKN2A-positive families have been reported to develop cutaneous malignant melanoma. The authors note that additional studies are warranted to further evaluate the role of genetic testing for CDKN2A.

Yang et al. studied 28 families with 537 genotyped individuals (107 genotyped cutaneous malignant melanoma cases). Nineteen families were CDKN2A positive and nine were CDKN2A negative. Among 136 CDKN2A mutation carriers genotyped, only half were affected with melanoma. The authors note that additional genetic factors are likely to modulate cancer susceptibility.

**Professional Societies/Organizations:** There are no widely accepted guidelines in place regarding genetic testing for CDKN2A mutations. Consensus statements by the American Society of Clinical Oncologists and the Melanoma Genetics Consortium do not advocate the use of routine clinical genetic testing until further evidence to indicate clinical utility (Ward, 2012; Kefford, 2002; Kefford, 1999).

**National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™):** The NCCN (2014) Clinical Practice Guideline in Oncology for Melanoma notes “if a patient is seeking enrollment in a clinical trial of targeted therapy a biopsy should be performed to obtain tissue for genetic testing.”

**Summary for Genetic Testing for CDKN2A Mutations:** Evidence suggests that the presence of CDKN2A gene mutations may be associated with an increased risk for hereditary melanoma and other cancers; however, the degree to which they are influenced by other genetic and environmental factors is unknown. The published peer-reviewed evidence does not demonstrate improved net health outcomes with genetic testing. At present there are no established treatment strategies dependent on genetic testing of this gene. The standard of care remains surveillance and attention to sun exposure. At this time the clinical utility of such testing has not been established.

**Genetic Testing for Fragile X Syndrome (FMR1 Gene):** Fragile X syndrome/fragile X-associated disorders (FXD) refers to a family of conditions which are caused by a mutation in the FMR1 gene in 99% of individuals (Saul, 2012). This syndrome is inherited in an X-linked dominant pattern and is the most common cause of inherited intellectual disability. The FMR1 gene provides instructions for making a protein called FMRP which helps regulate the production of other proteins and plays a role in the development of synapses that are critical for relaying nerve impulses. Individuals with 55 to 200 repeats of the CGG trinucleotide segment are said to have a permutation and are usually intellectually normal; although they may have mild physical and behavioral characteristics of fragile X syndrome. Individuals with >200 copies of the CGG segment are said to have fragile X syndrome. The huge expansion of this repeat means that the FMR1 gene is not expressed, so no FMRP protein is made (Saul, 2012; Sherman, 2005). The lack of the gene product, FMRP, an RNA-binding protein, is responsible for the intellectual disability (Sherman, 2005).

Fragile X is nearly always characterized by moderate intellectual disability in affected males and mild intellectual disability in affected females. A small percentage of children with autism will have fragile X syndrome; however, approximately 50% of children with this syndrome have autistic behaviors (Miles, et al., 2003/2010). Males with an FMR1 full mutation accompanied by aberrant methylation may have a characteristic appearance (e.g., large head, long face, prominent forehead and chin, protruding ears), connective tissue findings (joint laxity), and large testes after puberty (Saul, et al., 2012). When a male is a premutation carrier he is considered a "transmitting male." All of the daughters and none of the sons will inherit the premutation; all daughters of transmitting males are unaffected premutation carriers. A female who is a premutation carrier has a 50% risk of transmitting an abnormal premutation or full mutation allele in each pregnancy. In general, the risk of a maternal premutation becoming a full mutation on transmission to her offspring is correlated with the number of CGG trinucleotide repeats in the premutation (Saul, 2012).

**Genetic Testing Strategy:** Molecular genetic testing of the FMR1 gene is appropriate for individuals of either sex with intellectual disability, developmental delay, or autism (Saul, et al., 2012). Targeted mutation analysis and methylation analysis have a mutation detection frequency for FMR1 of 99%–100%. Deletion/duplication analysis and sequence analysis have a mutation detection frequency of less than 1% and may be used when the targeted mutation analysis and methylation analysis are negative and clinical suspicion of fragile X syndrome remains high (Saul, et al., 2012). Testing for the known familial mutation to determine preconception and prenatal carrier status may be appropriate for a prospective biologic parent when a mutation has been
identified in a blood relative or when there is a family history of unexplained intellectual disability or developmental delay, autism, or premature ovarian insufficiency (American College of Medical Genetics [ACMG], 2006); American College of Obstetricians and Gynecologists [ACOG], 2013). Prenatal testing of a fetus or preimplantation genetic diagnosis (PGD) is appropriate when the mother is a known carrier of a disease-causing mutation of the FMR1 gene.

**Clinical Utility:** Genetic testing may be appropriate in situations where the results will directly impact clinical decision-making and/or clinical outcome. Diagnostic (confirmatory) testing for FMR1 mutations may allow for identification of early intervention strategies for affected individuals. Prenatal or preconception testing and prenatal testing of a fetus allows for informed reproductive choices.

**Genetic Counseling**
Genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex clinical decision-making. Post-genetic testing counseling should be planned. The genetic counseling should be provided by an independent specialty-trained genetics professional such as a medical geneticist or a genetic counselor who is an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counseling professional, or a Clinical Genetics Nurse (CGN) or an Advanced Practice Nurse in Genetics (APNG) who is unaffiliated with the genetic testing lab performing the test(s).

**Professional Societies/Organizations**
**American College of Medical Genetics (ACMG):** On behalf of the ACMG, Sherman et al. (2006) published recommendations for diagnostic and carrier testing for fragile X syndrome. According to the AMCG, genetic testing is recommended for an individual with intellectual disability, developmental delay, or autism, especially if they have any physical or behavioral characteristics of fragile X syndrome. Testing is also recommended if there is a family history of fragile X syndrome, or relatives with undiagnosed intellectual disability, for an individual seeking reproductive counseling who has a family history of fragile X syndrome or a family history of undiagnosed intellectual disability, a fetus of a known carrier mother and an affected individual or their relatives in the context of a positive cytogenetic fragile X test who is seeking further counseling related to the risk carrier status among themselves or their relatives. Deoxyribonucleic acid (DNA) testing is appropriate to accurately identify a permutation carrier and to distinguish permutation from a full mutation carrier woman.

**American College of Obstetricians and Gynecologists (ACOG, 2010):** A Committee Opinion by ACOG recommends genetic counseling and fragile X permutation testing for a woman with a family history of fragile X-related disorders, unexplained intellectual disability or developmental delay, autism, or premature ovarian insufficiency without known cause. ACOG notes that a woman who requests fragile X carrier testing, regardless of family history, should be offered FMR1 DNA mutation analysis after genetic counseling. Prenatal testing for fragile X syndrome by amniocentesis or chorionic villus sampling (CVS) should be offered to known carriers of the fragile X permutation or full mutation.

**Summary for Genetic Testing for Fragile X Syndrome (FMR1 Gene):** Fragile X syndrome is the most common inherited form of intellectual disability. Genetic testing for the FMR1 gene is appropriate when fragile x syndrome is suspected in the presence of intellectual disability, developmental delay, or autism. Genetic testing for preconception or prenatal carrier status may be appropriate when a known mutation has been identified in a blood relative. If targeted mutation analysis and methylation analysis are negative and suspicion for fragile X syndrome remains high deletion/duplication analysis and sequence analysis may also be appropriate.

**Preconception and Prenatal Carrier Panel Testing:** Multi-disease preconception and prenatal carrier screening panel testing is being offered on a commercial basis to screen for certain disorders. The National Institutes of Health Task Force on Genetic Testing (Holtzman, et al., 2006) defines genetic screening as a “search in a population for persons possessing certain genotypes that (1) are already associated with disease or predisposed to disease, (2) may lead to disease in their descendants, or (3) produce other variations not known to be associated with disease. Although genetic screening typically uses the same assays as those used for genetic testing, it is distinguished from testing by its target population. Under this definition, testing an asymptomatic person in a family with several relatives affected with disease does not constitute screening but predictive genetic testing instead” (Holtzman, 2006). Despite progress, there are still unknowns about the risks and benefits of genetic testing including: the lack of effective interventions available to improve the outcome of most inherited diseases; negative (normal) test results might not rule out future occurrence of disease; and/or
positive test results might not mean the disease will inevitably develop. According to the Task Force, genetic screening tests should have a high positive predictive value and should provide information that can result in either disease prevention or a useful clinical therapeutic intervention. In most diseases, a negative carrier test decreases the likelihood that a person is a carrier but cannot completely eliminate the possibility (Holtzman, et al., 2006).

Although preconception and prenatal carrier panel tests typically use the same assays as those used for testing for individual disorders, next-generation sequencing methods now available permit screening for many more disorders with high fidelity, quick turnaround time, and lower costs (Grody, 2013). The number and type of genetic diseases offered per panel varies. A carrier screening panel is distinguished from predictive testing by its target population. Under the Task Force definition, testing an asymptomatic person in a family with several relatives affected with disease does not constitute screening but predictive genetic testing instead” (Holtzman, 2006).

Certain ethnic groups are at an increased risk for particular genetic diseases (e.g., Eastern European Ashkenazi Jewish individuals) and a preconception and prenatal carrier screening panel test may have clinical utility. The ACMG notes that the following criteria should be met for a particular disorder to be included on the testing panel:

- Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction.
- When adult-onset disorders (disorders that could affect the offspring of the individual undergoing carrier screening once the offspring reaches adult life) are included in screening panels, patients must provide consent to screening for these conditions, especially when there maybe implications for the health of the individual being screened or other family members.
- For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed.
- There must be validated clinical association between the mutation(s) detected and the severity of the disorder.
- Compliance with the American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, including quality control and proficiency testing.

A preconception and prenatal carrier screening panel test which has clinical utility is the so-called Ashkenazi Jewish screening panel which tests for multiple diseases found at increased incidence in an individual of Eastern European Ashkenazi Jewish descent. Use of this panel test is supported by published Guidelines by the ACMG (2013) and ACOG (2008). This panel tests for the following diseases: Tay Sachs disease, Canavan disease, cystic fibrosis, familial dysautonomia, Bloom syndrome, Fanconi anemia, Niemann-Pick disease, Gaucher disease, and Mucolipidosis IV. Because each of these disorders is caused by a small number of common mutations, the carrier tests are very sensitive (94–99% detection rates).

For other multi-disease screening panels clinical utility has not been established (e.g., Counsyl Universal Genetic Test [UNIT], Counsyl, Redwood City, CA). This is a saliva-based test proposed for screening for over 100 genetic diseases, applicable to all ethnic groups and not targeted to a specific population (Counsyl, 2012; Srinivasan, et al., 2010; Klugman and Gross, 2010; American College of Obstetricians and Gynecologists [ACOG], 2009).

**Genetic Counseling:** As with all genetic tests, genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex clinical decision-making. Post-genetic testing counseling should be planned. The genetic counseling should be provided by an independent specialty-trained genetics professional such as a medical geneticist or a genetic counselor who is an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counseling professional, or a Clinical Genetics Nurse (CGN) or an Advanced Practice Nurse in Genetics (APNG) who is unaffiliated with the genetic testing lab performing the test(s).

**Professional Societies/Organizations**
American College of Obstetricians and Gynecologists (ACOG): In their recommendations for preconception and prenatal carrier screening in individuals of Eastern European Jewish descent, the ACOG Committee on Genetics (2009) stated that carrier screening for Tay-Sachs Disease, Canavan disease, cystic fibrosis, and familial dysautonomia "should be offered to Ashkenazi Jewish individuals before conception or during early pregnancy so that a couple has an opportunity to consider prenatal diagnostic testing options. If the woman is already pregnant, it may be necessary to screen both partners simultaneously so that the results are obtained in a timely fashion to ensure that prenatal diagnostic testing is an option." If only one of the couple is Ashkenazi Jew, that person should be screened first. ACOG also stated that patients may inquire regarding carrier screening for mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease and urges providing educational material to the patient so an informed decision regarding testing can be made. Individuals with a positive family history of any one of these diseases should be offered carrier screening for the specific disorder.

American College of Medical Genetics ([ACMG], 2013): On behalf of the ACMG, Grody et al., defined standard-of-care criteria for carrier screening for a panel of single-gene autosomal recessive disorders specifically for the Ashkenazi Jewish population. The ACMG notes these protocols have successfully guided reproductive decision making. "The information provided about disorders with mild phenotypes, variable expression, low penetrance, and/or characterized by an adult onset should be complete and transparent, allowing patients to opt out of receiving these test results. Patients also must be made aware of the concept of residual risk following negative test results." Gross et al. (2008, reaffirmed 2013) also published a practice guideline for “Carrier Screening in Individuals of Ashkenazi Descent.” The Guideline recommends” carrier screening for cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease be offered to all Ashkenazi Jews who are pregnant or considering pregnancy, according to current American College of Medical Genetics and/or the American College of Obstetricians Gynecologists (ACOG) guidelines. In addition, we recommend that carrier screening be offered for Fanconi anemia (Group C), Niemann-Pick (Type A), Bloom syndrome, mucolipidosis IV, and Gaucher disease.”

Use Outside of the US
No relevant information.

Summary for Preconception and Prenatal Carrier Panel Testing: Preconception and prenatal carrier screening panel tests may have clinical utility if certain criteria defined by the ACMG and ACOG are met. Preconception and prenatal carrier screening for genetic diseases in individuals of eastern European Jewish descent is used to test for a targeted group of genetic disorders which have increased prevalence in this population. Results of the test enable informed reproductive choice.

Other Genetic Testing Methods:
Next generation sequencing technology allows high throughput rapid DNA sequencing at a much lower price than prior sequencing methods. The evolution of this technology has spurred the development of tests that sequence multiple genes simultaneously, and such testing is expected to enable widespread evaluation of patients’ genomes in the clinical setting (Johansen Taber, 2014). These tests range from small to large gene panels, all the way to whole sequencing of the exome or genome.

Whole Exome Sequencing: Whole exome sequencing (WES) consists of analysis of the protein-coding regions of the human genome. This comprises <2% of the genome and involves the areas currently believed to be the most likely to include mutations that result in clinical phenotypes and disease. Such large-scale genomic sequencing has been proposed for use in scenarios of undiagnosed disorders that involve multiple congenital anomalies suggesting a single genetic etiology, but lacking a clear diagnostic testing path and in which stepwise testing can result in costly and prolonged diagnostic odyssey (American College of Medical Genetics [ACMG], 2012; ACMG, 2013).

Determining genetic causality for disease and establishing a molecular diagnosis in clinical practice can: confirm a suspected or established clinical diagnosis; inform prognosis; aid in selecting treatment, surveillance or preventive options; reveal mode of inheritance; identify carrier/risk status of family members; and/or guide research regarding new therapies or patient management (Blue Cross Blue Shield [BCBS] Tec; 2013). Overall analytical sensitivity is still being defined for whole exome sequencing (WES).
One of the most complex issues surrounding genomic testing is the risk of incidental findings, where mutations unrelated to the clinical phenotype or variants of uncertain significance are identified. While incidental identification of clinically significant mutations pose issues of informed consent, these findings often have clear medical management recommendations (ACMG 2013; Green 2013). Due to their uncertain nature, such variants often lead to increased utilization of evaluation, diagnostic, or screening procedures that may be unnecessary, resulting in increased risk of adverse events and costs.

Although the 2012 ACMG statement suggests consideration of genomic testing for fetuses likely to have a genetic disorder, the ACMG highlights the significant limitations of such testing in the prenatal testing. While genomic testing has been proposed to play a role in prenatal diagnosis, there is very limited evidence regarding the clinical utility of such testing. Additionally, the complexities associated with incidental findings are amplified by the limitations of prenatal diagnosis and the risk of uncertainty when considering pregnancy management options (Donley, 2012; Winand, 2014). Alternatives to prenatal genomic testing include postnatal evaluation, or for pregnancies that may not proceed to delivery, deoxyribonucleic acid (DNA) banking of chorionic villus or amniocentesis samples for possible future testing based on fetal autopsy findings.

In addition to the diagnostic power of WES, the cost-effectiveness of such testing is a compelling reason to include it in clinical practice. However, WES is only cost effective if it replaces the need for multiple individual gene tests, and it is not cost-effective when it is utilized after performing and receiving uninformative results from multiple other genetic tests. For this reason, when WES should be performed is best determined prior to more traditional testing, such as chromosome microarray or targeted panels.

**Literature Review**

While WES may be useful in diagnosing complex phenotypes, targeted testing has a lower risk of incidental findings. The expertise of clinical genetics specialists allows them to accurately evaluate patients and determine whether targeted testing would produce a more cost-effective and higher yield than WES. Shashi et al. (2014) retrospectively evaluated a cohort of 500 patients who received traditional medical genetics evaluations. Thirty-nine patients were determined to not have a genetic disorder; 212 of the remaining 461 (46%) received a genetic diagnosis, and 72% of these were diagnosed on the first visit. WES would not have contributed to the care of these diagnosed individuals, but it may be clinically and economically useful in the remaining pool of undiagnosed individuals. The authors propose that the clinical utility of genomic testing is greater when testing is applied after an initial clinical genetics evaluation.

A review by BCBS TEC (2013) noted the diagnostic yield of exome sequencing in the six larger patient series (n>10; each study sequenced 12 to 118 exomes) varied from 10% to 54%. The studies were largely positive or negative on the basis of the index case, and few negative results were found in this group of studies, selective reporting of positive results could have occurred. Beyond diagnostic yield, occasional anecdotal reports were identified of clinical benefit following molecular diagnosis by exome sequencing; however, no systematic study of clinical outcomes was identified. The authors note “For some patients, exome sequencing obtained after initial diagnostic evaluation (that may include other genetic testing) has failed may avoid the diagnostic odyssey and return a likely causal variant. Currently, the diagnostic yield appears to be no greater than 50% and possibly less for patients with suspected genetic disorder accompanied by multiple anomalies. Medical management decisions, including initiation of new treatment or discontinuing inappropriate treatment, may result for only a subset of those diagnosed. Reproductive decisions for parents considering an additional pregnancy may be informed by determining the mode of inheritance. Appropriate use of exome sequencing requires considerable genetic, clinical, and genetic counseling expertise”.

**Professional Societies/Organizations**

**American College of Medical Genetics (ACMG, 2012):** The ACMG published a statement regarding use of genomic testing that recommends testing be considered in phenotypically affected individuals when:

- The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
- A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.
- A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
- A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests available for that phenotype have failed to arrive at a diagnosis.

Prenatal diagnosis by genomic (i.e., next-generation whole exome- or whole genome) sequencing has significant limitations. The current technology does not support short turn-around times which are often expected in the prenatal setting. There are high false positive, false negative, and variants of unknown clinical significance rates. These rates can be expected to be significantly higher than seen when array comparative genomic hybridization (CGH) is used in prenatal diagnosis. Nonetheless, whole exome sequencing may be appropriate if the results will directly affect medical management, clinical presentation is consistent with a genetic etiology, the individual has been evaluated by a board-certified medical geneticist, the phenotype warrants testing of multiple genes and a relevant differential diagnosis list is documented, and documentation supports the cost effectiveness of the test compared to separate testing for each gene in question, and test results may preclude the need for more costly and/or invasive procedures, follow-up, or screening.

Large Panel Testing
Multi-gene testing panels rapidly sequence hundreds of genes. Unlike whole exome sequencing (WES), large panels target testing to genes that have been associated with a certain phenotype, or encompass a set of genes associated with heterogeneous and overlapping phenotypes. These panels vary in cost, and may be more or less expensive than WES depending on how many genes are included in the panel. The issues and principles discussed above for WES apply to large panel tests. However, a benefit of targeting testing to a smaller subset of genes is the lower risk of incidental findings since the genes on the panel are expected to correlate with the patient's phenotype. As expected, the risk of incidental findings is lowest with highly targeted smaller panels, and increases as the number and type of genes on the panel increases. Large panel testing may be more cost-effective than testing for individual genes testing. Like WES, large panel testing may be appropriate if the results will directly affect medical management, clinical presentation is consistent with a genetic etiology, the individual has been evaluated by a board-certified medical geneticist, the phenotype warrants testing of multiple genes and a relevant differential diagnosis list is documented, and documentation supports the cost effectiveness of the test compared to separate testing for each gene in question, and test results may preclude the need for more costly and/or invasive procedures, follow-up, or screening.

Whole Genome Sequencing
Whole genome sequencing (WGS) consists of analysis of most of the DNA content in an individual’s genome. WGS has been used as a tool to establish a diagnosis in individuals with exceptionally complex and severe phenotypes and has also been used in the oncology setting to characterize tumor genomes. WGS has typically been performed at tertiary medical centers under the care of large multidisciplinary teams, with a large research component significantly contributing to the diagnostic and evaluation process. High-quality clinical trial data are lacking in the published peer-reviewed scientific literature to inform on the use and effectiveness of whole genome sequencing outcome the research setting. At this time the clinical utility of such testing has not been established.

Use Outside of the US
No relevant information.

Summary for Other Genetic Testing: Whole exome sequencing (WES) may have clinical utility value for use in scenarios of undiagnosed disorders that involve multiple congenital anomalies suggesting a single genetic etiology, but lacking a clear diagnostic testing path. In this case stepwise testing may result in costly and prolonged diagnostic assessment. However, sequencing has significant limitations, including long turn-around times, high false positive and negative values, and high variants of unknown clinical significance rates. Similar limitations exist for large panel testing and clinical utility has not been established in large high-quality clinical trials. Clinical utility of whole genome sequencing (WGS) has not been established. Data are limited in the published peer-reviewed scientific literature regarding the use of these tests in routine clinical practice.

Coding/Billing Information
**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Covered when medically necessary:**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>81243</td>
<td>FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles</td>
</tr>
<tr>
<td>81244</td>
<td>FMR1 (fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and methylation status)</td>
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| 81401      | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)  
- AFF2 (AF4/FMR2 family, member 2 [FMR2]), (eg, fragile X mental retardation 2 [FRAXE]), evaluation to detect abnormal (eg, expanded) alleles |
| 81402      | Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])  
| 81404      | Molecular pathology procedure, Level 5 (eg, 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)  
- AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]), characterization of alleles (eg, expanded size and methylation status) |
| 81405      | Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)  
- CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide2) (eg, steroid 21-hydroxylase isoform, congenital adrenal hyperplasia), full gene sequence |

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<th>HCPCS Codes</th>
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<tr>
<td>S3866</td>
<td>Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known mutation in the family</td>
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**Experimental/Investigational/Unproven/Not Covered when used to report genetic testing for the screening, diagnosis or management of ANY of the disorders associated with the tests below:**

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<td>81291</td>
<td>MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary)</td>
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<td>HCPCS Codes</td>
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<tr>
<td>S3800</td>
<td>Genetic testing for amyotrophic lateral sclerosis (ALS)</td>
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<tr>
<td>S3861</td>
<td>Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (scn5a) and variants for suspected Brugada syndrome</td>
</tr>
<tr>
<td>S3865</td>
<td>Comprehensive gene sequence analysis for hypertrophic cardiomyopathy</td>
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</table>

Covered when medically necessary and when used to report preconception or prenatal carrier testing with a genetic testing panel for a prospective biologic parent of Ashkenazi Jewish descent. Not medically necessary/not covered when used to report disease carrier panel testing in the general population:
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<td>81200</td>
<td>ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)</td>
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<tr>
<td>81209</td>
<td>BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant</td>
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<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)</td>
</tr>
<tr>
<td>81221</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines), known familial variants</td>
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<tr>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines), duplication/deletion variants</td>
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<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines), full gene sequence</td>
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<td>81224</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines), intron 8 poly-T analysis (eg, male infertility)</td>
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<td>81242</td>
<td>FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A&gt;T)</td>
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<td>81251</td>
<td>GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
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<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G&gt;C, G269S)</td>
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<td>81260</td>
<td>IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T&gt;C, R696P)</td>
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<td>81290</td>
<td>MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A&gt;G, del6.4kb)</td>
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<td>81330</td>
<td>SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)</td>
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<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt; 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
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<tr>
<td></td>
<td>• Known familial variant not otherwise specified, for gene listed in Tier 1 or Tier 2, DNA sequence analysis, each variant exon</td>
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<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, 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)</td>
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<td>• NPC2 (Niemann-Pick disease, type C2 [epididymal secretory protein E1]) (eg, Niemann-Pick disease type C2), full gene sequence</td>
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<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)</td>
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<td>• HEXA (hexosaminidase A, alpha polypeptide) (eg, Tay-Sachs disease) full gene sequence NPC1 (Niemann-Pick disease, type C1) (eg, Niemann-Pick disease), full gene sequence</td>
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<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<td>• HEX B full gene sequence</td>
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<td></td>
<td>• Full gene sequence SMID1 (sphingomyelin phosphodiesterase 1, acid lysosomal)</td>
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<tr>
<td></td>
<td>• Genetic testing for Gaucher Disease with sequence analysis</td>
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<td></td>
<td>• Sequence analysis of ASPA (aspartoacylase)</td>
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<tbody>
<tr>
<td>S3849</td>
<td>Genetic testing for Niemann-Pick disease</td>
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References


59. Rice K, Verwoert GC, Launer LJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, Caulfield M, van Duijn CM, Ridker PM, Munroe PB, Levy D; Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; Global BPgen Consortium; Women's Genome Health Study.


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