Medical Coverage Policy

Effective Date.....**10/15/2021**
Next Review Date..... **9/15/2022**
Coverage Policy Number **0052**

Genetic Testing for Hereditary and Multifactorial Conditions

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Overview

This Coverage Policy addresses germline pathogenic or likely pathogenic variant genetic testing for hereditary and multifactorial conditions. Germline pathogenic or likely pathogenic variants occur in the egg and sperm cells; also known as the germ cells. These variants are inherited; that is, passed down in families by blood relatives.

Some conditions, such as sickle cell disease, are caused by a single germline pathogenic or likely pathogenic variant. Other conditions, such as diabetes and heart disease, are more complex. These complex conditions are referred to as multifactorial conditions. Multifactorial conditions are also inherited, but may be caused by more than one germline pathogenic or likely pathogenic variant. Environmental factors, such as nutrition, exercise, weight, smoking, drinking alcohol, and medication use may influence the observable characteristics of the condition.

Types of genetic testing used to identify germline pathogenic or likely pathogenic variants that cause hereditary and multifactorial conditions include single gene pathogenic or likely pathogenic variant testing, targeted analysis, and multigene sequencing panels.

Coverage Policy

Many benefit plans limit coverage of laboratory tests, genetic counseling and genetic testing. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

If coverage for laboratory tests, genetic counseling and genetic testing is available and disease- or condition-specific criteria for genetic testing or genetic counseling are not outlined in a related Cigna Coverage Policy, the following criteria apply.

For additional information regarding coverage for specific genetic tests please refer to the Genetic Testing Collateral Document.

Laboratory Testing

Medically Necessary

Laboratory testing, including genetic testing (proprietary or non-proprietary, individual test or panel) is considered medically necessary when ALL of the following criteria are met:

- The proposed test or each proposed test in a panel is Food and Drug Administration (FDA)-approved and/or performed in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory.
- The proposed test or each proposed test in a panel is medically necessary for the diagnosis(es)/indication(s) listed.
- Results of the proposed test or each proposed test in a panel will directly impact clinical decision making.

For an out-of-network request to be covered at an in-network benefit level, the proposed test or each proposed test in a panel must not be available from an in-network laboratory for the indication(s) or diagnoses listed.

Genetic Counseling

Medically Necessary

Pre- and post-test genetic counseling is recommended for any individual undergoing genetic testing for any indication.

Pre-and post-test genetic counseling is considered medically necessary for EITHER of the following:

- an individual undergoing genetic testing

- an individual who is a potential candidate for genetic testing

by ANY 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 (APNG) 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.

Single Gene Genetic Testing for Germline Conditions

Medically Necessary

Single gene genetic testing for a heritable disorder is considered medically necessary when EITHER of the following criteria 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.

And ALL of the following criteria are met:

- Results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
- Testing methodology targeting DNA and/or RNA is considered scientifically valid for identification of a genetically-linked heritable disease and is the most appropriate method unless technical limitations (e.g., poor quality sample) necessitate the need for alternate testing strategies.
- If testing guidelines exist, the clinical scenario falls within those recommendations.
- The clinical benefit of testing outweighs the potential risk of psychological or medical harm to the individual being tested.

Single gene genetic testing is considered medically necessary when the above criteria are met for ALL of the following conditions including but not limited to:

Alpha-1 antitrypsin disease	**Muscular dystrophies (DMD, BMD, EDMD, DM1, DM2, SM)**
Alpha and beta thalassemia	**Niemann-Pick disease**
Canavan disease	**Nuclear mitochondrial genes**
Cystic fibrosis	**Rett syndrome**
DFNB1 nonsyndromic hearing loss and deafness	**Sickle cell disease**
Familial hypercholesterolemia (homozygous and heterozygous)	**Tay-Sachs disease**
Fragile X syndrome	**21-hydroxylase deficiency**
Gaucher disease	

Genetic testing with targeted analysis for coagulation factor V Leiden (i.e., 1691G to A nucleotide variant) and prothrombin (i.e., coagulation factor II; 20210G to A nucleotide variant) is considered medically necessary for ANY of the following indications:

- pregnant woman who has a personal history of venous thromboembolism (VTE)
- in an individual with an unprovoked VTE (e.g., not associated with fracture, surgery, prolonged immobilization, cancer) when test results will impact long term medication management and at least one of the following:
  - concern for homozygous F2 or F5 or compound heterozygous F2/F5
  - high risk of recurrent VTE
- individual who has a first-degree relative* with factor V Leiden thrombophilia or F2 G2021A (prothrombin) thrombophilia and ONE of the following:
  - surgery is planned
  - individual is pregnant
  - female who is considering estrogen contraception or hormone replacement therapy if results would influence decision to use estrogen

*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.

Not Medically Necessary

Genetic testing for coagulation factor V Leiden (i.e., 1691G to A nucleotide variant) or prothrombin (i.e., coagulation factor II; 20210G to A nucleotide variant) for ANY of the following indications is considered not medically necessary (this list may not be all-inclusive):

- general population screening
- routine screening during pregnancy or prior to the use of oral contraceptives, hormone replacement therapy (HRT), or selective estrogen receptor modulators (SERMs)
- newborn testing, or routine testing in an asymptomatic child
- routine initial testing in an individual with arterial thrombosis
- testing of an asymptomatic first-degree* relative of an individual with proven symptomatic VTE and a proven coagulation factor V Leiden or prothrombin variant, for the purpose of considering primary prophylactic anticoagulation (except, as noted above, any female who is considering estrogen contraception or hormone replacement therapy if results would influence decision to use estrogen)
- neonate or child with asymptomatic central venous catheter-related thrombosis

Genetic testing is considered not medically necessary for the screening, diagnosis or management of ANY of the following conditions because there is insufficient evidence to demonstrate improved health outcomes:

- familial amyotrophic lateral sclerosis (FALS)
- genetic variants:
  - MTHFR
  - ACE
  - AGT
  - Apolipoprotein E (APOE)
  - APP
  - Presenilin 1 (PSEN1)
  - Presenilin 2 (PSEN2)
  - Prothrombin gene variant for the screening, diagnosis or management of coronary heart disease
  - Interleukin 6-174 variant
  - Chromosome 9 (9p21)
  - Kinesin-like protein 6
  - rs3798220 allele-lipoprotein A variant

Genetic testing or gene mapping in the general population is considered not medically necessary.

Multi-Gene Genetic Testing Panels

Medically Necessary

Genetic testing for hereditary conditions using a multigene sequencing panel is considered medically necessary when ALL of the following criteria are met:

- results will directly impact medical management of the individual being tested
- clinical presentation is consistent with a genetic etiology
- phenotype warrants testing of multiple genes and a relevant differential diagnosis list is documented
- test results may preclude the need for multiple and/or invasive procedures or tests, follow-up, or screening that would be recommended in the absence of panel testing

Genetic testing for nonsyndromic forms of hearing loss using a multigene sequencing panel as recommended by the American College of Medical Genetics is considered medically necessary when ALL of the following criteria are met:

- individual lacks physical findings suggestive of a known genetic syndrome
- family history is suggestive of autosomal recessive inheritance or the individual lacks a family history of prelingual hearing loss
- medical and birth histories are not suggestive of an environmental (i.e., non-genetic) cause of hearing loss, including but not limited to:

    - otitis media
    - tympanic membrane perforation
    - temporal bone fractures
    - auditory tumors
    - congenital rubella
    - congenital syphilis
    - congenital toxoplasmosis
    - congenital malformations of the inner ear
    - congenital cytomegalovirus (CMV) infection
    - prematurity
    - exposure to noise or ototoxic drugs (e.g., aminoglycosides and cyclophosphamides)

Genetic testing for multifactorial diseases using panels, gene expression classifiers, or polygenic risk scores is considered medically necessary when EITHER of the following conditions is met:

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

And ALL of the following are met:

- the test has been shown to improve clinical outcomes
- results will directly impact clinical decision-making and clinical outcome for the individual being tested
- presence of genetic variant(s) is highly predictive for the development of the multifactorial condition

Not Medically Necessary

Genetic screening in the general population is considered not medically necessary.

Newborn Screening

Covered

Cigna covers newborn screening for genetic disorders (e.g., screening for metabolic, endocrine, hemoglobin and other disorders) performed in accordance with state mandates.

General Background

Laboratory Testing

Some general principles apply to reimbursement of all laboratory tests. The testing method being used must be scientifically validated for each indication for which the test or panel is being proposed. Due to the high complexity of genetic tests the proposed test or each proposed test in a panel must be Food and Drug Administration (FDA)-approved and/or performed in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory. There are several important advantages to a test being CLIA certified, including the test having a higher degree of precision and performance by trained laboratory professionals. Tests performed in CLIA-accredited laboratories must meet regulatory CLIA standards. The results of each individual test or each test in a panel must be clinically useful for the diagnoses or indications for which the test is being performed. Further, outcomes must be meaningful, that is, they must directly impact clinical decision making and result in improved outcomes for the individual being tested.

Genetic Counseling

Genetic counseling is defined as the process of helping individuals understand and adapt to the medical, psychological, and familial indications of genetic contributions to disease. Genetic counseling services span the life cycle from preconception counseling to infertility evaluation, prenatal genetic screening and diagnosis, and include predisposition evaluation and genetic diagnosis. Genetic counseling is recommended both pre-and post-genetic test to interpret family and medical histories to assess the chance of disease occurrence and recurrence, educate regarding inheritance, testing, management prevention and resources, and counsel to promote informed choices and adaptation to risk or condition. Germline and somatic genetic testing may identify secondary and incidental findings unrelated to the primary testing indication. Pre-test genetic counseling can elicit patient preferences regarding these findings, and assist in formulating a plan for returning such results before testing occurs (National Society of Genetic Counselors [NSGC], 2020).

A variety of genetics professionals provide these services: Board-Certified or Board-Eligible Medical Geneticists, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor, and genetic nurses credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC). Individuals should not be employed by a commercial genetic testing laboratory, although counseling services by these individuals 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.

Genetic Testing

Disease can result when there is an alteration or pathogenic variant in a DNA sequence which causes the cell to produce the wrong protein, or too much or too little of the correct protein. When the pathogenic variant occurs in an egg or sperm it is referred to as a germline variant. Germline gene variants are inherited; that is, passed down in families by blood relatives.

Some conditions, such as sickle cell disease, are caused by a single germline pathogenic variant. Other conditions, such as diabetes and heart disease, are more complex. These complex conditions are referred to as multifactorial conditions. Multifactorial conditions are also inherited, but may be caused by more than one germline pathogenic variant. The presence of a pathogenic variant(s) may increase an individual's risk of developing one of these conditions; however, a combination of genetic and environmental factors such as nutrition, exercise, weight, smoking, drinking alcohol, and medication use may influence the observable characteristics of the condition.

Genetic testing involves the analysis of human deoxyribonucleic acid (DNA), ribonucleic acid (RNA), chromosomes, proteins, and certain metabolites in order to detect alterations or changes related to an inherited disorder. Types of genetic testing used to identify germline pathogenic variant(s) that cause hereditary and multifactorial conditions include single gene testing and targeted analysis. The test must have clinical utility. Clinical utility refers to the usefulness of the test to impact health outcomes and treatment.

The National Human Genome Research Institute Task Force on Genetic Testing (NHGRI) recommended the following underlying principles to ensure the safety and effectiveness of genetic tests (Holtzman and Watson, 1998):

- 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, independently replicated and subject to peer review.
- Analytical sensitivity and specificity of a genetic test must be determined before it is made available in clinical practice.
- Data to establish the clinical validity of genetic tests (clinical sensitivity, specificity, and predictive value) must be collected under investigative protocols. In clinical validation, the study sample must be drawn from a group of subjects representative of the population for whom the test is intended. Formal validation for each intended use of a genetic test is needed.
- 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.

Genetic testing may be used to aid in diagnosis or confirmation of a disorder in a symptomatic individual (i.e., diagnostic or confirmatory testing), to predict risk of future disease in an asymptomatic individual (i.e., predictive testing), to allow reproductive planning (i.e., reproductive carrier testing), prenatal testing of a fetus, preimplantation genetic diagnosis, and newborn screening. The scope of this policy includes diagnostic and confirmatory, single or multigene testing for hereditary and multifactorial conditions.

Single Gene Testing for Germline Conditions

Single gene germline genetic testing is frequently performed to diagnose or confirm the presence of a disease-causing pathogenic or likely pathogenic variant and may be appropriate if an individual demonstrates characteristics of a genetically-linked heritable disease or has a direct risk factor for the development of the specific disease in question. Diagnostic testing may also be performed to help determine the course of a disease or choice of treatment. Genetic testing for a number of genetically linked heritable conditions is supported by various professional society guidelines.

Coagulation Factor V Leiden (FVL) (i.e., 1691G to A nucleotide variant) and Coagulation Factor II (i.e., 20210G to A nucleotide variant) (F2) Prothrombin Thrombophilia: This Coverage Policy addresses confirmatory genetic testing for FVL and F2 prothrombin (i.e., 20210G to A nucleotide variant) thrombophilia. For discussion of genetic testing for these variants in recurrent pregnancy loss please see Cigna Coverage Policy 0514 Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis.

Factor V Leiden (FVL) variant (i.e., p.Arg506G1n) is the most common inherited thrombophilia (an increased tendency to form blood clots [thromboses]). It is characterized by an activated protein C resistance and an increased risk of occurrence of venous thromboembolism (VTE). In the United States, the FVL variant is found in 5.2% of individuals of European origin and 2.2% of Hispanic Americans; it is very rare in individuals of Asian or

African descent, and in the Native American population (less than 1.3%). Clinical expression of the FVL variant is variable and many individuals with the FVL allele never develop thrombosis. A family history of thrombosis in a first-degree relative is associated with a threefold increased risk of VTE; the risk is increased if the VTE occurred before age 50, and/or there are two or more affected relatives (Kujovich, 2018).

The allele 20210G to 6 (c.*97G to A) is known to be associated with coagulation factor II (F2) prothrombin-related thrombophilia. As with FVL, the 20210G>A F2 variant is more prevalent in Americans of European descent (2-5%), and Hispanic Americans (2.2%), but rarely occurs in the African, Asian, or Native American populations (Kujovich, 2021). Individuals heterozygous for this variant (that is, two different alleles) have an approximately two- to four-fold increased risk of VTE as compared to individuals without the variant. Individuals who are homozygous (two copies of the same allele) may have a more severe thrombophilia and/or an increased risk for thrombosis; however, the number of individuals who are homozygous for the variant is small and it is difficult to determine the risk of VTE in this population (Zhang, et al., 2018).

Pregnancy is associated with an increased risk for blood clotting, and individuals with FVL and/or F2 variants are at even higher risk. Individuals heterozygous for the Leiden variant have a five to eight times greater chance of a pregnancy-related VTE than those without the variant, and the risk increases to 34-fold in individuals homozygous for the variant. For those with the F2, the risk is 15-fold (heterozygotes) to 26-fold (homozygotes) (Kujovich, 2021; Kujovich 2018).

There is general consensus by a number of professional societies/organizations that testing for FVL and F2 is appropriate in selected individuals as an option to inform treatment. The decision to test should be based on clinical utility, that is, the likelihood that test results will impact clinical management (Zhang, et al., 2018; Bates, et al., 2012; Kahn, et al., 2012; Evaluation of Genomic Applications in Practice and Prevention Working Group [EGAPP], 2011). Testing allows for prophylactic and/or ongoing clinical management including thromboprophylaxis and/or modification of risk factors. Persons for whom there is professional consensus regarding clinical utility for testing are:

- pregnant woman who has a personal history of venous thromboembolism (VTE)
- in an individual with an unprovoked VTE (e.g., not associated with fracture, surgery, prolonged immobilization, cancer) when test results will impact long term medication management and at least one of the following:
    - concern for homozygous F2 or F5 or compound heterozygous F2/F5
    - annual risk of recurrent VTE is estimated to be between 5% and 10%
- individual who has a first-degree relative* with factor V Leiden thrombophilia or F2 G2021A (prothrombin) thrombophilia and ONE of the following:
    - surgery is planned
    - pregnant
    - female who is considering estrogen contraception or hormone replacement therapy if results would influence decision to use estrogen

Per Kujovich (2018), molecular genetic testing for the factor V Leiden variant specifically (or a panel which included the variant) may be indicated for the following clinical scenarios:

- individuals receiving direct thrombin inhibitors or direct factor Xa inhibitors, which may interfere with an activated protein C (APC) resistance assay
- to confirm the diagnosis (in positive APC-resistance assay values), and to distinguish factor V Leiden variant heterozygotes from homozygotes and pseudohomozygotes with positive borderline or very low APC resistance assay results
- strong lupus inhibitors and a markedly prolonged baseline aPTT when the results of testing would affect clinical management
- persons with a first unprovoked VTE who are planning to stop anticoagulation
- female relatives of persons with VTE or hereditary thrombophilia considering estrogen contraception or hormone replacement
- female relatives of persons with VTE or hereditary thrombophilia contemplating prophylactic anticoagulation during pregnancy

Potential consequences of identifying a thrombophilic defect in a patient with venous thromboembolism (VTE) include prolonging the anticoagulant therapy beyond three to six months, or prescribing a more aggressive thromboprophylaxis in at-risk situations such as surgery, pregnancy, or prolonged immobility (Zhang, et al., 2018).

The EGAPP (2011) notes for asymptomatic family members of index cases, no prophylaxis trials have been reported; therefore, there is no direct evidence of particular benefit to family members. Potential net harm is possible if primary prophylaxis is administered to asymptomatic family members with one or more variants, because the absolute risk of an initial venous thromboembolism (VTE) event is low, and the risk of anticoagulant-induced hemorrhage is relatively high. Although technically possible, prenatal testing of a fetus and preimplantation genetic diagnosis (PGD) to determine the presence of these variants is rarely performed. Presence of the variant only increases the relative risk for thrombophilia and is not predictive of a thrombotic event (Kujovich, 2018).

U.S. Food and Drug Administration (FDA)
The FDA has given 510(k) approval to several deoxyribonucleic acid (DNA)-based laboratory tests designed to test for Factor II and FV Leiden (FVL) variants including the IMPACT Dx Factor V Leiden and Factor II Genotyping Test (Sequenom, Inc., 2014, San Diego, CA), Invader Factor V and Invader Factor II (Hologic, Inc., 2011, Marlborough, MA), and the INFINITI System Assay (AutoGenomics, Inc., 2007, Carlsbad, CA).

Literature Review
Targeted genetic testing to confirm diagnosis of coagulation factor V Leiden (i.e., FVL, 1691G to A nucleotide variant) and prothrombin (i.e., F2 20210G to A nucleotide variant) is appropriate in selected populations. Professional society support for testing is available in the form of published guidelines.

No randomized controlled trials have confirmed that early identification of thrombophilia affects the risk for recurrent VTE. On behalf of the AHRQ, Segal et al. (2009) published an evidence report/technology assessment of 124 studies to determine whether FVL testing alone, or in combination with prothrombin G20210A leads to improved clinical outcomes in adults with a personal history of VTE, or in adult family members of variant-positive individuals. The authors reported that there was no direct evidence in the studies that addressed this primary objective. There was moderate evidence to support the conclusion that neither harms nor benefits of testing have been demonstrated conclusively. A single study supported the hypothesis that clinicians might change management based on test results. The authors concluded that the test results have variable clinical validity for predicting VTE in these populations and have only weak clinical utility.

Marchiori et al. (2007) conducted a systematic review of prospective studies to assess the risk of recurrent VTE associated with heterozygous carriage of FVL and prothrombin G20210A (PTM) variants. The studies included a total of 3203 patients, 557 of whom were heterozygous carriers of FV Leiden (FVL). Eleven studies were included in the review, ten (seven prospective cohort studies and three randomized trials) of which examined the risk of recurrent venous thromboembolism (VTE) in heterozygous carriers of FVL. Recurrent thromboembolism occurred in 114 of the 557 heterozygous FVL carriers (20.5%) and in 382 of the 2646 non-carriers (14.4%). This data suggests that heterozygous carriers of the FVL variant may have an increased risk of recurrent VTE when compared to non-carriers.

Wu et al. (2006) performed a systematic review and meta-analysis (i.e., Thrombosis: Risk and Economic Assessment of Thrombophilia Screening [TREATS]) to establish the risk of clinical complication associated with thrombophilia in women who used oral estrogen therapy, women who were pregnant, and individuals who had undergone major orthopedic surgery. The study also measured the relative cost-effectiveness in universal and selective, history-based screening for thrombophilia. Eighty-one studies were included in the review. The highest risk of VTE in individuals who used oral contraception and hormone replacement therapy was in women with FVL (odds ratio [OR] 15.62 and 13.16 respectively). The meta-analysis also suggested that during pregnancy, women with FVL were at a significantly higher risk to develop venous thromboembolism (VTE) and to experience recurrent pregnancy loss (OR 2.06) or late pregnancy loss (2.06). The odds ratio for the association between FVL and postoperative VTE following hip or knee replacement surgery was 1.86. The authors concluded that universal thrombophilia screening is not supported by the evidence.

Amyotrophic Lateral Sclerosis (ALS)
No one test can provide a definitive diagnosis of ALS; a reliable biochemical abnormality shared by all patients with the disease has not been identified. 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.

A number of genetic variants, including those of the superoxide dismutase 1 (SOD1), TAR DNA binding protein (TARDP or TDP-43), FUS, and C9orf72 genes have been implicated in familial ALS. About 10%–20% of all familial cases result from a specific genetic pathogenic variant of SOD1, which is inherited in an autosomal dominant manner. Greater than 100 pathogenic or likely variants have been identified. Although molecular genetic testing is available for several genes associated with familial ALS, including SOD1, the presence of these pathogenic or likely pathogenic variants may not provide prognostic information; interpretation of the significance of a variant regarding disease severity and progression depends on the specific variant because of the wide variability in genotype/phenotype correlations. Additionally, the absence of a pathogenic or likely pathogenic variant in a family where one has not been identified is not informative as it does not rule out familial ALS caused by other pathogenic or likely pathogenic variants.

Literature Review
Several genome-wide associations indicate that no definitive or common highly penetrant allele causes sporadic or familial ALS. Additionally, a number of gene variants initially thought to be causative only for familial ALS, such as SOD1, TARDBP (TDP-43) and FUS have been identified in individuals diagnosed with sporadic ALS (Belzil, et al. 2011; Siddique and Siddique, 2019; Wijesekera and Leigh, 2009). These data suggest the clinical utility of genetic testing for these variants is not firmly established.

There is insufficient evidence in the published, 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 pathogenic or likely pathogenic variant does not diagnose familial ALS, and does not impact treatment or health outcomes. Data are also lacking regarding the utility of prenatal or preconception carrier testing, prenatal testing of the fetus, or its use in preimplantation genetic diagnosis (PGD).

Methylenetetrahydrofolate Reductase (NAD(P)H) (MTHFR) Gene Variants
Polymorphisms in the MTHFR gene have been associated with an increased risk of homocystinuria, 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. Increased levels of homocysteine have also been associated with an increased risk of thromboembolism (Genetics Home Reference [GHR], 2021). Although MTHFR has been associated with increased risk of homocystinuria; genetic testing is not indicated because these variants are not associated with thromboembolism (Hickey, et al., 2013).

MTHFR variants have also been associated with an increased risk of neural tube defects, such as anencephaly or spina bifida. The 677C>T variant is the most commonly studied. 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. It is estimated that over 25% of individuals of Hispanic origin and 10-15% of North American Caucasians are homozygous for this variant (Hickey, et al., 2013).

U.S. Food and Drug Administration (FDA)
The FDA has granted 510(k) approval to several genomic DNA in vitro diagnostic tests for MTHFR mutation, including Invader MTHFR 677 and Invader MTHFR 1298 (Hologic, Inc., 2011, Marlborough, MA), eSensor MTHFR Genotyping Test (Osmetech Molecular Diagnostics, 2010, Pasadena, CA), and Verigene MTHFR Nucleic Acid Test (Nanosphere, Inc., 2007, Northbrook, IL).

Literature Review
Although there are a number of observational studies in the published peer-reviewed scientific literature regarding the association of MTHFR variants 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.

Several variants of the MTHFR gene have been associated with increased risk of developing a number of conditions; however, its role in these conditions has not been established (GHR, 2021; Hickey, et al., 2013). There is insufficient evidence in the published peer-reviewed scientific literature to determine the clinical utility of MTHFR 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.

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.

ACE and AGT Gene Variants

ACE Gene: The ACE gene (i.e., angiotensin I converting enzyme [peptidyl-dipeptidase A] 1) is part of the renin-angiotensin system (GHR, 2020a). 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, variants in the ACE gene have been identified as the most common cause of renal tubular dysgenesis; at least 33 variants 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. The contribution of other genetic and environmental influences on these risk factors is unknown (GHR, 2020a).

Angiotensinogen (AGT) Gene Variants: Individuals with an inherited variant in the AGT gene are more likely to become hypertensive and to experience more severe forms of the disease earlier in life. AGT polymorphism may be associated with increased risk of cardiovascular disease and increased responsiveness to angiotensin converting enzyme (ACE) inhibitor therapy, salt restriction and weight loss. Analysis of the gene may have potential to help individualize therapy by determining the patient's responsiveness to certain types of antihypertensive interventions. Evidence in the peer-reviewed, published scientific literature is insufficient to support the clinical utility of this testing and does not support that the detection of AGT leads to improvement of clinical outcomes in patient management.

The AGTR1 gene (i.e., angiotensin II receptor type 1 [AT1 receptor]) is also part of the renin-angiotensin system. Like variants associated with the ACE gene, AGTR1 gene variations have also been linked to renal tubular dysgenesis. Other variants, 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, 2020b).

Although it has been suggested that the presence of ACE and AGTR1 gene variants increase risk and susceptibility for a number of conditions, the influence of environmental factors and other variables on the development of these conditions is unknown. There are limited data in the published peer-reviewed scientific literature to inform improved health outcomes using the results of this testing. Established strategies for genetic testing of this gene are lacking. Genetic testing for ACE and AGTR1 gene variants remains a continued focus of

research; however, the role of such testing to inform clinical practice and improve health outcomes has not yet been established.

Literature Review
Randomized controlled trial data to inform on the ability of genetic testing to improve health outcomes are lacking. Evidence in the published peer-reviewed scientific literature regarding genetic testing for ACE and AGTR1 gene variants 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.

Apolipoprotein E (APOE) Gene Variants
Genetic testing for apolipoprotein-E epsilon (APOE) testing has been proposed as a means to provide additional risk information for those patients currently identified as low- or intermediate-risk for cardiovascular disease by standard lipoprotein test and risk factor assessment. APOE controls the metabolism of the highly atherogenic apolipoprotein B (apo B) containing lipoproteins. It is a protein constituent of VLDL and chylomicrons. The APOE gene provides instructions for making Apo E; Apo E binds to the cell surface receptors to form molecules called lipoproteins. However, there is no uniform standard for analyzing the relationship of APOE genotypes or phenotypes to cardiovascular disease (CVD) risk. At this time, genotype-phenotype correlations are incompletely understood (Bird, 2018).

Genetic testing for APOE has also has been proposed as a means to diagnose or predict susceptibility to early- and late-onset Alzheimer's disease (AD). At least three different alleles of APOE epsilon have been identified: APOE epsilon-2 (APOE e2), APOE epsilon-3 (APOE e3) and APOE epsilon-4 (APOE e4). APOE is a susceptibility polymorphism; the presence of one or two e4 alleles increases the risk but does not guarantee that someone will develop AD. Neuropathologic findings of beta-amyloid plaques and intraneuronal neurofibrillary tangles on autopsy examination remain the gold standard for diagnosis of AD (Bird, 2018). Clinical diagnosis prior to autopsy confirmation is made by use of diagnostic testing. Recommendations by the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer’s Disease and Related Disorders Association ([NINCDS-ADRDA]) criteria were published by McKhann et al. (2011), on behalf of the National Institute on Aging and the Alzheimer’s Association. These criteria correctly diagnose the disease 80%-90% of the time.

The role of APOE in late-onset AD is a topic of research interest. The APOE e4 genotype is found in many elderly persons without dementia and about 42% of persons with late-onset AD do not have an apolipoprotein-E (APOE) epsilon-4 allele. The absence of this allele does not rule out the diagnosis of Alzheimer’s disease, however the association of the APOE e4 allele with AD is significant; however, APOE genotyping is neither fully specific nor sensitive. Additional genes and loci under investigation include ABCA7, AKAP9, BIN1, CASS4, CD2AP, CD33, CLU, EPHA1, FERMT2, HLA-DRB5/DRB1, INPP5D, MEF2C, MS4A6A/MS4A4E, PICALM, PLD3, PTK2B, SORL1, and UNC5C (Bird, 2018).

There is insufficient evidence in the peer-reviewed, scientific literature to support the use of APOE testing for the screening, diagnosis or management of cardiovascular disease or Alzheimer disease (AD). APOE genotyping does not reduce the risk of developing Alzheimer’s disease, change the clinical treatment, or substantially modify disease progression in individuals with Alzheimer’s disease

U.S. Food and Drug Administration (FDA)
In 2020, the FDA granted 510(k) approval for the over-the-counter, direct-to-consumer Helix Genetic Health Risk App for Late-Onset Alzheimer’s Disease (Helix OpCo, LLC, 2020, Toronto, Canada). The manufacturer claims that the test reports the lifetime risk of developing Alzheimer’s disease at or above age 65 years based on six genotypes of the APOE gene. The predicate test for this approval was the 23andMe PGS Genetic Health Risk Report for Late-onset Alzheimer’s Disease (23andMe, 2017, Sunnyvale, CA), which reported on the e4 variant only. Potential users of either test are advised that the tests are not diagnostic, do not detect all genetic variants associated with late-onset Alzheimer’s disease, and that an individual’s race, ethnicity, age, and/or sex may affect result interpretation.

Literature Review

The Agency for Healthcare Research and Quality (AHRQ) identified 15 cohort studies involving 8509 subjects that examined the association between APOE and the risk of cognitive decline. Various studies reported that APOE epsilon-4 (e4) was associated with greater decline on some, but not all, cognitive measures. Presence of an APOE e4 allele was not, however, significantly different in those who maintained cognitive performance compared to those with minor declines (Williams, et al., 2010).

Tsuang et al. (1999) prospectively evaluated APOE testing for AD in a community-based case series of 132 persons with no previous diagnosis of dementia. Clinical diagnosis yielded a sensitivity of 84%, specificity of 50%, and positive and negative predictive values of 81% and 56%, respectively. Neuropathologic AD was confirmed in 94 of 132 patients, with a prevalence of 71%.The presence of an APOE epsilon-4 allele was associated with an estimated sensitivity of 59%, specificity of 71%, and positive and negative predictive values of 83% and 41%, respectively. The authors noted that findings do not support the use of APOE genotyping alone in the diagnosis of AD in the general medical community. In a neuropathologically confirmed series, the addition of APOE testing increased the positive predictive value of a diagnosis of AD from 90% to 94%. In those patients with a clinical diagnosis of non-Alzheimer's dementia the absence of an APOE e4 allele increased the negative predictive value from 64% to 72% (Waldemar, 2007).

Amyloid Precursor Protein (APP), Protein Presenilin 1 (PSEN1) and Protein Presenilin 2 (PSEN2)
Early onset familial Alzheimer disease (EOFAD) is diagnosed in families with multiple affected individuals with mean age of onset before 65 years and/or with a documented pathogenic variant in one of the genes known to be associated with this disorder. Although clinically indistinguishable by phenotype, three subtypes have been recognized, based on differences in the causative gene variant: Alzheimer disease type 1 (AD1), caused by pathogenic variant of APP (10%-15% of EOFAD); Alzheimer disease type 3 (AD3), caused by pathogenic variant of PSEN1, (30%-70% of EOFAD); and Alzheimer disease type 4 (AD4), caused by pathogenic variant of PSEN2 (<5% of EOFAD). Kindreds with autosomal dominant EOFAD with no identifiable pathogenic variants in PSEN1, PSEN2, or APP have been described; thus, it is likely that variants in additional genes are causative (Bird, 2018).

Genetic testing of at-risk asymptomatic adults for early-onset familial Alzheimer's disease is clinically available for PSEN1, PSEN2 and APP variants. However, genetic testing is not helpful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. At this time genotyping for PSEN1, PSEN2, and APP variants does not reduce the risk of developing Alzheimer's disease, change the clinical treatment, or substantially modify disease progression in individuals with early-onset disease.

Literature Review
The clinical utility of genetic testing for APP, PSEN1 and PSEN2 to diagnose or manage early-onset familial Alzheimer disease in at-risk individuals or as a screening tool in the general population has not yet been established. At this time there is insufficient evidence in the published, peer-review scientific literature to demonstrate improved health outcomes with such testing.

Cardiac Disease – Risk Factors
Prothrombin Gene Variants: Genetic testing for prothrombin gene variants has been proposed as a means to screen, diagnose and manage coronary heart disease. Thrombosis has been implicated as a risk factor for cardiovascular disease. However, there is insufficient evidence in the published, peer-reviewed scientific literature to establish a role of genetic testing for this indication.

Interleukin 6–174 Variant: Interleukin 6 is an inflammatory cytokine that is believed to play a role in the acute phase response and inflammatory cascade similar to C-reactive protein. One polymorphism, –174, has been reported to be of specific importance (Lieb, et al., 2004). However, evidence regarding the relationship between interleukin 6–174 and cardiovascular disease has not been consistently demonstrated in the peer-reviewed, published scientific literature. The results of some studies show an association between plasma levels and cardiovascular disease (Reichert, 2016; Bermudez, et al., 2002) and, in other studies, authors have reported it is not a suitable marker for coronary heart disease and that significant associations have not been found (Sukhija, et al., 2007; Sie, et al., 2006; Lieb at al., 2004). The limitations of the overall body of published evidence preclude the ability to draw strong conclusions on the clinical utility of interleukin 6–174 testing at this time.

Kinesin-like protein 6 (KIF6): Kinesin-like protein 6 is a protein involved in intracellular transport expressed in many tissues and cell types. Theoretically, variants of KIF6 (719Arg allele) may be a risk factor associated with cardiovascular disease (CVD), in particular with myocardial infarction. While the role of KIF6 in CVD is not clearly established in the peer-reviewed scientific literature, there are a few studies that support an association with CVD (Shiffman, et al., 2008a; Bare, et al., 2007; Shiffman, et al., 2008b; Iakoubova, et al., 2008). Furthermore, preliminary evidence has shown that high dose statin therapy compared with standard dose reduced the risk of death or major cardiovascular events in patients who were carriers of the gene (Iakoubova, et al., 2008). However, further studies are needed to clearly define the functional effect of the gene, the affect KIF6 has on CVD, and to determine how testing impacts medical management strategies and improves clinical outcomes.

Chromosome 9 Polymorphism 9p21: Genomic profiling (evaluating multiple genes) has recently been evaluated as a method of improving cardiac risk determination compared to traditional cardiac risk factors. The Genomic Applications in Practice and Prevention (EGAPP) Working Group (launched by the Centers for Disease Control and Prevention) sought indirect evidence to support that genomic profiling has an impact on cardiac risk estimation and that improvement in risk determination would result in management changes that improved clinical outcomes. EGAPP acknowledged direct evidence is lacking. Overall, 29 gene candidates were evaluated with 58 different gene variant associations. Only one marker, chromosome 9p21 SNPs (single nucleotide polymorphisms), had strong credibility; other combinations were moderate or weak (Palomaki, et al., 2010). Based on the published recommendations (EGAPP, 2010) there was insufficient evidence to support testing in the general population for the 9p21 variant or for any of the 57 other variants found in 28 genes. As a result, the magnitude of health benefit for these was tests were found to be insignificant. The extent to which genomic profiling alters cardiac risk estimation remains unknown and genomic testing cannot be recommended until evidence supports improved clinical outcomes.

rs3798220 allele-lipoprotein A (LPA) variant: Genetic variants of the Lp(a) gene are being investigated to evaluate the influence of the variants on Lp(a) levels and associated cardiac risk. One single nucleotide polymorphism (LPA rs3798220) has been identified in the LPA gene as being associated with both elevated levels of lipoprotein(a) and an increased risk of thrombosis. Theoretically patients with a positive test for the LPA genetic variant rs3798220 may derive more benefit from the anti-thrombotic properties of aspirin due to the increased risk for thrombosis, thereby reducing cardiac disease risk. As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment.

The U.S. Preventive Services Task Force (USPSTF) guidelines do support aspirin therapy for a specific subset of individuals for reducing the risk of stroke or myocardial infarction. Aspirin therapy is a well-established but may be associated with gastrointestinal bleeding. Authors contend that testing for the LPA genetic variant may help to better define the risk/benefit ratio of aspirin therapy when the Lp(a) level is elevated.

Evidence in the published, peer-reviewed scientific literature evaluating the association of lipoprotein A variant and elevated Lp(a) is in early stages with mixed outcomes being reported (Li, et al., 2014; Anderson, et al , 2013; Koch, et al., 2013; Hopewell, et al., 2011; Chasman, et al., 2009; Clarke, et al., 2009; Shiffman, et al., 2008a; Shiffman, et al., 2008b). Currently the evidence does not lend support that testing offers any additional prognostic value compared to Lp(a).

Gene Expression Profiling for Cardiovascular Disease Risk: Gene expression is a process by which a gene's coded information is translated into the structures present and operating in the cell and has been investigated as a diagnostic tool for evaluating individuals with cardiovascular disease.

U.S. Food and Drug Administration (FDA)
While many genetic and genomic tests are regulated by the FDA, laboratory developed tests (i.e., in vitro diagnostic tests that are designed, manufactured and used within a single laboratory) go to market without independent analysis. One such example was the Corus CAD Assay from CardioDx Inc. (Palo Alto, CA), which was proposed as a quantitative gene expression test intended to rule out coronary artery disease (CAD) in stable, nondiabetic individuals. However in 2019, a Medicare Local Coverage Decision of non-coverage was issued, stating “the manufacturer has failed to demonstrate that testing resulted in improved patient outcomes or that testing changed physician management to result in improved patient outcomes”, (CMS, 2021). The test is no longer commercially available.

Literature Review
Although there are some data in the published, peer-reviewed scientific literature evaluating risk factors as a method of assessing cardiovascular disease, the added value beyond that associated with traditional testing has not been firmly established. Consensus support from professional societies/organizations in the form of published guidelines is lacking. The impact of genetic testing on meaningful clinical outcomes such as morbidity and mortality has not yet been clearly defined.

Evidence in the published peer-reviewed scientific literature evaluating gene expression for determining cardiovascular disease risk (e.g., Corus CAD) is limited to prospective validation studies and case control studies (Filsoof, 2015; Ladapo, 2015; Daniels, 2014; Vargas 2013; Wingrove, et al., 2008; Rosenberg, et al., 2010; Elashoff, et al., 2011; Rosenberg, et al., 2012; Lansky, et al., 2012; McPherson, et al., 2013; Thomas, et al., 2013). Wingrove et al. (2008) and Elashoff, et al. (2011) evaluated genes associated with CAD as part of the development of the gene expression assay algorithm for assessing CAD in nondiabetic patients. Rosenberg and colleagues published results of the PREDICT trial (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) in 2010, a trial designed to validate the diagnostic accuracy of gene expression, and reported sensitivity and specificity were 85% and 43% respectively. The authors noted the algorithm score was moderately correlated with maximum percent stenosis ($p<0.001$).

As a follow-up to the 2010 trial, Rosenberg and associates reported on the relation of gene expression testing to major adverse cardiovascular events and revascularization procedures. The study group involved an extended cohort of the PREDICT trial that included the validation cohort (n=526) as well as the algorithm development cohort (n=640). Subjects underwent angiography and gene expression testing and were followed for one year post angiography (n=1116). The study endpoint was major adverse cardiac event or procedures. At one year the endpoint rate was 25% overall for all subjects. The gene expression score (GES) was associated with composite overall endpoint of both major events and procedures at one year ($p<0.001$) and at 12 months the sensitivity and specificity were 86% and 41% respectively. Elevated GES scores (>15) trended towards an increased rate of adverse events and procedures. The authors noted study limitations included limited follow-up period post index angiography, and exclusion of individuals with high risk unstable angina and low risk asymptomatic subjects. Further studies with larger cohorts and evaluation of longer term outcomes are needed.

Thomas et al. (2013) reported the results of a prospective, multicenter, double blind trial evaluating gene expression as a method to assess obstructive CAD (n=431) (COMPASS study). The study population consisted of a cohort of subjects referred for diagnostic myocardial perfusion imaging (MPI) stress testing with angina or angina equivalent symptoms. The subjects had blood samples for gene expression obtained prior to MPI and based on MPI results were referred for either invasive coronary angiography or CT angiography. The subjects were followed for six months with a study end point of a major adverse cardiac event. Angiography results were compared to GES and MPI results. GES was significantly correlated with maximum percent stenosis (≥ 50). Negative predictive value, sensitivity and specificity were reported at 96%, 89% and 52%, respectively. In the authors' opinion gene expression scoring was more predictive of obstructive CAD compared to MPI and other clinical factors. Limitations noted by the authors included potentially lower disease prevalence in the subjects due to inclusion/exclusion criteria, and lack of comparison of GES scores to other noninvasive imaging modalities.

In another clinical trial, McPherson et al. (2013) evaluated the impact of gene expression testing on disease management by a group of cardiology specialists. The results of this study (n=88) demonstrated that subjects with low gene expression scores (i.e., ≤ 15) were more likely to have a decrease in the intensity of diagnostic testing. In addition, patients with elevated levels were more likely to undergo additional testing for the evaluation of obstructive CAD. Limitations of this study include small sample population, evaluation of short term outcomes (six months), and inclusion criteria of low risk individuals.

Herman et al. (2014) published the results of a prospective clinical trial (n=261) to evaluate the impact of GES testing on reduction of diagnostic uncertainty in the evaluation of subjects presenting with symptoms suggestive of obstructive CAD. The trial is referred to as the "Primary Care Providers Use of a Gene Expression Test in Coronary Artery Disease Diagnosis (IMPACT-PCP)" trial. Subjects were nondiabetic patients presenting with stable, nonacute typical and atypical symptoms of obstructive CAD. Ten subjects were excluded, primarily due to

GES exclusion criteria. Preliminary clinical decisions, without GES results were made by the primary care physician and compared to final decisions made with the GES results. Primary outcomes included the change in patient management between preliminary and final decisions; secondary outcomes included assessment of the pattern of change for each patient, including the effect the change had on patient outcomes. The average pretest probability of obstructive CAD was 28±17%. There was a change in diagnostic plan in 145 subjects with 93 having a reduction in intensity of testing ($p<0.001$). GES was not associated with untoward outcomes within the first 30 days follow-up; one major adverse cardiac event occurred within the 30 day period. GES testing in this study group allowed physicians to reclassify subjects for subsequent testing. Limitations of the study included sample population of nondiabetic subjects, and short-term follow-up of 30 days for monitoring of adverse events.

Ladapo et al. (2014) published the results of the REGISTRY trial which was a prospective, multicenter observation registry of data collected regarding utilization of health care services for subjects at seven primary care sites who underwent GES testing. Following GES testing medical assessments of the subjects were followed for 45 days to determine how clinicians managed the subjects (e.g., cardiology referrals, cardiac stress tests, angiography). Primary outcomes included the 45 day assessment outcomes, in addition to six-month follow up for evaluating major cardiac adverse events. The GES showed statistically significant relationships with patterns of cardiac referrals; subjects with a low GES had 94% decreased odds of referral versus subjects with an elevated GES. The overall major adverse cardiac event rate was 5/339 during the follow-up period. Ladapo and colleagues concluded GES had an effect on patient management that was clinically relevant and the test was safe as evidenced by a low major cardiac adverse cardiac event rate. The study is limited by lack of a control group.

Multi-Gene Genetic Testing Panels (Germline Genetic Testing Panels)

Overall, the clinical utility of genetic testing is dependent upon the particular phenotype or observable characteristics of a disease, and set of genes being tested. Similar to genetic testing for single genes, smaller, more targeted panels to assess for a particular disorder may have clinical utility when used to aid in diagnosis of heterogeneous genetic conditions. As with single gene testing, results of testing should directly impact clinical management and improve clinical outcomes for the individual being tested. Test results may preclude the need for additional tests, follow up or screening that would be recommended if panel testing is not performed. Additional advantages of panel testing include possible time and cost effectiveness as compared with the time and cost of analyzing each gene separately. The role of panel testing has not been established when treatment is largely supportive and/or results of testing will not result in a direct change in clinical management of the individual or lead to an improvement in clinical outcomes.

Most multigene panels use next-generation sequencing (NGS) methodology, but some still use Sanger sequencing. Next generation sequencing technology allows large amounts DNA to be sequenced rapidly 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. Such testing is expected to enable widespread evaluation of patients' genomes in the clinical setting (Taber et al., 2014). Multigene test panels range from small to large numbers of genes. For testing of multifactorial conditions, testing panels may include gene expression classifier and polygenic risk score tests.

Multigene Panel Testing for Nonsyndromic Hearing Loss
More than 50% of prelingual deafness is genetic, with most of these cases being autosomal recessive and nonsyndromic. It has been noted that the reduction in the incidence of acquired causes of hearing loss has resulted in hereditary hearing loss accounting for a greater proportion of hearing loss in the general population (Hone and Smith, 2003).

Genetic forms are diagnosed by otologic, audiological, ancillary (i.e., computed tomography [CT] examination of the temporal bone), and DNA-based testing, as well as by physical examination and family history. Molecular testing of gene GJB2 (which encodes the protein connexin 26) and GJB6 should be considered in the evaluation of individuals with congenital nonsyndromic sensorineural hearing loss consistent with autosomal recessive inheritance or in families with apparent "pseudodominant" inheritance of DFNB1 (Smith, 2016). Approximately 98% of individuals with DFNB1 have two identifiable GJB2 variants. Approximately 2% of individuals with DFNB1 have one identifiable GJB2 variant and one of two large deletions that include a portion of GJB6. Diagnosis

depends upon molecular genetic testing to identify deafness-causing variants in the genes GJB2 and GJB6. GJB2 gene is the major gene responsible for nonsyndromic, recessive deafness and variants in GJB2 gene and GJB6 gene together account for 50% of autosomal recessive nonsyndromic hearing loss.

Multigene testing or screening with a panel of genetic tests has been proposed to test for many causes of hearing loss. The extreme genetic heterogeneity and the frequent lack of phenotypic variability make genetic diagnosis of nonsyndromic hearing loss (NSHL) difficult using single-gene screening techniques—for this reason, multigene screening panels for NSHL have been developed. For some syndromic forms of hearing loss, such as Usher syndrome or Pendred syndrome, the nonauditory features can be subtle, especially in early childhood and certain environmental or nongenetic factors play a major etiologic role in hearing loss.

Literature Review
Evidence in the peer-reviewed published literature supports the use of multigene panel testing for nonsyndromic hearing loss (NSHL) for select individuals. There is significant genetic heterogeneity in NSHL, with more than 6,000 causative variants having been found in over 110 genes; multigene panels have therefore overtaken single-gene testing as the preferred approach to testing (Shearer, et al., 2017).

Sloan-Heggen et al. (2016) completed targeted genomic enrichment and massively parallel sequencing (TGE + MPS) testing on patients referred for genetic testing for hearing loss (n=1119). Using a custom-developed panel of up to 89 genes, researchers identified a genetic cause of hearing loss in 440 patients (39%). The analysis identified 5,900 variants, 14% of which were deemed causally related to the hearing loss phenotype and reported as pathogenic or likely pathogenic. The four genes most frequently involved were GJB2 (22%), STRC (16%), SLC26A4 (7%), and TECTA (5%). Variants in GJB2 were the most common cause of severe-to-profound hearing loss (20%), and STRC accounted for 30% of diagnoses in subjects with mild-to-moderate hearing loss. Of note, ethnicity impacted the diagnostic rate ($p<0.005$). The diagnostic rate for Caucasian subjects was 38%, and in cohorts self-identified as Asian and Middle Eastern the diagnostic rate was 63 and 72%, respectively ($p<0.005$). The diagnostic rate was lowest in African Americans at 26% ($p<0.05$). The authors noted that a thorough history and physical was essential in guiding the comprehensive genetic testing and making an appropriate diagnosis.

Shearer and Smith (2015) noted similar diagnostic rates in their retrospective review of 20 studies of comprehensive genetic testing for hearing loss (n=603 subjects). There were significant differences in the number and type of genes included and whether copy number variations were examined. The overall diagnostic rate was 41% (ranging from 10% to 83% depending on the panel). The authors noted that disease-specific comprehensive (panel) testing provided a better overall diagnostic rate across varying ethnicities than single gene testing, which must be tailored to the phenotype and population being studied. For example, mutations in the gene GJB2 are the cause of between 15–40% of autosomal recessive NSHL in Caucasian individuals but mutations in this same gene very rarely cause genetic hearing loss in other populations; panel testing negated the need for possibly inappropriate sequential single gene testing.

Newborn Screening

Newborn screening is performed to limit the morbidity and mortality attributable to selected inherited diseases (American Academy of Pediatrics ([AAP], 2013). Newborn screening programs are organized through state governments and are generally mandated. According to the March of Dimes (2020), screening is available for disorders in which accurate diagnosis and early treatment of the disorder can improve health outcomes. Some genetic screening tests are not deoxyribonucleic acid (DNA) - or chromosome-based tests but use biochemical markers or phenotypic features.

Each year, over four million infants in the U.S. undergo screening, and approximately 12,900 infants are diagnosed with one of the 35 core conditions included in the panel. The most prevalent disorders are hearing loss, primary congenital hypothyroidism, sickle cell disease, and cystic fibrosis (Sontag et al., 2020).

Professional Societies/Organizations

Factor V Leiden and Prothrombin (i.e., Coagulation Factor II; 20210G>A variant)
American College of Chest Physicians (ACCP): On behalf of the ACCP, Bates et al. (2012) published the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines that provides treatment guidelines for the circumstance when a pregnant woman is known to be homozygous for FVL or the prothrombin 20210A variant:

- For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, ACCP suggests antepartum clinical vigilance and postpartum prophylaxis for six weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B)
- For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, ACCP suggests antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

American College of Medical Genetics (ACMG): On behalf of the ACMG, Zhang et al. (2018) recommended factor V Leiden and factor II testing for the following indications:

- unprovoked venous thrombosis, especially age <50 years
- venous thrombosis in unusual sites (such as hepatic portal, mesenteric, and cerebral veins)
- recurrent venous thrombosis
- personal history of venous thrombosis and two or more family members with a history of venous thrombosis or one first-degree relative with venous thrombosis at a young age
- individuals with low activated protein C (APC) resistance activity

Testing may also be considered in the following situations:
- females under the age of 50 who smoke tobacco and have a history of acute myocardial infarction
- siblings of individuals known to be homozygous for factor V Leiden or factor II
- asymptomatic pregnant female or female contemplating pregnancy, with a first-degree relative with unprovoked venous thrombosis or venous thrombosis provoked by pregnancy or contraceptive use
- pregnant female or female contemplating pregnancy or estrogen use who has a first-degree relative with a history of or venous thrombosis and is a known carrier for factor V Leiden and/or factor II
- pregnant female or female contemplating pregnancy with a previous non-estrogen-related or venous thrombosis or venous thrombosis provoked by a minor risk factor, because knowledge of the factor V Leiden or factor II status may alter pregnancy-related thrombophylaxis

Testing is not recommended for the following:
- personal or family history of arterial thrombotic disorders
- a general population screen
- all individuals with venous thrombosis
- asymptomatic minors
- routine prenatal testing
- a routine initial test during pregnancy, or prior to the use of oral contraceptives, hormone replacement therapy (HRT)

American Congress of Obstetricians and Gynecologists (ACOG): Practice Bulletin number 197 (2018) regarding inherited thrombophilias in pregnancy notes:

- Screening for inherited thrombophilias is not recommended for women with a history of fetal loss or adverse pregnancy outcomes (e.g., placental abruption, preeclampsia, fetal growth restriction) (Level B, based on limited or inconsistent scientific evidence).
- Because of the lack of association between either heterozygosity or homozygosity for the MTHFR C677T polymorphism and any negative pregnancy outcomes, increased risk of VTE, screening with

either MTHFR mutation analyses or fasting homocysteine levels is not recommended. (Level B, based on limited or inconsistent scientific evidence)
- Among women with personal histories of VTE, recommended screening tests for inherited thrombophilias should include factor V Leiden mutation and G20210A mutation. (Level C, based primarily on consensus and expert opinion)

Screening for inherited thrombophilias is useful only when results will affect management decisions, and is not useful in situations where treatment is indicated for other risk factors. Targeted assessment may be considered in the following clinical settings:

- A personal history of venous thromboembolism that was associated with or without a recurrent risk factor (e.g., fractures, surgery, and prolonged immobilization) and no prior thrombophilia testing.
- A first-degree relative (e.g., parent or sibling) with a history of high-risk thrombophilia.

Recommendations based primarily on consensus and expert opinion note screening for inherited thrombophilias should include FVL mutation; prothrombin G20210A mutation; and antithrombin, protein C, and protein S deficiencies. Additionally all patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions.

American Heart Association (AHA)/American Stroke Association: In their combined statement on Diagnosis and Management of Cerebral Venous Thrombosis (CVT), the American Heart Association and American Stroke Association recommended the following in relation to hereditary thrombophilia testing:

- Testing for prothrombotic conditions, including protein C, protein S, antithrombin deficiency, antiphospholipid syndrome, prothrombin G20210A mutation, and factor V Leiden, can be beneficial for the management of patients with CVT. Testing for protein C, protein S, and antithrombin deficiency is generally indicated 2 to 4 weeks after completion of anticoagulation. There is a very limited value of testing in the acute setting or in patients taking warfarin. (Class IIa; Level of Evidence B) (Saposnik, et al., 2011).

Centers for Disease Control and Prevention: Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2011): The EGAPP published guidelines regarding the routine testing for factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members (2011). According to the EGAPP there was adequate evidence to recommend against routine testing for FVL and/or prothrombin 20210G>A (PT) in the following circumstances: (1) adults with idiopathic venous thromboembolism (VTE). In such cases, longer term secondary prophylaxis to avoid recurrence offers similar benefits to patients with and without one or more of these mutations. (2) Asymptomatic adult family members of patients with VTE and an FVL or PT mutation, for the purpose of considering primary prophylactic anticoagulation. Potential benefits are unlikely to exceed potential harms. The overall certainty of these findings was deemed "moderate." The evidence was insufficient to determine whether FVL/PT testing might have clinical utility in some circumstances, such as for identifying FVL homozygosity among asymptomatic family members of adults with idiopathic VTE or counseling patients about the risks and benefits of antithrombotic therapy. Based on the available evidence, the certainty of net health benefit was deemed "low." The recommendations do not extend to patients with other risk factors for thrombosis, such as contraceptive use, as the evidence review that serves as the basis for the recommendations focused primarily on idiopathic VTE.

Methylenetetrahydrofolate Reductase (NAD(P)H) (MTHFR)
American College of Medical Genetics (ACMG): On behalf of the ACMG, Hickey et al. (2020) note the following recommendations:

- 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

American College of Obstetrics and Gynecology (ACOG): ACOG (2018) does not endorse testing for MTHFR polymorphisms for routine risk assessment, evaluation of thrombosis risk, or recurrent pregnancy loss.

Alzheimer's Disease: APOE, APP, PSEN1 and PSEN2 Gene Variants

American Academy of Neurology (AAN): The Quality Standards Subcommittee of the AAN updated an earlier practice parameter for the diagnosis of dementia in the elderly. Regarding Alzheimer's disease (AD), this evidence-based review concluded that there are no laboratory tests, including APOE genotyping or other genetic markers or biomarkers, which are appropriate for routine use in the clinical evaluation of patients with suspected AD. However, genotyping and biomarkers, as well as imaging, are promising avenues that are being pursued (Knopman, et al., 2004).

American Psychiatric Association (2007): Practice Guidelines for the treatment of patients with Alzheimer's disease and other dementias note that a definitive diagnosis of AD requires both the clinical syndrome and microscopic examination of the brain at autopsy, at which time the characteristic plaques and neurofibrillary tangles widely distributed in the cerebral cortex will be seen. A careful clinical diagnosis of disease conforms to the pathological diagnosis 70%–90% of the time. Further, the guideline notes although genes involved in a variety of dementia syndromes have been identified and family members of patients with dementia are often concerned about their risk of developing dementia, genetic testing is generally not part of the evaluation of patients with dementia except in very specific instances. In particular, testing for apolipoprotein E4 (APOE4) is not recommended for use in diagnosis. The presence of an APOE4 allele does not change the need for a thorough workup and does not add substantially to diagnostic confidence.

National Institute on Aging (NIA, 2019): The NIA published a fact sheet noting that although a blood test can identify which APOE alleles a person has, it cannot predict who will or will not develop Alzheimer's disease. It is unlikely that genetic testing will ever be able to predict the disease with 100% accuracy because too many other factors may influence its development and progression. Further, the NIA noted APOE testing is used in research settings to identify study participants who may have an increased risk of developing Alzheimer's.

National Institute on Aging (NIA)/Alzheimer's Association: The NIA/AA issued consensus recommendations regarding the diagnosis of AD. For probable AD dementia in a carrier of a causative genetic mutation the recommendations note that in persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2), increases the certainty that the condition is caused by AD pathology. Carriage of the 3/4 allele of the apolipoprotein E gene is not sufficiently specific to be considered in this category (McKhann, et al., 2011).

National Society of Genetic Counselors (NSGC)/American College of Medical Genetics (ACMG): On behalf of the NSGC/ACMG, Goldman et al. (2019) published consensus practice guidelines for genetic counseling and testing for AD. The Guidelines recommend that pediatric testing for AD should not occur. Additionally, the Societies note that direct-to-consumer APOE testing is not advised.

The Guidelines note that a risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with early-onset Alzheimer's disease (EOAD) or late-onset Alzheimer's disease (LOAD) and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance. Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression. The Guidelines also note:

For families in which an autosomal dominant AD gene mutation is a possibility:

- Testing for genes associated with early- onset autosomal dominant AD should be offered in the following situations:
    - a symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption)
    - autosomal dominant family history of dementia with one or more cases of EOAD
    - a relative with a mutation consistent with EOAD (currently PSEN1/2 or APP)
    - Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol. If the affected

relative, or their next of kin, is uninterested in pursuing tested, the option of deoxyribonucleic acid (DNA) banking should be discussed.

For families in which autosomal dominant AD is unlikely:

- Genetic testing for susceptibility loci (e.g., apolipoprotein-E [APOE]) is not clinically recommended due to limited clinical utility and poor predictive value.

Cardiac Disease Risk

American Academy of Family Physicians (AAFP): The AAFP recommends against genomics profiling to assess risk for cardiovascular disease, stating "the net health benefit from the use of any genomic tests for the assessment of cardiovascular disease risk is negligible and there is no evidence that they lead to improved patient management or increased risk reduction" (AAFP, 2012).

American College of Cardiology Foundation (ACCF) /American Heart Association (AHA) Task Force on Practice Guidelines: Greenland et al. (2010) published guidelines which note that genotype testing for CHD risk assessment in asymptomatic adults is not recommended. The task force noted that there is currently no proven benefit in risk assessment when genomic testing is added to the basic global risk assessment, such as Framingham. There is no data to support results of genotype testing alter management and improve clinical outcomes.

The task force conducted a systematic review of the current scientific evidence (March 2008 – April 2010) and used evidence based methodologies to weigh the evidence which was reviewed. Level A evidence represented data from multiple randomized controlled trials or meta-analyses, level B evidence was data from a single RCT or nonrandomized trial, and level C evidence represented consensus opinion, case studies or standard of care. The recommendations were approved and endorsed by the ACCF, AHA, American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published guidelines for assessment of cardiovascular risk in asymptomatic individuals (i.e., apparently healthy adult) (Greenland, et al., 2010). The guidelines do not support genotype testing (level B evidence) or measurement of lipid parameters such as lipoproteins, apolipoproteins, particle size and density, beyond the standard fasting lipid profile (level C evidence), or natriuretic peptide testing (level B evidence).

Updated ACC/AHA guidelines on the assessment of cardiovascular risk (Goff, 2013) do not address genetic testing to determine cardiovascular risk.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP, 2010): The working group concluded there was insufficient evidence to determine analytic validity, clinical validity, or clinical utility for gene expression testing for determining cardiovascular risk.

Multigene Panel Testing for Nonsyndromic Hearing Loss

American College of Medical Genetics and Genomics (ACMG): Guidelines for the clinical evaluation and etiologic diagnosis of hearing loss include the following recommendations regarding genetic testing for nonsyndromic hearing loss:

- For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories that do not suggest an environmental cause of hearing loss, a tiered diagnostic approach should be implemented:
    - Pretest genetic counseling should be provided, and, with patient's informed consent, genetic testing should be ordered.
    - Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology.
    - In the absence of any specific clinical indications and for singleton cases and cases with apparent autosomal recessive inheritance, the next step should be testing for DFNB1-related hearing loss (due to mutations in GJB2 and adjacent deletions in GJB6). If initial genetic testing is negative, genetic testing using gene panel tests, NGS technologies such as large sequencing panels targeted toward hearing loss–related genes, whole-exome sequencing (WES), or whole-

genome sequencing (WGS) strategies may be considered. Since several tests are clinically available, the clinician should be aware of the genes included in the panel chosen and the performance characteristics of the platform chosen, including coverage, analytic sensitivity, and the types of mutations that will be detected.
    - If genetic testing reveals mutation(s) in a hearing loss–related gene, mutation-specific genetic counseling should be provided, followed by appropriate medical evaluations and referrals.
    - If genetic testing fails to identify an etiology for a patient's hearing loss, the possibility of a genetic or acquired etiology remains. This point should be emphasized since it may be misunderstood by clinicians and by patients and their families. For interested patients and families, further genetic testing may be pursued on a research basis.
- Regardless of whether genetic test results are positive, negative, or inconclusive, results should be communicated through the process of genetic counseling (Alford, et al., 2014).

American Academy of Audiology/Joint Committee on Infant Hearing (JCIH): In its 2019 position statement on principles and guidelines for early hearing detection and intervention programs, the Joint Committee on Infant Hearing endorsed genetic counseling and testing for children with confirmed hearing loss, in accordance with the American College of Medical Genetics (ACMG) recommendations (JCIH, 2019).

Newborn Screening
American Academy of Pediatrics (AAP) and American College of Medical Genetics (ACMG): In a joint statement on ethical and policy issues in genetic testing, the AAP and ACMG expressed support for the mandatory offering of newborn screening for all children. The joint statement noted "After education and counseling about the substantial benefits of newborn screening, its remote risks, and the next steps in the event of a positive screening result, parents should have the option of refusing the procedure, and an informed refusal should be respected" (AAP, 2018).

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

The American Society for Clinical Laboratory Science: "Don't order a factor V Leiden (FVL) mutation assay as the initial test to identify a congenital cause for a thrombotic event. First, order a phenotypic activated protein C resistance (APCR) ratio assay" (released June 10, 2020).

The American Society of Hematology-American Society of Pediatric Hematology/Oncology: "Don't order thrombophilia testing on children with venous access (i.e., peripheral or central) associated thrombosis in the absence of a positive family history" (released December 9, 2019).

The Society for Maternal-Fetal Medicine: "Don't do an inherited thrombophilia evaluation for women with histories of pregnancy loss, fetal growth restriction (FGR), preeclampsia and abruption" (released February 3, 2014).

The American Society for Reproductive Medicine: "Don't routinely order thrombophilia testing on patients undergoing a routine infertility evaluation" (released December 3, 2013).

The American Society of Hematology: "Don't test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility)" (released December 4, 2013).

The Society for Vascular Medicine: "Don't do work up for clotting disorder (order hypercoagulable testing) for patients who develop first episode of deep vein thrombosis (DVT) in the setting of a known cause" (released February 21, 2013).

The Society for Maternal-Fetal Medicine: "Don't test women for MTHFR mutations" (released May 1, 2019).

The American College of Medical Genetics and Genomics: “Don’t order MTHFR genetic testing for the risk assessment of hereditary thrombophilia” (released July 20, 2015; updated September 15, 2016).

The American College of Medical Genetics and Genomics: “Don’t order APOE genetic testing as a predictive test for Alzheimer disease” (released July 10, 2015; updated September 15, 2016).

Use Outside of the US

Factor V Leiden and Prothrombin (i.e., Coagulation Factor II; 20210G>A variant)
Scottish Intercollegiate Guidelines Network (SIGN): In its 2014 updated national clinical guideline on prevention and management of venous thromboembolism (VTE), SIGN made the following recommendations in the setting of pregnancy and the puerperium:

- Routine testing for thrombophilia in pregnancy is not indicated.
- Women with inherited or acquired thrombophilia and no previous history of VTE do not routinely require pharmacological thromboprophylaxis antenatally. Exceptions include women with:
  - multiple thrombophilic defects (including homozygosity for factor V Leiden)
  - antithrombin deficiency
  - heritable thrombophilia and a strong family history of VTE, especially if pregnancy-related.

In the setting of diagnosed VTE, the recommendation is that testing for inherited forms of thrombophilia does not influence initial management and should not be performed routinely (SIGN, 2014).

British Committee for Standards in Hematology ([BSCH], 2010): On behalf of the BCSH, Baglin et al. noted that testing for heritable thrombophilias is not indicated in unselected patients presenting with venous thrombosis. Testing selected patients may give an indication of risk of recurrence following completion of anticoagulant therapy, for example those presenting with venous thrombosis at an early age (<40 years) and who are from apparent thrombosis-prone families (more than two other symptomatic family members). Other selected patient groups in whom the results of testing may influence treatment are children with purpura fulminans and pregnant women at risk of venous thrombosis. The decision to test these selected patients should be based on whether or not test results are likely to influence treatment decisions.

European Genetics Foundation, the Cardiovascular Disease Educational and Research Trust, the Mediterranean League on Thromboembolism, and the International Union of Angiology: In the International Consensus Statement for Thrombophilia and Thromboembolism, Nicolaides et al. (2005) provided guidelines for investigation and management of patients with thrombophilia (with or without VTE). According to the authors, heterozygote FVL is found in 0–15% of the normal population, 20% of patients with venous thrombosis and in 40% of families with thrombophilia, whereas the homozygote FVL mutation is found in only 0.02% of the normal population, but the relative risk is high. The authors researched the etiology, testing, diagnosis, risk factors, prevention and management of thrombophilia. Based on this research, the authors concluded that screening for thrombophilia should occur in:

- all patients with a first episode of spontaneous VTE
- patients with VTE under the age of 50, even with a transient predisposing factor
- patients with VTE whose only risk factor is oral contraceptive therapy or pregnancy. However, screening with other than the molecular tests should be performed at least two weeks after delivery or hormone therapy cessation.
- patients with recurrent VTE, irrespective of the presence of risk factors
- patients with recurrent superficial thrombophlebitis without cancer in the absence of varicose veins
- patients with VTE at unusual sites such as cerebral venous sinus, mesenteric or hepatic veins, and retinal vein occlusion under the age of 50
- patients with warfarin-induced skin necrosis and neonates with purpura fulminans not related to sepsis
- asymptomatic first-degree relatives of individuals with proven symptomatic thrombophilia. The authors felt this was particularly important for females in the child-bearing years.
- two consecutive or three nonconsecutive abortions at any gestational age, or one fetal death after week 20

- severe preeclampsia
- children with VTE

National Institute for Health and Care Excellence ([NICE], 2020): regarding testing for inherited thrombophilias, NICE notes the following:

- Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first‑degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment, but be aware that these tests can be affected by anticoagulants and specialist advice may be needed.
- Do not offer thrombophilia testing to patients who have had provoked DVT or PE.
- Do not offer testing for hereditary thrombophilia to people who are continuing anticoagulation treatment
- Do not routinely offer thrombophilia testing to first‑degree relatives of people with a history of DVT or PE and thrombophilia.

Royal College of Obstetricians and Gynaecologists (RCOG): The RCOG (2015) recommends that women with asymptomatic heritable thrombophilia be referred for expert consultation and antenatal thrombotic prophylaxis considered; they should be recommended for six weeks' postnatal prophylaxis even in the absence of additional risk factors (grade D recommendation).

Amyotrophic Lateral Sclerosis (ALS)
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."

The revised EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) note "there is no specific therapy for patients with SOD1 gene mutations, but three clinical trials targeting SOD1 specifically are currently underway. Presymptomatic (predictive) genetic testing is possible but is a sensitive issue with emotional, ethical and legal implications that must be addressed before analysis should take place. Special consideration should be taken before presymptomatic testing is performed in familial ALS families where the mutation is associated with reduced disease penetrance or variable prognosis" (EFNS, 2012).

Methylenetetrahydrofolate Reductase (NAD(P)H) (MTHFR)
Society of Obstetricians and Gynaecologists of Canada (SOGC): In its 2020 guideline on stillbirth investigation, SOGC advised that "routine testing for maternal inherited thrombophilia in stillbirth is not recommended because factor V Leiden, prothrombin G20210A, and methylene tetrahydrofolate reductase mutations are not associated with stillbirth" (Leduc, 2020).

Royal College of Obstetricians and Gynaecologists (RCOG): In its guideline on reducing the risk of venous thromboembolism (VTE) in pregnancy and the puerperium, RCOG (2015) states "homozygosity for a thermolabile variant of the gene for methylenetetrahydrofolate reductase (MTHFR) is sometimes included in thrombophilia testing but there is no evidence of an association with a clinically relevant increase in the risk of VTE in pregnancy and it should be ignored".

Alzheimer's Disease: APOE, APP, PSEN1 and PSEN2 Gene Variants
Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD):
Recommendations for risk assessment and prevention of Alzheimer's disease, based on the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia held in March 2006, were reported by Patterson and colleagues (2008). The recommendations for genetic risk factors included:

- Predictive genetic testing may be offered to the following at-risk individuals with an apparent autosomal dominant inheritance when a family specific mutation has been identified:
    - first-degree relatives (e.g., children and siblings) of an affected person with the mutation
    - first cousins of an affected person if the common ancestors (parents who were siblings) died before the average age of onset of dementia in the family

    - nieces and nephews of an affected person whose parent (sibling of the affected person) died before the average age of onset of dementia in the family
    - minors are not usually referred for predictive genetic testing
- Genetic screening for the APOE genotype in asymptomatic individuals in the general population is not recommended because of low sensitivity and specificity.

The fourth conference was held in May 2012. The subsequent report included the addition of a recommendation specific to early-onset dementia, in which autosomal-dominant variants (presenilin 1 and 2, or amyloid precursor protein) may be implicated. Due to the rarity of the condition, family physicians were advised to refer the individual to specialists with advanced expertise and access to genetic counseling and testing (Moore et al., 2014). Recommendations from the fifth conference did not address genetic testing.

European Federation of Neurological Societies (EFNS): On behalf of the EFNS, Waldemar et al. (2007) published guidelines for the diagnosis and management of Alzheimer's disease. The Guideline notes "Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. Routine apolipoprotein E (Apo E) genotyping is not recommended."

Cardiac Disease Risk
European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS): Guidelines for the management of dyslipidemias do not recommend genotype testing for cardiovascular risk estimation (Catapano, et al., 2011).

Multigene Panel Testing for Nonsyndromic Hearing Loss
World Health Organization (WHO): The 2010 WHO guidance on newborn and infant hearing screening encouraged all member states to educate health care providers on the importance of early identification of hearing loss and its etiology. Providers were advised to consider referrals to ophthalmology, genetic testing and counseling, and speech-language therapy. In addition, WHO advised member states to consider "the setting-up of mechanisms for collaboration with nongovernmental or other organizations for support to, and coordination of, action to prevent hearing impairment at country level, including the detection of hereditary factors, by genetic counseling" (WHO, 2010). The guidelines did not address specific genetic tests or protocols for testing.

Newborn Screening
Newborn screening has been integrated into the healthcare systems of all developed countries, and is increasing in developing nations as infant mortality rates decline (Kemper, 2020; Therrell and Padilla, 2018). The number and type of conditions screened varies widely by country and/or territory.

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD	Novitas Solutions, Inc.	Biomarkers Overview (L35062)	7/1/2020
LCD	Multiple LCDs	MolDX: Biomarkers in Cardiovascular Risk Assessment	Varies
LCD	Multiple LCDs	MolDX: Corus® CAD Assay	Varies
LCD	Multiple LCDs	MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	Varies
LCD	Multiple LCDs	MolDX: Molecular Diagnostic Tests (MDT)	Varies
LCD	Multiple LCDs	Molecular Pathology Procedures	Varies
LCD	Multiple LCDs	MolDX: Repeat Germline Testing	Varies
LCD	First Coast Service Options, Inc.	Molecular Pathology Procedures for Human Leukocyte Antigen (HLA) Typing (L34518)	1/08/2019

Note: Please review the current Medicare Policy for the most up-to-date information

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.

Genetic Counseling

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

HCPCS Codes	Description
S0265	Genetic counseling, under physician supervision, each 15 minutes

Single Gene Germline Genetic Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81105	Human Platelet Antigen 1 genotyping (HPA-1), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-1a/b (L33P)
81106	Human Platelet Antigen 2 genotyping (HPA-2), GP1BA (glycoprotein Ib [platelet], alpha polypeptide [GPIba]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-2a/b (T145M)
81107	Human Platelet Antigen 3 genotyping (HPA-3), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex], antigen CD41 [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-3a/b (I843S)
81108	Human Platelet Antigen 4 genotyping (HPA-4), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-4a/b (R143Q)
81109	Human Platelet Antigen 5 genotyping (HPA-5), ITGA2 (integrin, alpha 2 [CD49B, alpha 2 subunit of VLA-2 receptor] [GPIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant (eg, HPA-5a/b (K505E))
81110	Human Platelet Antigen 6 genotyping (HPA-6w), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa, antigen CD61] [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-6a/b (R489Q)
81111	Human Platelet Antigen 9 genotyping (HPA-9w), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41] [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-9a/b (V837M)
81112	Human Platelet Antigen 15 genotyping (HPA-15), CD109 (CD109 molecule) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-15a/b (S682Y)
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed.
81171	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

CPT®* Codes	Description
81172	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81173	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
81174	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
81177	ATN1 (atrophin 1) (eg, dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81178	ATXN1 (ataxin 1) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81179	ATXN2 (ataxin 2) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81180	ATXN3 (ataxin 3) (eg, spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81181	ATXN7 (ataxin 7) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81182	ATXN8OS (ATXN8 opposite strand [non-protein coding]) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81183	ATXN10 (ataxin 10) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; full gene sequence
81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; known familial variant
81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence
81190	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81204	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status)
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81234	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81238	F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence
81239	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)

CPT®* Codes	Description
81240†	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241†	F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81243	FMR1(fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	FMR1(fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-)
81248	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s)
81249	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81271	HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81274	HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
81284	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
81285	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size)
81286	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; full gene sequence
81289	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; known familial variant(s)
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; duplication/deletion variants

CPT®* Codes	Description
81312	PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81330	SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81333	TGFBI (transforming growth factor beta-induced) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q)
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81343	PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81344	TBP (TATA box binding protein) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81400††	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
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)
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])
81403††	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
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)
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, regionally targeted cytogenomic array analysis)

CPT®* Codes	Description
81406††	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)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of > 50 exons in a single gene by DNA sequence analysis)
81479†††	Unlisted molecular pathology procedure
83520†††	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
0180U	Red cell antigen (ABO blood group) genotyping (ABO), gene analysis Sanger/chain termination/conventional sequencing, ABO (ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase) gene, including subtyping, 7 exons
0181U	Red cell antigen (Colton blood group) genotyping (CO), gene analysis, AQP1 (aquaporin 1 [Colton blood group]) exon 1
0182U	Red cell antigen (Cromer blood group) genotyping (CROM), gene analysis, CD55 (CD55 molecule [Cromer blood group]) exons 1-10
0183U	Red cell antigen (Diego blood group) genotyping (DI), gene analysis, SLC4A1 (solute carrier family 4 member 1 [Diego blood group]) exon 19
0184U	Red cell antigen (Dombrock blood group) genotyping (DO), gene analysis, ART4 (ADP-ribosyltransferase 4 [Dombrock blood group]) exon 2
0185U	Red cell antigen (H blood group) genotyping (FUT1), gene analysis, FUT1 (fucosyltransferase 1 [H blood group]) exon 4
0186U	Red cell antigen (H blood group) genotyping (FUT2), gene analysis, FUT2 (fucosyltransferase 2) exon 2
0187U	Red cell antigen (Duffy blood group) genotyping (FY), gene analysis, ACKR1 (atypical chemokine receptor 1 [Duffy blood group]) exons 1-2
0188U	Red cell antigen (Gerbich blood group) genotyping (GE), gene analysis, GYPC (glycophorin C [Gerbich blood group]) exons 1-4
0189U	Red cell antigen (MNS blood group) genotyping (GYPA), gene analysis, GYPA (glycophorin A [MNS blood group]) introns 1, 5, exon 2
0190U	Red cell antigen (MNS blood group) genotyping (GYPB), gene analysis, GYPB (glycophorin B [MNS blood group]) introns 1, 5, pseudoexon 3
0191U	Red cell antigen (Indian blood group) genotyping (IN), gene analysis, CD44 (CD44 molecule [Indian blood group]) exons 2, 3, 6
0192U	Red cell antigen (Kidd blood group) genotyping (JK), gene analysis, SLC14A1 (solute carrier family 14 member 1 [Kidd blood group]) gene promoter, exon 9
0193U	Red cell antigen (JR blood group) genotyping (JR), gene analysis, ABCG2 (ATP binding cassette subfamily G member 2 [Junior blood group]) exons 2-26
0194U	Red cell antigen (Kell blood group) genotyping (KEL), gene analysis, KEL (Kell metallo-endopeptidase [Kell blood group]) exon 8
0195U	KLF1 (Kruppel-like factor 1), targeted sequencing (ie, exon 13)
0196U	Red cell antigen (Lutheran blood group) genotyping (LU), gene analysis, BCAM (basal cell adhesion molecule [Lutheran blood group]) exon 3
0197U	Red cell antigen (Landsteiner-Wiener blood group) genotyping (LW), gene analysis, ICAM4 (intercellular adhesion molecule 4 [Landsteiner-Wiener blood group]) exon 1
0198U	Red cell antigen (RH blood group) genotyping (RHD and RHCE), gene analysis Sanger/chain termination/conventional sequencing, RHD (Rh blood group D antigen) exons 1-10 and RHCE (Rh blood group CcEe antigens) exon 5
0199U	Red cell antigen (Scianna blood group) genotyping (SC), gene analysis, ERMAP (erythroblast membrane associated protein [Scianna blood group]) exons 4, 12
0200U	Red cell antigen (Kx blood group) genotyping (XK), gene analysis, XK (X-linked Kx blood group) exons 1-3

CPT®* Codes	Description
0201U	Red cell antigen (Yt blood group) genotyping (YT), gene analysis, ACHE (acetylcholinesterase [Cartwright blood group]) exon 2

†**Note: Considered Not Medically Necessary when used to report prothrombin gene mutation for the screening, diagnosis or management of coronary heart disease**

†† **Note: Considered Not Medically Necessary when used to report:**

- **ACE (angiotensin converting enzyme) (eg, hereditary blood pressure regulation), insertion/deletion variant (81400)**
- **AGTR1 (angiotensin II receptor, type 1) (eg, essential hypertension), 1166A>C variant (81400)**
- **ANG (angiogenin, ribonuclease, RNase A family, 5) (eg, amyotrophic lateral sclerosis), full gene sequence (81403)**
- **APOE (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4) (81401)**
- **APP (amyloid beta [A4] precursor protein) (eg, Alzheimer's disease), full gene sequence (81406)**
- **FUS (fused in sarcoma) (eg, amyotrophic lateral sclerosis), full gene sequence (81406)**
- **OPTN (optineurin) (eg, amyotrophic lateral sclerosis), full gene sequence (81406)**
- **PSEN1 (presenilin 1) (eg, Alzheimer's disease), full gene sequence (81405)**
- **PSEN2 (presenilin 2 [Alzheimer's disease 4]) (eg, Alzheimer's disease), full gene sequence (81406)**
- **SOD1 (superoxide dismutase 1, soluble) (eg, amyotrophic lateral sclerosis), full gene sequence (81404)**
- **TARDBP (TAR DNA binding protein) (eg, amyotrophic lateral sclerosis), full gene sequence (81405)**

†††**Note: Considered Medically Necessary when used to report any covered single gene genetic test that does not have an assigned CPT/HCPCS code when criteria in the applicable policy statements listed above are met.**

HCPCS Codes	Description
S3844	DNA analysis of the connexin26 gene (GJB2) for susceptibility to congenital, profound deafness
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin E beta-thalassemia
S3849	Genetic testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3853	Genetic testing for myotonic muscular dystrophy

Considered Not Medically Necessary:

CPT®* Codes	Description
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
0001U	Red blood cell antigen typing, DNA, human erythrocyte antigen gene analysis of 35 antigens from 11 blood groups, utilizing whole blood, common RBC alleles reported
0084U	Red blood cell antigen typing, DNA, genotyping of 10 blood groups with phenotype prediction of 37 red blood cell antigens
0156U	Copy number (eg, intellectual disability, dysmorphology), sequence analysis

CPT®* Codes	Description
0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis
0230U	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation), full sequence analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
0231U	CACNA1A (calcium voltage-gated channel subunit alpha 1A) (eg, spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions
0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
0233U	FXN (frataxin) (eg, Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions

HCPCS Codes	Description
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

Multigene Germline Mutation Genetic Testing Panels

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81410	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes,

CPT®* Codes	Description
	including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81479†	Unlisted molecular pathology procedure
0012U	Germline disorders, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gene rearrangement(s)
0268U	Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid
0269U	Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid
0271U	Hematology (congenital neutropenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid
0273U	Hematology (genetic hyperfibrinolysis, delayed bleeding), genomic sequence analysis of 8 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, PLAU), blood, buccal swab, or amniotic fluid
0274U	Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid
0276U	Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid
0277U	Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid
0282U	Red blood cell antigen typing, DNA, genotyping of 12 blood group system genes to predict 44 red blood cell antigen phenotypes

†**Note: Considered Medically Necessary when used to report any covered genetic testing panel that does not have an assigned CPT/HCPCS code**

Considered Not Medically Necessary:

CPT®* Codes	Description
81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score
81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (eg, positive or negative for high probability of usual interstitial pneumonia [UIP])
81599††	Unlisted multianalyte assay with algorithmic analysis
82397	Chemiluminescent assay
83520††	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
84999††	Unlisted chemistry procedure
88346	Immunofluorescence, per specimen; initial single antibody stain procedure
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
0004M	Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score
0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions
0270U	Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid
0272U	Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive
0278U	Hematology (genetic thrombosis), genomic sequence analysis of 12 genes, blood, buccal swab, or amniotic fluid

††**Note: Considered Not Medically Necessary when used to report any non-covered genetic testing panel that does not have an assigned CPT/HCPCS code**

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