Medical Coverage Policy

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Genetic Testing for Hereditary and Multifactorial Conditions

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers *must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.*

Overview

This Coverage Policy addresses testing for harmful or likely harmful changes in the genetic information of cells that occur in the egg or sperm cell at conception. These changes, also called variants, are inherited or passed down through generations by blood relatives. The changes may increase a person's risk or tendency to have a certain disease or disorder. When a combination of gene changes and other factors influence whether or not a condition results in a trait or health condition, it is known as multifactorial. Examples of factors other than genes are lifestyle, smoking and the environment.

Several types of testing are discussed in this Coverage Policy, including testing for a single change in a gene or part of a gene and testing for multiple changes in a gene or genes. Also discussed are tests that measure how a gene is turned on or off, which is referred to as gene expression.

Coverage Policy

Coverage for genetic testing varies across plans. Refer to the customer's benefit plan document for coverage details.

Note:
If coverage for genetic testing is available and disease- or condition-specific criteria for genetic testing are not outlined in a separate policy or guideline, the following criteria apply.

Laboratory Testing

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.

Single Gene Genetic Testing for Germline Conditions

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 deoxyribonucleic acid (DNA) and/or ribonucleic acid (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.

Multigene Genetic Testing Panels

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 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

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Not Covered or Reimbursable

The following tests do not meet medical necessity criteria outlined above and are additionally not covered or reimbursable:

- apolipoprotein E (APOE) (HCPCS code S3852)
- Apolipoprotein L1 (APOL1) Renal Risk Variant Genotyping (CPT code 0355U)
- CARDIO inCode-Score (CPT code 0401U)
- Clarifi ASD (CPT code 0170U)
- Epi+Gen CHD (CPT code 0439U)
- Esopredict (CPT code 0398U)
- KawasakiDx (CPT code 0389U)
- MTHFR variants (CPT code 81291)
- PrecisionCHD (CPT code 0440U)
- ScoliScore (CPT code 0004M)
- SMASH assay (CPT code 0156U)
- Vectra (CPT code 81490)

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

Significant disparities in the clinical usefulness of genomic information across diverse groups are due to underrepresentation in genetic databases and inequitable access to genetic services. According to some estimates, over 80% of genome datasets originate from people of European ancestry, with many ancestries not well represented. If individuals across diverse ancestries are not included in sufficient numbers in studies, there likely will be insufficient power to identify genetic variants that are observed exclusively or predominantly in one ancestral group. As a result of these limitations, variants in ancestral groups that are insufficiently represented in disease and reference genomic datasets are more likely to be classified as variants of uncertain significance (VUSs) (Lee, et al., 2022).

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 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, targeted analysis, and multigene sequencing panels. 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 Genetic 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.

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], 2019). 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) clearance 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, 2019; 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 zero and year seven) 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 zero. 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 U.S., measurement of tHcy rather than genotyping of MTHFR 677TT should be used as the primary assay for the diagnosis and monitoring of moderate hyperhomocysteinemia.

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 testing 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 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. Nevertheless, 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’s 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) clearance 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).

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. 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 testing for determining cardiovascular disease risk (e.g., Corus CAD) is limited to prospective validation studies and case control studies (Filsoof, et al., 2015; Ladapo, et al., 2015; Daniels, et al., 2014; McPherson, et al., 2013; Thomas, et al., 2013; Vargas, et al., 2013; Lansky, et al., 2012; Rosenberg, et al., 2012; Elashoff, et al., 2011; Rosenberg, et al., 2010; Wingrove, et al., 2008). 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.

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 who underwent GES testing at seven primary care sites. 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 was limited by lack of a control group.

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.

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.

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 (2012) 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 which 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. 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.

Multigene 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 multi-gene panels use next-generation sequencing (NGS) methodology, but some still use Sanger sequencing. Next generation sequencing technology allows large amounts of 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.

A polygenic risk score (PRS) is an assessment of a person's risk of developing a specific condition based on the collective influence of many genetic variants. A PRS may only explain a person's relative (not absolute) risk for a disease, as the data used for generating a PRS comes from large-scale genomic studies. Approximately 79% of participants in genome-wide association studies are of European descent, despite comprising only 16% of the global population. Thus, there may not be adequate data about genomic variants from other populations to calculate a PRS in those populations. There is currently limited generalizability of genetic risk scores across diverse populations (NHGRI, 2020; Martin, et al., 2019). The American College of Medical Genetics and Genomics (ACMG) cautions the use of these tests, noting that genetic studies on complex traits and disease susceptibility is an "inexact science" (ACMG, 2021). For testing of multifactorial conditions, testing panels may include gene expression classifier and polygenic risk score tests.

Professional Societies/Organizations

Genetic Testing for Alzheimer's Disease (including APOE)

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 (APA): The 2007 practice guidelines for the treatment of patients with Alzheimer's disease and other dementias noted 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 noted that, 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): In 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. Per the NIA, 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/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 and Genomics (ACMG): On behalf of the NSGC/ACMG, Goldman et al. (2018) 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 stated that direct-to-consumer APOE testing is not advised.

The Guidelines noted 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 noted:

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.

Genetic Testing for 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 Heart Association (AHA)/American College of Cardiology (ACC): Greenland et al. (2010) published guidelines which noted 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 guidelines did 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 (Arnett, et al., 2019) did 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.

Genetic Testing for Methylenetetrahydrofolate Reductase (NAD(P)H) (MTHFR) Polymorphisms

American College of Medical Genetics and Genomics (ACMG): The reaffirmed ACMG practice guideline on the lack of evidence for MTHFR polymorphism testing noted (Bashford, et al., 2020):

- 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 Obstetricians and Gynecologists (ACOG): ACOG (2018) does not endorse testing for MTHFR polymorphisms for routine risk assessment, evaluation of thrombosis risk, or recurrent pregnancy loss.

Polygenic Risk Scores

American College of Medical Genetics and Genomics (ACMG, 2023): The ACMG notes the following regarding polygenic risk scores (PRS):

- PRS test results do not provide a diagnosis, instead they provide a statistical prediction of increased clinical risk.
- A low PRS does not rule out significant risk for the disease or condition in question.
- If the risk prediction of a PRS is derived from a population that is different from the patient being tested, then the results may have a poor predictive value for the patient.
- Isolated PRS testing is not the appropriate test for clinical scenarios in which monogenic etiology is known or suspected.
- Before testing, a patient and provider should discuss the indications for the PRS test, and the patient should be informed how the PRS results will be used to guide medical management.
- PRS-based medical management should be evidence-based; however, there is currently limited evidence to support the use of PRS to guide medical management.
- Clinical follow-up for PRS should be consistent with best practices outlined by professional societies with appropriate expertise in instances when and where evidence-based practice guidelines exist.
- The ACMG's position is that preimplantation PRS testing is not yet appropriate for clinical use and should not be offered at this time.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No Determination found	
LCD	Multiple LCDs	Genetic Testing for Cardiovascular Disease	Varies
LCD	Multiple LCDs	Molecular Pathology Procedures	Varies
LCD	Multiple LCDs	MolDX: Biomarkers in Cardiovascular Risk Assessment	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	Novitas Solutions	Biomarkers Overview (L35062)	12/12/2021
LCD	Multiple LCDs	MolDX: Repeat Germline Testing	Varies

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Not Covered or Reimbursable:

CPT®* Codes	Description
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score
0004M	Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score
0156U	Copy number (eg, intellectual disability, dysmorphology), sequence analysis
0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis
0355U	APOL1 (apolipoprotein L1) (eg, chronic kidney disease), risk variants (G1, G2)
0389U	Pediatric febrile illness (Kawasaki disease [KD]), interferon alpha-inducible protein 27 (IFI27) and mast cell-expressed membrane protein 1 (MCEMP1), RNA, using quantitative reverse transcription polymerase chain reaction (RT-qPCR), blood, reported as a risk score for KD
0398U	Gastroenterology (Barrett esophagus), P16, RUNX3, HPP1, and FBN1 DNA methylation analysis using PCR, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as risk score for progression to high-grade dysplasia or cancer
0401U	Cardiology (coronary heart disease [CHD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event
0439U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD
0440U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675

CPT®* Codes	Description
	[PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1], cg04988978 [MPO], cg17901584 [DHCR24-DT], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD

HCPCS Codes	Description
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	• Added section and statement for not covered or reimbursable tests. • Removed policy statements for genetic testing and gene mapping in the general population; testing for global developmental delay or intellectual disability; genetic testing for mitochondrial disorders; and newborn screening.	10/11/2025
Focused Review	• Removed policy statements for genetic counseling; multigene panel testing for nonsyndromic hearing loss; and testing for connective tissue disorders and thoracic aortic aneurysm/dissection. • Revised policy statement for single gene genetic testing.	11/1/2024
Focused Review	• Revised noncoverage statement of specific variants.	5/17/2024