

GENE EXPRESSION TESTS FOR CARDIAC INDICATIONS

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[Instructions for Use](#) ⓘ

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COVERAGE RATIONALE

Gene expression tests are unproven and not medically necessary for predicting the likelihood of obstructive coronary artery disease (e.g., Corus® CAD).

There is insufficient evidence in the clinical literature demonstrating that this test has a role in clinical decision-making or has a beneficial effect on health outcomes. Further studies are needed to determine the clinical utility of this test.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

CPT Code	Description
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score <i>CPT® is a registered trademark of the American Medical Association</i>

DESCRIPTION OF SERVICES

Gene expression is the process by which the coded information of a gene is translated into the structures present and operating in the cell (either proteins or ribonucleic acids (RNA)). Gene expression profiling (GEP) studies the patterns of many genes in a tissue sample at the same time to assess which ones are turned on (producing RNA and proteins) or off (not producing RNA or proteins). By simultaneously measuring the levels of RNA of thousands of genes, GEP creates a snapshot of the rate at which those genes are expressed in a tissue sample.

Gene expression tests are not the same as genetic tests. Genetic tests measure an individual DNA signature to identify genetic changes or mutations. Genetic tests can help estimate an individual's risk of developing disease in the future. In contrast, gene expression tests measure the activity of RNA in a given tissue or bodily fluid at a given point in time to provide information about an individual's current disease state or the likelihood of future disease. RNA levels are dynamic and change as a result of disease processes or environmental signals. Because gene expression changes under pathological conditions, dynamic changes in these processes can be studied over time. Certain patterns of gene activity may be used to diagnose a disease or to predict how an individual responds to treatment (Arnett et al., 2007; CardioDX website; Centers for Disease Control and Prevention; National Cancer Institute; National Human Genome Research Institute).

From 2000–2004, the Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics (OPHG) established and supported the ACCE Model Project, which developed the first publicly-available analytical process for evaluating scientific data on emerging genetic tests. The 4 main components of the ACCE process included analytic validity, clinical validity, clinical utility and ELSI. Analytic validity refers to how accurately and reliably the test measures the genotype of interest. Clinical validity refers to how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest. Is what's measured associated with the outcome of interest? Clinical utility refers to how likely the test is to significantly improve patient outcomes. What is the clinical value? ELSI refers to the ethical, legal and social implications that may arise in the context of using the test (CDC, 2010).

The CDC-supported EGAPP™ initiative builds on the ACCE model structure and experience. In 2004, the CDC launched the EGAPP initiative to establish and test a systematic, evidence-based process for evaluating genetic tests and other applications of genomic technology that are in transition from research to clinical and public health practice. A key EGAPP goal is to provide objective, timely, and credible information that is clearly linked to available scientific evidence. This information serves to provide health care providers, policymakers, and others to distinguish genetic tests that are safe and useful (CDC, 2016).

Gene expression profiling, using Corus CAD, has been proposed as a noninvasive diagnostic tool for evaluating patients who present with stable symptoms suggestive of obstructive coronary disease (CAD), such as chest discomfort or shortness of breath. Corus CAD is a blood test that integrates expression levels of 23 genes and other patient characteristics to predict the likelihood of obstructive CAD. According to the manufacturer, the test yields an objective result of cardiac risk in the form of a numeric score (0-40) that quantifies the likelihood that a patient with stable chest pain has obstructive CAD. The test is intended for nondiabetic patients without a history of obstructive CAD, who have not had a prior myocardial infarction or revascularization procedure and who are not currently taking steroids, immunosuppressive agents, or chemotherapeutic agents (CardioDX® website).

CLINICAL EVIDENCE

Using data from the prospective Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings (PRESET) registry, Ladapo et al. (2017) evaluated the clinical utility of Corus CAD in symptomatic patients with suspected obstructive coronary artery disease (CAD). The registry enrolled 566 stable, nonacute, nondiabetic adult patients without a history of CAD. Patients with a low Corus CAD score (≤ 15) were less likely to undergo cardiac referral, were unlikely to have positive findings on further cardiac work-up and had a low rate of adverse cardiovascular events after one year compared to patients with a score greater than 15. In a subset of 176 patients 65 and older, Ladapo et al. (2018) reported that clinicians referred 12.5% of participants with a low Corus CAD score and 49.3% with a high score to cardiology or advanced cardiac testing. Higher scores were associated with greater likelihood of post-test cardiac referral. At 1-year follow-up, the incidence of a major cardiac event was 10% (13/136) in the high score group and 0% (0/40) in the low score group. In both studies, the authors concluded that the Corus CAD test showed potential clinical utility in the evaluation of outpatients with symptoms suggestive of obstructive CAD. A potential for bias exists due to manufacturer sponsorship of the study. One of the author noted study limitations included the absence of a control group, which limits direct comparisons with usual care. Clinical trial #NCT01677156.

In the IMPACT-CARD study, McPherson et al. (2013) assessed the impact of gene expression testing (Corus CAD) on clinical decision-making in patients with symptoms of suspected CAD presenting to the cardiology setting. The study included a prospective cohort of 83 patients eligible for analysis, including 57 (69%) women. These patients were referred to six cardiologists for evaluation of suspected CAD and were matched to 83 patients in a historical cohort. The cardiologist's diagnostic strategy was evaluated before and after gene expression score (GES) testing. The primary objective of the study was to measure whether the use of the GES changed the cardiologist's evaluation and management of the patient. After GES, changes in diagnostic testing occurred in 58% of patients ($n = 48$). Of note, 91% (29/32) of patients with decreased testing had low GES (≤ 15), whereas 100% (16/16) of patients with increased testing had elevated GES. The historical cohort had higher diagnostic test use compared with the post-GES prospective cohort. The authors concluded that the GES showed clinical utility in the evaluation of patients with suspected obstructive CAD presenting to the cardiologist's office. A potential for bias exists due to manufacturer sponsorship of the study. Additional limitations include short term follow-up, small sample size and inclusion of individuals at low risk for CAD. Clinical trial #NCT01251302.

In a companion study (IMPACT-PCP), Herman et al. (2014) assessed the impact of gene expression testing (Corus CAD) on clinical decision-making in patients with symptoms of suspected CAD presenting to a primary care setting. Providers initially determined patients' pretest probability for CAD based on risk factors, assessment of clinical symptoms and results of any prior testing. All patients underwent gene expression score (GES) testing, with clinicians documenting their planned diagnostic strategy both before and after GES. The primary objective was to assess whether the use of GES altered patient management. The study enrolled 261 consecutive stable, nonacute, nondiabetic patients presenting with typical and atypical symptoms of CAD. Of the 251 eligible study patients, 140 were women (56%). After 30 days, a change in the diagnostic plan before and after GES testing was noted in 145

patients (58%). More patients had decreased (n=93, 37%) versus increased (n=52, 21%) intensity of testing. In particular, among the 127 low score Corus CAD patients (51% of study patients), 60% (76/127) had decreased testing, and only 2% (3/127) had increased testing. The authors concluded that the incorporation of GES into the diagnostic workup showed clinical utility above and beyond conventional clinical factors by optimizing the patient's diagnostic evaluation. A potential for bias exists due to manufacturer sponsorship of the study. Additional limitations include short term follow-up, modest sample size and inclusion of individuals at low risk for CAD. Clinical trial #NCT01594411.

The prospective, multicenter COMPASS validation study (Thomas et al., 2013) evaluated the performance of the Corus CAD test in symptomatic patients referred for myocardial perfusion imaging (MPI). Blood samples for gene expression scoring (GES) were obtained prior to MPI. Based on MPI results, 431 patients were referred for either invasive coronary angiography or computed tomographic angiography. Patients were followed for 6 months with clinical end points defined as major adverse cardiac events. Sensitivity, specificity and negative predictive value were reported at 89%, 52% and 96%, respectively. The GES outperformed clinical factors and showed significant correlation with maximum percent stenosis ($\geq 50\%$). Six-month follow-up on 97% of patients showed that 27 of 28 patients with adverse cardiovascular events or revascularization had GES >15 . The authors concluded that GES has high sensitivity and negative predictive value for obstructive CAD. In this population clinically referred for MPI, the GES outperformed clinical factors and MPI. A potential for bias exists due to manufacturer sponsorship of the study. Additional limitations include short term follow-up and inclusion of individuals at low risk for CAD. Clinical trial #NCT01117506.

The PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) trial was a prospective, multicenter validation study of a peripheral blood-based gene expression test for determining the likelihood of obstructive CAD. Patients with chronic inflammatory disorders, elevated levels of leukocytes or cardiac protein markers or diabetes were excluded. Blood samples were obtained from 526 patients with chest pain or another indication for coronary angiography. Obstructive CAD was defined as 50% or greater stenosis in 1 or more major coronary arteries by quantitative coronary angiography. The sensitivity and specificity for the gene expression test were 85% and 43% respectively. The investigators reported a statistically significant but modest improvement in classification of patient CAD status compared with clinical factors or noninvasive imaging (myocardial perfusion imaging). Further studies are needed to define the performance characteristics and clinical utility of these tests in the general population (Rosenberg et al., 2010). A potential for bias exists due to manufacturer sponsorship of the study. Clinical trial #NCT00500617.

Assimes and Roberts (2016) summarized the evolution and discovery of genetic risk variants for CAD and their current and future clinical applications. In order to maximize the clinical utility of the current knowledge gained, the authors propose future tasks which include the identification of the remaining susceptibility loci for CAD, proving the clinical utility of genetic data in the prevention of CAD, and acquiring a solid appreciation of the cellular and/or extracellular mechanisms responsible for genetic associations observed at the population level. They conclude that extremely large sample sizes are needed for additional discoveries, given the distribution of effect sizes observed to date for both common and rare variants, as well as the estimated proportion of the heritability of CAD explained by these variants to date. In the coming years, the authors suggest that this need could be fulfilled by mega-biobanks to assist in the determination of the clinical utility of genetic risk scores, and to conduct additional, well-powered MR studies to complement studies published to date.

In a follow-up to the PREDICT study, Rosenberg et al. (2012) evaluated the relationship between gene expression testing and both major adverse cardiovascular events (MACE) and revascularization. A cohort of the original trial (n=1,116) underwent angiography and gene expression scoring (GES), and was followed for 1 year. A total of 267 (23.9%) patients had clinical endpoints within 30 days of testing. An additional 25 (2.2%) patients had clinical endpoints within a year. Overall, the rate of MACE was 1.5% for 12 months. Using a GES cutoff of ≤ 15 (i.e., low likelihood of CAD), the sensitivity, specificity, PPV and NPV for MACE or revascularization within 12 months of testing were 86%, 41%, 33% and 90%, respectively. The authors concluded that a low GES appeared to identify individuals at low risk for both obstructive CAD and subsequent procedures or events. The authors noted several limitations to the study including limited follow-up and exclusion of patients with high-risk unstable angina and low-risk asymptomatic patients. Further studies with larger patient populations and long-term outcomes are needed.

In an additional analysis of the PREDICT study, Lansky et al. (2012) reported that Corus CAD performed similarly in women and men.

Vargas et al. (2013) conducted a literature review and assessment regarding the analytical and clinical validity as well as the clinical utility of the Corus[®] CAD test in symptomatic non-diabetic patients. Given the scope of the deleterious effects of CAD and the considerable costs involved in diagnosing obstructive CAD, the authors comment that a blood test that can help in this determination is certainly valuable and that the Corus CAD test promises to have an important role in this regard particularly if it continues to perform this well in larger, more diverse cohorts. The authors caution that the results of this review should be interpreted carefully as patients with diabetes mellitus and

chronic inflammatory or autoimmune disorders were excluded from test development and validation. Furthermore, this test was derived and tested in predominantly Caucasian patient populations. Given the known variations in the prevalence of CAD in different ethnic/racial backgrounds, results of this test in non-Caucasian populations should be interpreted with caution.

Using a series of microarray and real-time polymerase chain reaction (RT-PCR) data sets, comprising more than 1000 patients, Elashoff et al. (2011) developed a blood-based gene expression algorithm for assessing obstructive CAD in non-diabetic patients. The algorithm consists of the expression levels of 23 genes, sex and age.

Wingrove et al. (2008) performed a microarray analysis on 41 patients with angiographically significant CAD and 14 controls without coronary stenosis to identify genes expressed in peripheral blood that may be sensitive to the presence of CAD. A multistep approach was used, starting with gene discovery from microarrays, followed by real-time polymerase chain reaction (RT-PCR) replication. The authors observed that gene expression scores based on 14 genes, independently associated with the presence or absence of CAD, were proportional to the extent of disease burden. This study is limited by its size and retrospective nature. Larger, prospective studies are needed to confirm these initial results.

The U.S. Preventive Services Task Force (USPSTF) recommendations on the use of nontraditional risk factors in coronary heart disease risk assessment do not address genetic/genomic markers (USPSTF, 2009).

Professional Societies

American College of Cardiology (ACC)

ACC guidelines do not address gene expression profiling for predicting the likelihood of obstructive coronary artery disease.

American Heart Association (AHA)

In a scientific statement, the AHA summarizes the emergence and state of the science of several transformational technologies, including Corus CAD, for the refinement of cardiovascular disease mechanisms. Technologies such as epigenomics, transcriptomics, proteomics and metabolomics, are now making it possible to address the contributions of the expressed genome to cardiovascular disorders. The statement also identifies issues that need to be addressed to enable the use of the expressed genome for diagnosis and prediction in the clinical setting. Each of the approaches remains a work in progress, and many of the initial findings are still awaiting systematic replication in independent studies (Musunuru et al., 2017).

In a separate AHA scientific statement, Mital et al. (2016) affirm that advances in genomics are enhancing the understanding of the genetic basis of cardiovascular diseases, both congenital and acquired, and stroke. These advances include finding genes that cause or increase the risk for childhood and adult-onset diseases, finding genes that influence how patients respond to medications, and the development of genetics-guided therapies for diseases. The AHA recommends that cardiovascular and stroke clinicians develop a set of core competencies in genetics so that they can systematically and effectively integrate genetics into clinical practice.

In an AHA policy statement on genetics and cardiovascular disease, Ashley et al. (2012) strongly advocate the involvement of physicians and centers with expertise in cardiovascular genetics to guide the appropriate initiation, interpretation, and implementation of genetic testing and to gain clinical consensus as to what constitutes clinical utility. The potential of whole-genome sequencing to impact medicine is highly significant and as such, they recommend that genetics and genomics be included as a fundamental part of the training curriculum for all health professionals.

In a published scientific statement on the relevance of genetics and genomics for the prevention and treatment of cardiovascular disease (CVD), the AHA states that RNA gene expression profiling shows great promise. However, further results from large, patient cohorts are needed to determine the clinical utility of this methodology. The statement also proposes several recommendations to guide future research (Arnett et al. 2007).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Laboratories that perform gene expression tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: <http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm>. (Accessed April 15, 2018)

Medicare does not have a National Coverage Determination (NCD) for gene expression tests. Local Coverage Determinations (LCDs) exist; see the LCDs for [Corus® CAD Test](#), [MolDX: Molecular Diagnostic Tests \(MDT\)](#), [Molecular Diagnostic Tests \(MDT\)](#) and [Molecular Pathology Procedures](#). (Accessed April 19, 2018)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
11/01/2018	<ul style="list-style-type: none"> • Reorganized policy template: <ul style="list-style-type: none"> ○ Simplified and relocated <i>Instructions for Use</i> ○ Removed <i>Benefit Considerations</i> section • Updated coverage rationale; modified language to clarify the listed service is unproven and not medically necessary • Archived previous policy version 2018T0552L

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG[™] Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.