Clinical Policy Title: CORUS® CAD gene expression test

Clinical Policy Number: 02.01.12

Effective Date: October 1, 2014
Initial Review Date: June 18, 2014
Most Recent Review Date: June 5, 2018
Next Review Date: June 2019

Policy contains:
- CORUS® CAD Gene Expression Test.
- Coronary artery disease.
- Risk assessment.

Related policies

None.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state and federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina's clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of CORUS® CAD Gene Expression Test to predict clinical events or alter the treatment of individuals to be investigational/experimental and, therefore, not medically necessary.

Limitations:

All other uses of CORUS® CAD Gene Expression Test are not medically necessary.

Alternative covered services:

- Exercise/stress electrocardiography exercise/stress or resting.
- Exercise/stress echocardiography with or without a contrast agent.
- Nuclear myocardial perfusion imaging.
- Stress myocardial perfusion and wall motion magnetic resonance imaging.
- Coronary computed tomography angiography.
• Invasive coronary angiography.

**Background**

Heart disease is the leading cause of death in the United States in both men and women (CDC, 2014). The most common type of heart disease is coronary artery disease (CAD). The most common cause of CAD is atherosclerosis. Atherosclerosis is a hardening and narrowing of arteries that slowly and often silently progresses to ischemia, or may rupture causing thrombosis within an artery (CDC, 2014).

In 2016, 247,432 Americans died from CAD (ICD-10 code I25), a decline of nearly 50 percent from 1999. About 94 percent of these 2016 deaths were age 54 or older, and the age-adjusted male mortality rate was 94 percent higher than the female rate. Asian non-Hispanics had the lowest rate of any major racial/ethnic group, compared to Hispanics (36 percent greater), white non-Hispanics (80 percent greater) and black non-Hispanics (107 percent greater) (CDC, 2018).

Conservative estimates suggest that angina pectoris (angina) is the initial manifestation of CAD in at least 50 percent of patients (Fihn, 2012). Symptoms of angina are usually uncomfortable pressure, fullness, squeezing, or pain in the center of the chest and discomfort in the neck, jaw, shoulder, back, or arm (AHA, 2015). Persons presenting with chest pain may represent the initial clinical recognition of chronic stable angina, reflecting either gradual progression of obstruction in their coronary arteries or an increase in supply/demand mismatch precipitated by a change in activity or concurrent illness (e.g., anemia or infection), or acute coronary syndrome, most likely caused by an unstable plaque causing acute thrombosis (Fihn, 2012). Other patients, in particular women and the elderly, can present with atypical symptoms such as nausea, vomiting, midepigastric discomfort, or sharp (atypical) chest pain (Mieres, 2005).

Risk assessment in patients who present with chest pain but are not known to have CAD is performed to assess the probability of obstructive CAD before additional testing. Patients who present with acute angina are categorized as stable or unstable, and patients with unstable angina should be further categorized as being at high, moderate or low risk (Fihn, 2012). Choice of testing (either noninvasive or invasive) in patients with symptoms suspicious for CAD takes into consideration the pretest probability of CAD and the testing/action thresholds for patients based on American College of Cardiology/American Heart Association guidelines for stable angina and appropriate use criteria for the various modalities (Dolor 2012; Fihn, 2012; AHA, 2018).

The diagnosis of CAD in women presents challenges not seen in testing men. Women more frequently develop microvascular heart disease within the very small branches of the coronary arteries than obstructive CAD, and women are generally at lower risk for obstructive CAD than their male counterparts until the seventh decade of life (Mieres, 2005). Guideline-supported prediction models are based on studies in which women with a spectrum of CAD were under-represented. As a result, the risk of obstructive CAD is frequently overestimated in women, as demonstrated in studies suggesting up to 50 percent of women with anginal symptoms who undergo cardiac catheterization do not have the obstructive type of CAD (AHA 2014a). A systematic review found that noninvasive testing performance
in women is not as good as in men, likely due to these reasons (Dolor, 2012).

For patients who have a guideline-defined low-to-intermediate pretest probability of obstructive CAD, ideally a noninvasive test with a high negative predictive value in this population and low risk of adverse events is preferred, to “rule out” disease (Dolor, 2012). In contrast, in patients with high pretest probability of obstructive CAD (greater than 70 percent chance), a test with very high positive predictive value in this population and potentially more risk may be chosen since the disease of interest is thought to be present. For patients generally within the spectrum of intermediate probability, between 20 and 70 percent, clinicians must choose noninvasive tests that provide the right balance of sensitivity, specificity, and clinical risk to warrant testing. The choice of testing may also depend on physical functioning, existing comorbidity, clinician preference, availability, setting (outpatient versus chest pain unit of an emergency department) and patient preference (Fihn, 2012; Dolor, 2012).

Invasive coronary angiography is the reference (gold) standard for clinical care of patients who have chest pain suggestive of CAD and are at high risk for obstructive CAD (Fihn, 2012). Coronary angiography enables visualization of the coronary arteries with greater anatomic precision and resolution, and combines diagnosis and treatment in a single procedure. As an invasive procedure, the risks associated with coronary angiography include arterial bleeding at the access site, procedure-related embolus, arterial dissection, exposure to ionizing radiation and, on rare occurrences, internal bleeding (Dolor, 2012).

Noninvasive tests are important options for patients at intermediate risk of obstructive CAD or for whom invasive catheterization is contraindicated (Fihn, 2012). Noninvasive tests may be preferred for patients at higher risk for complications with invasive screening, such as embolic stroke due to extensive vascular disease in the aorta, endocarditis involving the aortic valve or a pseudoaneurysm at the site of catheter insertion because of underlying vascular disease. Noninvasive tests include, but are not limited to, the following (Dolor, 2012):

- Exercise/stress electrocardiography exercise or resting.
- Exercise/stress echocardiography with or without a contrast agent.
- Nuclear myocardial perfusion imaging.
- Stress myocardial perfusion and wall motion magnetic resonance imaging.
- Coronary computed tomography angiography.

Standard care in low to medium risk patients presenting with symptoms suggesting CAD involves a family history, risk factor assessment, and stress testing with or without non-invasive imaging. A positive stress test is often followed by invasive coronary angiography. This standard approach results in fewer than 40 percent of those referred for angiography being diagnosed with obstructive CAD; a more sensitive test is needed (Vargas, 2013).

**CORUS® CAD Gene Expression Test:**
Gene expression profiling is a method of laboratory testing that measures messenger ribonucleic acid (mRNA) expressed from various genes in many different cell types. Gene expression is not a genetic test, which predicts the likelihood of developing a disease, but one that, in this case, provides information on the status of obstructive CAD. Using gene expression profiling to predict the likelihood of obstructive CAD has the potential to increase the proportion of patients selected for coronary angiography who truly have the disease and reduce the number of patients who might otherwise be inappropriately exposed to radiation, contrast agent, and an invasive procedure. The first appearance in the literature of CORUS® CAD was a study of 526 non-diabetic persons with a clinical indication for coronary arteriography; the results of the yet-unnamed test showed that this genetic test could be useful in assessing obstructive CAD (Rosenberg, 2010).

According to the manufacturer, CORUS® CAD (CardioDx Inc., Redwood City, California) is blood-based, diagnostic gene expression test for identifying patients unlikely to have obstructive CAD in patients with typical and atypical presentations of stable chest pain (CardioDx, 2014). CORUS® CAD measures 23 distinct RNA sequences associated with atherosclerosis biology and involving inflammation, cell death, and adaptive and innate immunity. The test involves a routine blood draw administered in the clinician’s office. The CORUS® CAD test score is provided on a scale of 1 – 40; a score < 15 indicates a low risk of underlying obstructive CAD. The results are available within 72 hours. CORUS® CAD is the only sex-specific test for the assessment of obstructive CAD that accounts for critical biological differences between men and women (CardioDx, 2014).

CORUS® CAD is intended for use in stable, nondiabetic patients presenting with symptoms suggestive of obstructive CAD, and who (CardioDx, 2014):

- Have not been diagnosed with prior myocardial infarction nor have had a previous revascularization procedure.
- Are not currently taking steroids, immunosuppressive agents, or chemotherapeutic agents.

Regulation:

The CORUS® CAD test is not a manufactured test kit and has not been reviewed by the US. Food and Drug Administration. It is a commercially available laboratory-developed assay offered by the CardioDx Commercial Laboratory. Laboratories that perform gene expression tests are regulated under the Clinical Laboratory Improvement Amendments Act of 1988 (42 CFR §493).

Searches

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).
Searches were conducted on April 4, 2018, using the terms (“gene expression profiling,” “coronary artery disease,”, and “CORUS® CAD.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews**.

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Guidelines recommending the use of CORUS® CAD are not yet in existence. The U.S. Preventive Services Task Force recommendation statement addressing coronary artery disease risk assessment did not address the technique (USPSTF, 2009). It was mentioned, but not recommended, in an American Hospital Association scientific statement (Arnett, 2007).

Select Health of South Carolina identified no systematic reviews or meta-analyses for this topic. An Agency for Healthcare Research and Quality report entitled “Update on Mapping the Landscape of Genetic Tests for Non-Cancer Diseases/Conditions” summarized a list of genetic tests in current clinical use with specific applicability to older adults; CORUS® CAD was listed with supportive evidence from four studies listed on the manufacturer’s website, but no critical appraisal of the studies was conducted (Raman, 2012). These studies are included below.

Two clinical validation studies - Personalized Risk Evaluation and Diagnosis in the Coronary Tree (PREDICT) and Coronary Obstruction Detection by Molecular Personalized Gene Expression (COMPASS) - two clinical utility studies - The Primary Care Providers Use of a Gene Expression Test in Coronary Artery Disease Diagnosis Trial (IMPACT), A Registry to Evaluate Patterns of Care Associated With the Use of CORUS® CAD in Real World Clinical Care Settings (PRESET) - and one cost-effectiveness analysis were included for this policy. Patients included in these studies represent a narrow spectrum of patients without diabetes mellitus or known CAD, known chronic inflammatory or autoimmune disorders, prior revascularization, or a history of myocardial infarction. Except for the cost-effectiveness analysis, the studies were industry-sponsored and employed centralized processing of RNA and polymerase chain reaction analysis. One analysis on expanded cohorts of the PREDICT and COMPASS validation trials showed similar results to those of the original validations suggesting analytical stability across populations and over time (Daniels, 2014).
Personalized Risk Evaluation and Diagnosis in the Coronary Tree (PREDICT):

PREDICT (Clinicaltrials.gov identifier NCT00500617) is a validation study of a gene expression profiling algorithm in 526 nondiabetic patients (57 percent male) with a clinical indication for coronary angiography (Rosenberg, 2010). Obstructive CAD was defined as 50 percent or greater stenosis in one or more major coronary arteries by quantitative coronary angiography. Results of the gene expression profiling were compared to the Diamond-Forrester risk score and coronary angiography. Overall, 37 percent of subjects had obstructive CAD and 26 percent had no detectable CAD. At a score threshold that corresponded to a 20 percent likelihood of obstructive CAD (14.75), the sensitivity and specificity were 85 percent and 43 percent, respectively, yielding a negative predictive value of 83 percent and a positive predictive value of 46 percent, with 33 percent of patient scores below this threshold. The area under the receiver operating characteristic curve was 0.70 +/- 0.02 (P < 0.001). When added to clinical variables Diamond-Forrester risk score the area under the curve was 0.72 with the test versus 0.66 without (P = 0.003). When added to an expanded clinical model, the area under the curve was 0.745 with the test versus 0.732 without (P = 0.089). The test improved net reclassification over both the Diamond-Forrester score and the expanded clinical model (P < 0.001). A follow up of the PREDICT study (n=1160) found a 30-day major cardiovascular event rate of 23 percent, and a further 2.2 percent at 12 months. Patients with a gene expression score over 15 had close to a significantly higher risk of an event. For those with low gene expression scores, the predictive value was 90 percent for a major cardiovascular event with revascularization, and 99 percent for a major event alone (Rosenberg, 2012).

The follow up PREDICT trial of 1160 patients with suspected obstructive CAD found a prevalence of 46.7 percent in men and 22.0 percent in women. The gene expression score independently predicted CAD in men, women, and the overall populations, each statistically significant. Prediction by non-invasive myocardial perfusion was not significant (Lansky, 2012).

These results suggest that this test could be used to increase the proportion of patients selected for coronary angiography who truly have disease and reduce the number of patients who might otherwise be inappropriately exposed to radiation, contrast agent, and an invasive procedure. The test may improve CAD prediction beyond that of simple prediction models such as Diamond-Forrester, but the improvement in CAD prediction when added to routine clinical evaluation is uncertain. Further studies are needed to define the performance characteristics and clinical utility in populations with lower pretest probability.

Coronary Obstruction Detection by Molecular Personalized Gene Expression (COMPASS):

COMPASS (ClinicalTrials.gov identified NCT01117506) is a validation study of a blood-based gene expression profiling in 537 symptomatic, nondiabetic patients referred for myocardial perfusion imaging (Thomas, 2013; Herman, 2014). The pre-specified primary end point was GEP receiver operating characteristic analysis to discriminate ≥ 50 percent stenosis (15 percent prevalence by core laboratory analysis). The area under the curve for gene expression profiling was 0.79 (95 percent confidence interval, 0.73 to 0.84; P<0.001), with sensitivity, specificity, and negative predictive value of 89 percent,
52 percent, and 96 percent, respectively, at a pre-specified threshold of ≤ 15; 46 percent of patients were below this score. The gene expression profiling outperformed clinical factors by receiver operating characteristic and reclassification analysis and showed significant correlation with maximum percent stenosis. Six-month follow-up on 97 percent of patients showed that 27 of 28 patients with adverse cardiovascular events or revascularization had GEP > 15. Site and core-laboratory myocardial perfusion imaging had an area under the curve of 0.59 and 0.63, respectively, significantly less than gene expression profiling.

The overall accuracy of the gene expression profiling score in predicting cardiac events was superior to myocardial perfusion imaging in patients who were referred for myocardial perfusion testing. However, the reported sensitivity of myocardial perfusion imaging was considerably lower than generally reported in the literature. Also, it is unclear from the COMPASS study whether patients with a positive myocardial perfusion imaging could safely forego further testing based on a low gene expression profiling score.

Using data from the PREDICT and COMPASS studies, Voros et al. examined the association between the gene expression profiling and coronary arterial plaque burden and stenosis by CT-angiography (Voros, 2014). The gene expression profiling was significantly associated with plaque burden by coronary artery calcium scoring (r = 0.50; p < 0.001) and CT-angiography (segment involvement score index: r = 0.37, p < 0.001); a low score (≤ 15) had sensitivity of 0.71 and a high score (≥ 28) had a specificity of 0.97 for the prediction of zero versus non-zero coronary artery calcium. Increasing gene expression profiling was associated with a greater degree of categorical stenosis by ANOVA (P < 0.001); gene expression profiling significantly correlated with maximum luminal stenosis (r = 0.41; p < 0.01) and segment stenosis score index (r = 0.38; p < 0.01). A low score had sensitivity of 0.90 and a high score a specificity of 0.87 for ≥ 70 percent stenosis. Results suggest a moderate correlation between gene expression profiling score and coronary arterial plaque burden and stenosis by CT-angiography.

**IMPACT-PCP:**

The IMPACT-PCP study (ClinicalTrials.gov identifier NCT01594411) assessed the impact of a GEP test on patient management decisions in patients who presented with chest pain and related symptoms at four primary care practices (Herman, 2014). Of the 251 study patients, 140 were women (56 percent). The participants had a mean age of 56 years and a mean body mass index of 30 mg/kg². The average pretest probability of obstructive CAD as determined by the primary care clinician was 28 percent. The mean gene expression profiling was 16, and 127 patients (51 percent) had a low gene expression profiling ([ltqueu]15). A change in the diagnostic testing pattern before and after gene expression profiling testing was noted in 145 of 251 patients (58 percent observed versus 10 percent predefined expected change; P < .001). The gene expression profiling was associated with a decrease in intensity of testing in 60 percent (76 of 127) of patients with a low gene expression profiling.

One study examined the cost-effectiveness of CAD diagnostic strategies including "no test," a gene expression profiling score, myocardial perfusion imaging, and sequential strategies combining gene expression profiling and myocardial perfusion imaging in patients presenting to clinicians with
symptoms suggestive of obstructive CAD (Phelps, 2014). Diagnostic testing for obstructive CAD with a novel gene expression profiling strategy in a two-threshold model is cost-effective by conventional standards. This diagnostic approach is more efficient than usual care of myocardial perfusion imaging alone or a one-threshold gene expression profiling strategy in most scenarios.

**PRESET:**

PRESET (ClinicalTrials.gov identifier NCT01677156) is an ongoing study to assess the impact of a gene expression profiling score on subsequent cardiac referral decisions by primary care providers (Ladapo, 2015a). Of the 342 stable, nonacute patients evaluated, the mean age was 55 years, 53 percent were female, and mean gene expression profiling was 16. Low gene expression profiling (≤15), indicating a low current likelihood of obstructive CAD, was observed in 49 percent of patients. After clinical covariate adjustment, each 10-point decrease in gene expression profiling score was associated with a 14-fold decreased odds of cardiac referral (P < .0001). Patients with a low gene expression profiling had a 94 percent reduced odds of referral relative to elevated gene expression profiling patients (P < .0001), with follow-up supporting a favorable safety profile. Results of this study suggest that gene expression profiling demonstrates clinical utility by guiding decision-making during assessment of symptomatic patients with suspected obstructive CAD.

While these results are encouraging, one study identified many unanswered clinical, biological, and technical considerations that should be taken into account before more widespread clinical use (Zeller, 2013):

- **CORUS® CAD must be tested in a broader population to define its clinical utility for obstructive CAD.**
- **CORUS® CAD that has been tested in small selected populations should be rigorously tested against existing noninvasive standards.** These include modern stress test techniques such as stress echocardiography or other modern state-of-the-art techniques that might provide higher diagnostic sensitivity. Using a predefined threshold for risk of coronary stenosis that is lower than the currently accepted cutoff of 70 percent may have introduced bias and inflated these estimates.
- **Gene expression data will vary inter-individually, temporally, and between different disease states.** The impact of factors such as smoking, medication, and RNA quality on expression should be adequately taken into account.
- **Variation caused by technical factors, such as RNA quality, storage time of whole blood, and the RNA processing and amplification batch can substantially influence gene expression data and should be considered.** In the clinical setting, differences in sample collection, sample processing and assay performance in different clinical centers are to be expected and will influence the accuracy of the data. Ideally, the gene expression profiling should be validated in a multicenter real-world study, including decentralized processing of RNA and polymerase chain reaction analysis and optimization of (decentralized) clinical laboratory testing procedures.
Finally, other questions concerning the translation of the gene expression profiling score into clinical practice will need to be addressed, such as clinical applicability, feasible time frame for expression analysis before patient treatment, ethical issues, and optimal cost-benefit analysis.

A study of 176 persons older than 65 presenting with symptoms of obstructive CAD who underwent the CORUS® CAD gene expression test, found that 12.5 and 49.3 percent of participants with low and high age, sex, and gene expression scores had been referred to cardiology or advanced cardiac testing \( (p<.001) \). After one year, incidence of a major adverse cardiac event or revascularization was 0 and 10 percent for the low and high gene expression score groups (Ladapo, 2018). A similar study 320 women with stable symptoms suggesting obstructive CAD and given an age, sex, and gene expression score found that the referral rate for further cardiac evaluation was 4.0 and 83.3 percent of those with low and elevated scores \( (p<.0001) \). CardioDx Inc. supported these studies (Ladapo, 2015b).

For various reasons, it is more difficult to successfully diagnose CAD in women. One review recommended greater awareness in new approaches, specifically the CORUS CAD gene expression test, in improved diagnosis. However, all authors of this report were either employees of CardioDx Inc., or worked for the Jefferson School of Population Health in Philadelphia PA, which received funds from CardioDx Inc. to prepare the manuscript (Clarke, 2015).

Policy updates:

A total of one guideline/other and four peer-reviewed articles were added to this policy in April 2018.

A total of two guidelines/other and two peer-reviewed articles were added to this policy, in 2017.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniels (2014)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Gene expression score, PREDICT and COMPASS studies</td>
<td>• Gene expression score to predict obstructive coronary artery disease has been validated in two multicenter studies ( (n=1502) ).</td>
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<tr>
<td></td>
<td>• Similar performance was observed for Caucasians and non-Caucasians.</td>
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<tr>
<td></td>
<td>• Scores for stored samples from 526 subjects re-tested after 5 years did not change over time (average 20.3 to 19.8).</td>
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<tr>
<td>Voros (2014)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Association of gene expression score with coronary arterial plaque burden and stenosis by CT-angiography</td>
<td>• Six-hundred-and-ten patients from 59 centers, comparing gene expression scores with likelihood of coronary arterial plaque burden and stenosis by CT angiography.</td>
</tr>
<tr>
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<td>• Gene scores significantly associated with plaque burden by coronary artery calcium and CT angiography.</td>
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<td>• Increasing gene scores associated with a greater degree of categorical stenosis.</td>
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<td></td>
<td>• Gene scores significantly linked with maximum luminal stenosis and segment stenosis.</td>
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## Citation, Content, Methods, Recommendations

<table>
<thead>
<tr>
<th>Citation</th>
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<tbody>
<tr>
<td>Thomas (2013)</td>
<td><strong>Key points:</strong></td>
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</tbody>
</table>
| Gene expression testing – COMPass study | • Multi-center study (n=537), non-diabetic patients.  
• Gene expression score had sensitivity, specificity, and negative predictive value of 89%, 52%, and 96%, respectively, out-performing clinical factors.  
• After six months, 27 of 28 patients with adverse cardiovascular events or revascularization had a high gene expression score (>15).  
• Gene expression score outperformed clinical factors and myocardial perfusion imaging. |
| Rosenberg (2012)              | **Key points:**                   |
| Blood gene expression tests for CAD | • Angiography patients (n=1160) whose gene expression score was analyzed for predicting major adverse cardiac events and revascularization.  
• Thirty-day event rate was 23%, further 12 month rate was another 2.2%.  
• Gene expression score was significantly linked with events and revascularization.  
• Patients with scores >15 were associated with high event rate + revascularizations.  
• For patients with low scores, negative predictive value was 90% for events and revascularization, 99% for events alone (within 12 months). |

## References

### Professional society guidelines/other:


**Peer-reviewed references:**


Ladapo JA, Lyons H, Yau M, et al. Enhanced assessment of chest pain and related symptoms in the primary care setting through the use of a novel personalized medicine genomic test: Results from a


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local coverage determinations (LCDs):**

L35025 MolDX: Molecular Diagnosis Tests (MDT). Effective date October 1, 2015. [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35025&ver=55&Cove rageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Molecular+diagnostic+tests&KeyWordLookUp=Title&KeyWordSearchType=And&FriendlyError=InvalidVer%2cNoLCDIDVersion&bc=gAAAAACAAAAA&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35025&ver=55&Cove rageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Molecular+diagnostic+tests&KeyWordLookUp=Title&KeyWordSearchType=And&FriendlyError=InvalidVer%2cNoLCDIDVersion&bc=gAAAAACAAAAA&). Accessed April 4, 2018.

L35160 MolDX: Molecular Diagnosis Tests (MDT). Effective date October 1, 2015. [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35160&ver=21&Cove rageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Molecular+diagnostic+tests&KeyWordLookUp=Title&KeyWordSearchType=And&FriendlyError=InvalidVer%2cNoLCDIDVersion&bc=gAAAAACAAAAA&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35160&ver=21&Cove rageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Molecular+diagnostic+tests&KeyWordLookUp=Title&KeyWordSearchType=And&FriendlyError=InvalidVer%2cNoLCDIDVersion&bc=gAAAAACAAAAA&). Accessed April 4, 2018.

L36021 Molecular Diagnostic Tests. Effective date October 1, 2015. [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36021&ver=24&Cove rageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Molecular+diagnostic+tests&KeyWordLookUp=Title&KeyWordSearchType=And&FriendlyError=InvalidVer%2cNoLCDIDVersion&bc=gAAAAACAAAAA&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36021&ver=24&Cove rageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Molecular+diagnostic+tests&KeyWordLookUp=Title&KeyWordSearchType=And&FriendlyError=InvalidVer%2cNoLCDIDVersion&bc=gAAAAACAAAAA&). Accessed April 4, 2018.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<tr>
<td>81493</td>
<td>Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, reported as a risk score</td>
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<table>
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