Anthem

Medical Policy

Subject:	**Gene Expression Profiling for Coronary Artery Disease**		
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Description/Scope

This document addresses gene expression profiling for coronary artery disease (CAD). There is a commercially available gene expression blood test for obstructive coronary artery disease, the Corus® CAD (CardioDx Inc., Palo Alto, CA). The test is intended to be used for non-diabetic individuals with stable symptoms suggestive of obstructive CAD.

Please refer to the documents indicated below for information regarding genetic testing for cardiovascular disease and gene expression profiling:

- **CG-MED-57 Cardiac Stress Testing with Electrocardiogram**
- **MED.00074 Computer Analysis and Probability Assessment of Electrocardiographic-Derived Data**
- **RAD.00001 Computed Tomography to Detect Coronary Artery Calcification**

Position Statement

Investigational and Not Medically Necessary:

The use of gene expression profiling for coronary artery disease is considered investigational and not medically necessary.

Rationale

Elashoff and colleagues (2011) described the initial validation study of the Corus CAD test. The researchers used a series of microarray and real-time polymerase chain reaction (RT-PCR) data sets to develop a blood-based gene expression algorithm for assessing obstructive CAD in non-diabetic subjects. The components of the algorithm were the expression levels of 23 genes, sex and age.

Two multicenter prospective clinical validation studies on the Corus CAD test, the PREDICT and COMPASS studies, have been published. Rosenberg and colleagues (2010) reported results of the PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) trial. This study included non-diabetic individuals referred for diagnostic coronary angiography. A total of 1343 individuals met the inclusion criteria. Of these, 694 were included in the development phase and 649 in the validation phase. After exclusions, 526 nondiabetic individuals were included in the final clinical validation analysis. Of the 526 participants, 192 positive for CAD and 334 negative for CAD were used to validate the gene expression score (GES) algorithm. CAD was defined as at least 50% stenosis in at least one major coronary artery. To assess performance, receiver operating characteristics (ROC) area under the curve (AUC) were calculated for the GES algorithm in addition to two clinical risk assessment models (the Diamond-Forrester risk score and an expanded clinical factor model which was developed by the researchers). Both clinical risk assessment

models included age, sex, and chest pain type. However, the expanded clinical model also included race, systolic blood pressure, the presence of hypertension and dyslipidemia and the use of medications (statins, aspirin, antiplatelet medications, and ACE inhibitors). The ROC AUC for the GES only was 0.70 ± 0.02 (p<0.001). The ROC AUC for the use of the GES along with the Diamond-Forrester score was 0.72, a statistically significant improvement compared to the use of the Diamond-Forrester score alone (0.66; p=0.003). The ROC AUC for the use of the GES as well as the expanded clinical model was similar to that of the expanded clinical model alone (0.745 versus 0.732; p=0.089 for the difference). An analysis of reclassification found that the net reclassification improvement was 20% (p<0.001) for the GES compared to the Diamond-Forrester score, and 16% (p0.001) for the expanded clinical model in addition to GES versus the expanded clinical model alone.

In 2012, Rosenberg and colleagues published additional data from the PREDICT trial. Individuals were monitored for major adverse cardiovascular events (MACE) and interventions for 12 months from the initial diagnostic coronary angiography. One-year follow-up data were available for 1166 individuals including 526 from the clinical validation subset of PREDICT participants. The GES was significantly associated with composite primary endpoint of MACE and interventions over 12 months (p<0.001). In, logistic regression models, the GES added to clinical factors such as Framingham risk scores. At a score threshold of ≤ 15, the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were 86%, 41%, 90% and 33%, respectively.

Findings of the COMPASS study were published by Thomas and colleagues in 2013. The study included 537 individuals with angina or angina equivalent symptoms who were referred for diagnostic myocardial perfusion imaging (MPI) stress testing. Blood samples for gene expression were obtained prior to MPI and participants were referred for either invasive coronary angiography or CT angiography based on MPI results. Participants were followed for 6 months with the study end point being a major adverse cardiac event. Results of the angiography were compared to the GES and MPI results. The final cohort of evaluable individuals who completed all testing included 431 of the 537 enrolled individuals. The GES was a significant predictor of obstructive CAD by ROC analysis (AUC, 0.79, 95% confidence interval [CI], 0.73 to 0.84; p<0.001). Sensitivity, specificity, NPV and PPV were 89%, 52%, 96% and 24%, respectively. The researchers found that GES was significantly correlated with maximum percent stenosis (≥ 50). During the 6-month follow-up period after index MPI and GES, there were 28 adverse clinical events. The GES was significantly associated with MACE and likelihood of revascularization (0-0.0015). At a score threshold of ≤ 15, the GES had a sensitivity of 96% and an NPV of 99%. The authors acknowledged that the study included potentially lower disease prevalence in the subjects due to the inclusion/exclusion criteria, and the lack of comparison of GES scores to other noninvasive imaging modalities.

Voros and colleagues (2014) used data from 610 individuals who participated in the PREDICT and COMPASS studies to evaluate the association between the GES and atherosclerotic plaque burden and stenosis. Individuals had undergone CT angiography, CT angiography-based plaque and stenosis measurements and coronary artery calcium (CAC) scoring. There was a significant correlation between calcified plaque burden and the GES (r=0.50, p<0.001). In addition, the GES was significantly associated with maximum percent diameter stenosis (r=0.41, p<0.001).

Several studies have addressed the impact of the CORUS CAD test on patient management. McPherson and colleagues (2013) evaluated the impact of gene expression testing on disease management by a group of

cardiology specialists. Participants (n=171) presenting with stable chest pain and related symptoms without a history of CAD were referred to six cardiologists for evaluation. In the prospective cohort of 88 participants, the cardiologist's diagnostic strategy was evaluated before and after GES testing. A total of 83 individuals were evaluable for study analysis, which included 57 (69%) women, mean age 53 ± 11 years, and mean GES 12.5 ± 9. Presenting symptoms were classified as typical angina, atypical angina, and noncardiac chest pain in 33%, 60%, and 7% of the participants (n=27, 50, and 6), respectively. This study found that individuals with low gene expression scores (≤ 15) were more likely to have a decrease in the intensity of diagnostic testing. Individuals with elevated GES were more likely to undergo additional testing for the evaluation of obstructive CAD. Limitations of this study include its small sample size and the evaluation of short-term (6 months) outcomes.

Herman and colleagues (2014) conducted a study (IMPACT-PCP) which assessed the impact of gene expression testing on clinical decision-making in individuals presenting to a primary care setting with symptoms of suspected CAD. The study was comprised of 261 consecutive stable, nonacute, nondiabetic participants presenting with typical and atypical symptoms of CAD. Of the 251 eligible study participants, 140 (56%) were women. Providers initially determined the subjects' pretest probability for CAD based on risk factors, assessment of clinical symptoms and results of any prior testing. All of the participants underwent GES testing, with clinicians documenting their planned diagnostic strategy both prior to and after GES. The primary objective was to assess whether the utilization of GES altered patient management. After 30 days, a change in the diagnostic plan before and after GES testing was noted in 145 (58%) of the participants. A total of 93 (37%) of the participants had decreased intensity of testing versus the 52 (21%) which experienced an increase in the intensity of testing. In particular, among the 127 low score Corus CAD individuals (51% of study participants), 60% (76/127) experienced decreased testing, and only 2% (3/127) experienced increased testing. The authors concluded that including the GES into the diagnostic workup demonstrated clinical utility above and beyond conventional clinical factors by optimizing the individual's diagnostic evaluation. Limitations of the study include inclusion of individuals at low risk for CAD, short term follow-up and modest sample size.

Lapado and colleagues (2016) published an analysis of the PRESET Registry, with a focus on physician decision-making for individuals who had a high versus low score on the Corus CAD GES. The GES incorporated age- and sex-related factors and was known as the age/sex/gene expression score (ASGES). The PRESET Registry enrolled stable, non-acute adults with symptoms suggestive of obstructive CAD. The analysis yielded that the referral rate to cardiology or advanced cardiac imaging was 10% (26/252) among individuals with low scores on the ASGES (≤ 15) compared with 44% (137/314) of individuals with elevated score (> 15) on the ASGES. Among 84 individuals with data available on advanced cardiac testing, there were major abnormal findings in 0 of 13 individuals with a low ASGES and 10 of 71 (14%) individuals with elevated ASGES. MACE were identified in 3 of 252 (1.2%) individuals with low ASGES and 14 of 314 (4.5%) of those with elevated ASGES. The study was not able to specify the role that the Corus CAD played in the physician's decision-making process and it did not compare physician decision-making with and without the ASGES.

Another analysis of the same PRESET Registry data (Gul, 2019) focused on the 288 women enrolled in the registry. Physicians referred 9% (20/218) of women with a low ASGES (≤ 15) for additional testing compared with 44% (31/70) with an elevated ASGES (>15). After 1 year of follow-up, women with low ASGES scores had experienced fewer MACE than those with elevated ASGES (1.3% versus 4.2%,

respectively). The difference between groups, however, was not statistically significant, p=0.16). As in the Lapado (2016) study described above, there was no comparison of physician decision-making with and without knowledge of an ASGES.

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found insufficient evidence to recommend the use of genomic profiling to assess cardiovascular risk and "discourages clinical use unless further evidence supports improved clinical outcomes" (EGAPP, 2010).

In summary, Corus CAD has been proposed as a means to help physicians identify individuals who are unlikely to have obstructive CAD and who may avoid invasive diagnostic testing. However, additional studies are needed which demonstrate that information provided by the CORUS CAD improves clinical outcomes compared with standard practice.

Background/Overview

Heart disease is the leading cause of mortality in the United States for both men and women, with more than 600,000 deaths per year. The most common type of heart disease is coronary artery disease (CAD), with more than 370,000 deaths annually. CAD is the narrowing or blockage of arteries that supply blood to the heart (coronary arteries). It is generally caused by atherosclerosis, the build-up of plaque, cholesterol and fatty deposits on the walls of the coronary arteries. Plaque build-up can reduce blood flow to the heart and, without this blood flow, the heart is unable to function properly. Angina, chest pain or discomfort, occurs when the heart muscle does not get sufficient blood. The symptoms of CAD may differ for women and women. Men commonly experience crushing chest pain whereas women are more likely to experience chest pain as pressure or tightness and have other symptoms such as shortness of breath, nausea and fatigue (CDC 2015; CDC 2017).

The diagnosis of CAD among individuals reporting signs or symptoms such as chest pain remains challenging. Clinical history-taking and physical examination are initial steps in assessment of these individuals. In addition, there are predictive tools that can help guide clinical decision-making. These include the Framingham risk score, QRisk algorithm and ASSIGN score which are all validated risk prediction tools (Ayerbe 2016). Laboratory tests include measurement of c-reactive protein levels and coronary artery calcium scores. Coronary angiography is considered the reference standard for diagnosing obstructive CAD, but it is invasive and therefore has an associated risk of harm. There is interest in additional non-invasive tests that can improve the diagnosis of obstructive CAD and lead to a reduction in the rate of adverse cardiac events.

Another approach to CAD diagnosis is gene expression analysis. There is one commercially available gene expression profiling test for coronary artery disease, the Corus® CAD (CardioDx Inc., Palo Alto, CA). The test did not go through the FDA approval or clearance process and is not required to do so. The Corus CAD is a peripheral blood test which integrates the expression levels of 23 genes known to play a role in the development of or response to atherosclerosis. Data on the expression of the 23 genes as well as the individual's age and sex are combined in a mathematical algorithm to generate a gene expression score (GES) which ranges from 1-40. Higher GES scores are associated with an increased likelihood of CAD. Corus CAD is intended to be used in stable, nondiabetic individuals suspected of having obstructive CAD and to complement other non-invasive tests. It is not intended for individuals with a history of obstructive CAD or who had a history of myocardial infarction or revascularization procedures.

Definitions

Coronary angiography: A procedure that uses dye (contrast material) and x-rays to evaluate the extent of narrowing in coronary arteries.

Diamond-Forrester risk score: A classification tool used to estimate the pretest probability of coronary artery disease in patients with chest pain. The tool was developed in an outpatient setting.

Gene expression profiling: A laboratory test that measures the activity of multiple genes at once for diagnostic or prognostic purposes. The test result is often reported as a proprietary summary score.

Obstructive coronary artery disease: A reduction in blood flow to the heart muscle due to a narrowing of arteries that supply blood to the heart. The narrowing or blockage is caused by plaque that has built up in the arteries (atherosclerosis). Also known as ischemic heart disease.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure code; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
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 Corus® CAD, CardioDx, Inc**
ICD-10 Diagnosis	
	All diagnoses

References

Peer Reviewed Publications:

1. **Ayerbe L, González E, Gallo V et al.Clinical assessment of patients with chest pain; a systematic review of predictive tools. BMC Cardiovasc Disord. 2016;16:18.**
2. **Cagle SD Jr, Cooperstein N. Coronary Artery Disease: Diagnosis and Management. Prim Care. 2018; 45(1):45-61.**

3. **Elashoff MR, Wingrove JA, Beineke P, et al. Development of a blood-based gene expression algorithm for assessment of obstructive coronary artery disease in non-diabetic patients. BMC Med Genomics. 2011; 4:26.**
4. **Gul B, Lansky A, Budoff MJ et al The clinical utility of a precision medicine blood test incorporating age, sex, and gene expression for evaluating women with stable symptoms suggestive of obstructive coronary artery disease: Analysis from the PRESET Registry. J Womens Health (Larchmt). 2019 Jan 17. [Epub ahead of print].**
5. **Herman L, Froelich J, Kanelos D, et al. Utility of a genomic-based, personalized medicine test in patients presenting with symptoms suggesting coronary artery disease. J Am Board Fam Med. 2014; 27(2):258-267.**
6. **Ladapo JA, Budoff M, Sharp D et al. Clinical utility of a precision medicine test evaluating outpatients with suspected obstructive coronary artery disease. Am J Med. 2017; 130(4):482.**
7. **McPherson JA, Davis K, et al. The clinical utility of gene expression testing on the diagnostic evaluation of patients presenting to the cardiologist with symptoms of suspected obstructive coronary artery disease: results from the IMPACT (Investigation of a Molecular Personalized Coronary Gene Expression Test on Cardiology Practice Pattern) trial. Crit Path Cardiol. 2013; 12(2):37-42.**
8. **Rosenberg S, Elashoff MR, Beineke P, et al. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. Ann Intern Med. 2010; 153(7):425-434.**
9. **Rosenberg S, Elashoff MR, Lieu HD et al. PREDICT Investigators. Whole blood gene expression testing for coronary artery disease in nondiabetic patients: major adverse cardiovascular events and interventions in the PREDICT trial. J Cardiovasc Transl Res. 2012; 5(3):366-374.**
10. **Thomas GS, Voros S, McPherson JA, et al. A blood-based gene expression test for obstructive coronary artery disease tested in symptomatic nondiabetic patients referred for myocardial perfusion imaging the COMPASS study. Circ Cardiovasc Genet. 2013; 6(2):154-162.**
11. **Voros S, Elashoff MR, Wingrove JA et al. A peripheral blood gene expression score is associated with atherosclerotic plaque burden and stenosis by cardiovascular CT-angiography: results from the PREDICT and COMPASS studies. Atherosclerosis. 2014; 233(1):284-290.**

Government Agency, Medical Society, and Other Authoritative Publications:

1. **Centers for Disease Control and Prevention (CDC). Heart disease facts and statistics. Last updated 2017. Available at: https://www.cdc.gov/heartdisease/facts.htm. Accessed March 5, 2019.**
2. **Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genomic profiling to assess cardiovascular risk to improve cardiovascular health. Genet Med. 2010; 12(12):839-843.**

Websites for Additional Information

1. **Centers for Disease Control and Prevention (CDC). Coronary artery disease. Last updated 2015. Available at: https://www.cdc.gov/heartdisease/coronary_ad.htm. Accessed March 5, 2019.**

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CardioDx
Corus CAD

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	03/21/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development. Content on Corus CAD moved from GENE.00043, expanded and updated.