

Protocol

Gene Expression Testing to Predict Coronary Artery Disease

(20472)

Medical Benefit		Effective Date: 10/01/16	Next Review Date: 07/17
Preauthorization	No	Review Dates: 09/11, 09/12, 09/13, 07/14, 07/15, 07/16	

Preauthorization is not required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none">With increased risk of CAD due to suggestive symptoms (chest pain, suspected anginal equivalent) or elevated predicted risk in nondiabetic patients	Interventions of interest are: <ul style="list-style-type: none">Gene expression testing for CAD prediction	Comparators of interest are: <ul style="list-style-type: none">Clinical risk prediction models (e.g., Diamond-Forrester)Myocardial perfusion imaging	Relevant outcomes include: <ul style="list-style-type: none">Test accuracyTest validityChange in disease statusMorbid eventsResource utilization

CAD: coronary artery disease.

Description

Expression levels of various genes in circulating white blood cell or whole blood samples have been reported to discriminate between cases of obstructive coronary artery disease (CAD) and healthy controls. Multiplex gene expression testing can be combined with other risk factors to predict the likelihood of obstructive CAD in patients who present with chest pain or other suggestive symptoms, or in asymptomatic patients who are at high risk of CAD. These tests have potential to improve the accuracy of predicting CAD likelihood. A commercially available Gene Expression Score (GES) test, Corus CAD™, has been developed and validated for this purpose in nondiabetic patients.

Summary of Evidence

The evidence for gene expression testing for coronary artery disease (CAD) prediction in nondiabetic patients with increased CAD risk (due to suggestive symptoms or elevated predicted risk) includes retrospective case-control and prospective cohort studies. Relevant outcomes are test accuracy, test validity, change in disease status (CAD detected on angiography), morbid events (cardiac events), and resource utilization (rates of coronary angiography). The prospective PREDICT study raised the possibility 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. Results of initial validation studies reported that 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. The test also has been shown to have some predictive ability for future cardiac events and revascularization. In the COMPASS study, overall accuracy of Gene Expression Score (GES) in predicting cardiac events was superior to myocardial perfusion imaging (MPI) in patients who were referred for MPI testing. However, in that study, reported sensitivity of MPI was considerably lower than generally reported in the literature. Also, it is unclear from the COMPASS study whether patients with a positive MPI could safely forgo further testing based on a low GES. Clinical utility of GES has not been demonstrated. Three studies with methodologic limitations reported management changes as a result of the test, but the effect of these management changes is uncertain. Evidence for a significant incremental improvement in outcomes when gene expression testing is added to standard clinical evaluation is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Gene expression testing to predict coronary artery disease (CAD) is considered **investigational** for all indications, including but not limited to prediction of the likelihood of CAD in stable, nondiabetic patients.

Policy Guidelines

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

For Medicare Advantage the Corus CAD™ test may be **medically necessary** in members who meet the developers test indications: stable, nondiabetic patients suspected of CAD either because of symptoms, a high-risk history, or a recent positive or inclusive test result by conventional methods.

One typical symptom, or a combination of an atypical symptom and at least one common CAD risk factor are required to meet test indications. Lists of typical symptoms, atypical symptoms and common CAD risk factors follow:

Typical Symptoms

Angina pectoris

Shortness of breath

Precordial pain

Intercostal pain

Other and unspecified chest pain

Atypical symptoms

- Dorsalgia unspecified

- Pain in left arm
- Pain in left upper arm
- Palpitations;
- Unspecified abdominal pain
- Nausea
- Vomiting
- Nausea and vomiting
- Heartburn
- Dizziness and giddiness
- Other malaise
- Jaw pain

Common CAD Risk Factors

- Obesity
- Pure Hypercholesterolemia
- Pure Hyperglyceridemia
- Hyperlipidemia
- Metabolic syndrome
- Nicotine dependence, uncomplicated or nicotine dependence in remission
- Essential (primary) hypertension
- Atherosclerotic heart disease of native coronary artery with angina pectoris
- Occlusion and stenosis of carotid artery
- Cerebral atherosclerosis
- Atherosclerosis of the renal artery
- Atherosclerosis of native arteries of the extremities
- Family history of sudden cardiac death
- Family history of ischemic heart disease

Background

Heart disease is the leading cause of death in the United States and, together with cerebrovascular disease, accounted for 31% of deaths in 2007.¹ Patients with signs and symptoms of obstructive coronary artery disease (CAD), the result of a chronic inflammatory process that ultimately results in progressive luminal narrowing and acute coronary syndromes, may be evaluated with a variety of tests according to prior risk. Coronary angiography is the criterion standard for diagnosing obstructive CAD, but it is invasive and associated with a low but finite risk of harm. Thus, coronary angiography is recommended for patients at a high prior risk of CAD according to history, physical findings, electrocardiogram, and biomarkers of cardiac injury.² For patients initially assessed

at low to intermediate risk, observation and noninvasive diagnostic methods, which may include imaging methods such as coronary computed tomographic angiography, may be recommended. Nevertheless, even noninvasive imaging methods have potential risks of exposure to radiation and contrast material. In addition, coronary angiography has a relatively low yield, despite risk stratification recommendations. In one study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial or branch vessel that was more than 2.0 mm in diameter; result was 41% if using the broader definition, stenosis of 50% or more in any coronary vessel).³ Thus, methods of improving patient risk prediction before diagnostic testing are needed.

A CAD classifier has been developed based on expression levels, in whole blood samples, of 23 genes plus patient age and sex. This information is combined in an algorithm to produce a score from one to 40, with higher values associated with a higher likelihood of obstructive CAD. The test is marketed as Corus CAD™ (CardioDx, Palo Alto, CA). The intended population is stable, nondiabetic patients suspected of CAD either because of symptoms, a high-risk history, or a recent positive or inconclusive test result by conventional methods.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standard of the Clinical Improvement Act (CLIA). The Corus CAD™ test is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Related Protocols

Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm
KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation*. Aug 14 2007; 116(7):e148-304. PMID 17679616

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19. Noridian Healthcare Solutions, LLC, (Jurisdiction - California - Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) Local Coverage Determination (LCD): MoIDX: Molecular Diagnostic Tests (MDT) (L36249), original Effective Date for services performed on or after 10/01/2015.
20. MoIDX: Molecular Diagnostic Tests (MDT) (L36249) Noridian Healthcare Solutions, LLC, (Jurisdiction - California - Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) Local Coverage Article: MoIDX: Corus® CAD Test Billing and Coding Guidelines (A54428), Revision Effective Date 01/01/2016.