Protocol

Gene Expression Testing in the Evaluation of Patients with Stable Ischemic Heart Disease

(20472)

(Formerly Gene Expression Testing to Predict Coronary Artery Disease)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 07/18
Preauthorization	No	**Review Dates**: 09/11, 09/12, 09/13, 07/14, 07/15, 07/16, 07/17	

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: • With suspected stable ischemic heart disease without diabetes	Interventions of interest are: • Gene expression testing	Comparators of interest are: • Clinical risk prediction models (e.g., Diamond-Forrester) • Noninvasive testing for stable ischemic heart disease	Relevant outcomes include: • Test accuracy • Test validity • Change in disease status • Morbid events • Resource utilization

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 estimate the likelihood of obstructive CAD in patients who present with stable ischemic heart disease. These tests have potential to improve the accuracy of predicting CAD. A commercially available Gene Expression Score (GES) test, Corus CAD, has been developed and validated for this purpose in nondiabetic patients.

Summary of Evidence

For individuals who have suspected stable ischemic heart disease without diabetes who receive gene expression testing, the evidence includes retrospective case-control and prospective cohort studies. Relevant outcomes are test accuracy and validity, change in disease status. Results of initial validation studies have reported that the test may improve CAD prediction beyond that of simple prediction models (e.g., Diamond-Forrester), but the benefit of improved prediction when added to routine clinical evaluation is uncertain. The test also has been shown to have some predictive ability of future cardiac events and revascularization. In the COMPASS study, overall accuracy of the Gene Expression Score (GES) test in predicting cardiac events was superior to myocardial perfusion imaging (MPI) in patients referred for MPI testing. However, in that study, the reported sensitivity of MPI was considerably lower than that generally reported in the literature. Also, it is unclear from the COMPASS study whether patients with positive MPI could safely forgo further testing based on a low GES. The clinical utility of the 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 on patient outcomes 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 in the evaluation of patients with stable ischemic heart disease is considered **investigational** for all indications, including but not limited to prediction of coronary artery disease 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 considered **medically necessary.**

Medicare Advantage Policy Guidelines

The Corus CAD™ test may be considered medically necessary only when test indications published by the developer are followed. The following information was taken from the CardioDX website. (accessed 6/22/17 http://www.cardiodx.com/patient-resources/corus-cad-test/)

The Corus® CAD test is intended for patients who present with stable symptoms suggestive of obstructive coronary artery disease (CAD). The test should be performed on patients with a history of chest pain, with suspected anginal equivalent to chest pain, or with a high risk of coronary artery disease (CAD), but with no known prior myocardial infarction or revascularization procedures.

The test is not intended for patients with acute myocardial infarction, high-risk unstable angina, systemic infectious or systemic inflammatory conditions, diabetes, or who are currently taking steroids, immunosuppressive agents, or chemotherapeutic agents.

The Corus CAD test is NOT intended for patients who: Have a history of obstructive CAD, are diabetic, have been diagnosed with prior myocardial infarction (MI) or have had a previous revascularization procedure, are currently taking steroids, immunosuppressive agents or chemotherapeutic agents.

The test is not intended to be used to screen for stenosis among patients who are asymptomatic and not considered at high-risk for CAD, to predict or detect response to therapy, or to help select the optimal therapy for patients.

Background

Heart disease is the leading cause of death in the United States.[1] Patients with signs and symptoms of obstructive CAD 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. 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.[2] Nevertheless, some 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 a study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, ≥ 50% stenosis of the diameter of the left main coronary artery or ≥ 70% stenosis of the diameter of a major epicardial or branch vessel that was > 2.0 mm in diameter and 41% if using the broader definition, ≥ 50% stenosis in any coronary vessel).[3] Thus, methods of improving patient risk prediction before invasive coronary angiography are needed.

In an initial proof-of-principle study of the Gene Expression Score (GES) test in patients referred for invasive coronary angiography, Wingrove et al (2008) evaluated 27 cases (96% symptomatic) with and 14 controls without angiographically defined CAD for expression of genes that differed significantly between the two groups, selecting 50 genes.[4] To that authors added 56 genes selected from relevant literature reports and evaluated expression of these 106 genes in an independent set of 63 cases and 32 controls, resulting in the selection of 14 genes that independently and significantly discriminated between groups in multivariable analysis. The significance of 11 of these 14 genes was replicated in a third set of 86 cases and 21 controls. Expression of the 14 genes was proportional to maximal coronary artery stenosis in the combined cohort of 215 patients.

Elashoff et al (2011) described final test development of the GES.[5] Investigators conducted two successive case-control gene expression discovery studies using samples from independent cohorts. Cases were angiographically defined as 75% or greater maximum stenosis in one major vessel, or 50% or greater in two vessels, and controls defined as less than 25% stenosis in all major vessels. Of clinical factors, diabetes had the most significant effect on gene expression; in the first case-control study in symptomatic patients (CATHGEN; N=195), expression of 42 genes in nondiabetic patients and 12 genes in diabetic patients was found to significantly ($p<0.05$) discriminate between cases and controls with no overlap. As a result, the second case-control study, in a subset of 198 patients from the prospective PREDICT study (discussed next), and final development of the assay was limited to nondiabetic patients (62% symptomatic). Final variable selection comprised the expression of 20 CAD-associated genes, three normalization genes, and terms for age and sex, all incorporated into an algorithm that resulted in an obstructive CAD score ranging from one to 40. Receiver operating characteristic analysis in PREDICT resulted in an area under the curve for CAD of 0.77 (95% confidence interval, 0.73 to 0.81).

A CAD classifier has been developed based on expression levels derived from the previously described studies, in whole blood samples, of 23 genes plus patient age and sex. This information is used 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. 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 standards of the Clinical Laboratory

Improvement Amendments (CLIA). The Corus CAD™ test (CardioDx, Palo Alto, CA) 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 this test.

Related Protocol

KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

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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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20. Noridian Healthcare Solutions, LLC, (Jurisdiction California - Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35160), Revision Effective Date for services performed on or after 01/01/2017.