Protocol

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

(20472)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 07/19
Preauthorization	No	**Review Dates**: 09/11, 09/12, 09/13, 07/14, 07/15, 07/16, 07/17, 07/18	

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 or inflammatory conditions	Interventions of interest are: • Gene expression testing	Comparators of interest are: • Clinical risk prediction and risk stratification • Noninvasive testing without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • 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 has been 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 test, Corus CAD, has been developed for this purpose for patients without diabetes or inflammatory conditions.

SUMMARY OF EVIDENCE

For individuals who have suspected stable ischemic heart disease without diabetes or inflammatory conditions who receive gene expression testing, the evidence includes retrospective case-control and prospective cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, morbid events, and resource utilization. The diagnostic pathway for CAD includes information from a medical history, along with age and sex, stress testing, and imaging. Newer noninvasive methods are being tested, such as gene expression testing. It is not clear how the Corus CAD gene expression test fits in the current diagnostic pathway and how results would be used to change current guideline-based risk stratification before and/or after other noninvasive testing. Results of two validation studies (PREDICT, COMPASS) have reported that the test may improve CAD prediction beyond the Diamond-Forrester prediction model. In the COMPASS study, the sensitivity and negative predictive value of the Corus CAD score in diagnosing obstructive CAD was superior to myocardial perfusion imaging in patients referred for myocardial perfusion imaging testing.

However, in that study, the reported sensitivity of myocardial perfusion imaging was considerably lower than that generally reported in the literature. Neither PREDICT nor COMPASS used the guideline definition of obstructive CAD as the reference standard. The sensitivity and negative predictive value of clinical models were not reported. An analysis of a cohort from the PROMISE trial including patients with intermediate pretest probability of obstructive CAD confirmed a high negative predictive value for the Corus CAD score. The test also has been shown to have some predictive ability of future revascularization; too few major cardiac events have been observed during the limited duration of follow-up to assess predictive ability for that outcome. Evidence for the Corus CAD score has not directly demonstrated that the test is clinically useful and a chain of evidence cannot be constructed to supports its utility. 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.

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 6/21/18 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

Heart disease is the leading cause of death in the United States, accounting for approximately one-third of all

deaths in people over age 35.[1] The death rate is higher in men compared with women and in blacks compared with whites, but lower in Hispanic populations compared with blacks and whites. The most common form of heart disease is ischemic heart disease, also known as CAD.

Angina is the first symptom of CAD in approximately 50% of patients. However, women and the elderly are more likely to present with atypical symptoms such as nausea, vomiting, gastric discomfort, or atypical chest pain, which makes diagnosis more challenging.[2]

Diagnosis

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. Coronary angiography also has a relatively low yield. 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 > 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 Corus CAD score 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 the 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 the 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 Corus CAD score development.[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 ($p<0.05$) discriminate significantly 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, and final development of the assay was limited to nondiabetic patients (62% symptomatic). The participants were 76% male and 89% white. Final variable selection comprised the expression of 20 CAD-associated genes, three normalization genes, and terms for age and sex. The majority of the selected genes were immune and inflammatory-related. All terms were incorporated into an algorithm that resulted in an obstructive CAD score ranging from 1 to 40.

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 the CLIA. Laboratories that offer LDTS must be licensed by the 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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