MEDICAL POLICY

POLICY TITLE	GENE EXPRESSION TESTING IN PATIENTS WITH STABLE ISCHEMIC HEART DISEASE
POLICY NUMBER	2.313

Original Issue Date (Created):	**3/1/2013**	
Most Recent Review Date (Revised):	**6/4/2020**	
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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 the likelihood of coronary artery disease in stable, nondiabetic patients. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-references:

MP-2.309 KI6F Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

MP-2.311 Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease and Aneurysm

I. PRODUCT VARIATIONS TOP

This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual MP-2.04.72 Gene Expression Testing to Predict Coronary Artery Disease. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

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II. DESCRIPTION/BACKGROUND

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Heart Disease

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 without diabetes or inflammatory conditions.

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 2 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 2 successive case-control gene expression discovery studies using samples from independent cohorts. Cases were angiographically defined as 75% or greater maximum stenosis in 1 major vessel, or 50% or greater in 2 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, 3 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The Corus® CAD test (CardioDx, Palo Alto, CA) is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

III. RATIONALE

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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 2 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.

IV. DEFINITIONS TOP

NA

V. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VI. DISCLAIMER TOP

Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VII. CODING INFORMATION TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational: therefore, not covered:

CPT Codes®								
81493								

VIII. REFERENCES TOP

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30. *Blue Cross Blue Shield Association Medical Policy Reference Manual 2.04.72 Gene Expression Testing in the Evaluation of Patients with Stable Ischemic Heart Disease. Accessed July 17, 2019.*

IX. POLICY HISTORY

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MP 2.313	**CAC 10/28/12** New policy adopting BCBSA. Previously silent on this testing now listed as investigational. Codes reviewed 9/24/12
	8/1/13 Administrative update. Added Medicare variation to reference Palmetto GBA, LCD L32288 Molecular Diagnostic Tests (MDT) regarding gene expression testing to predict coronary artery disease
	CAC 11/26/13 Consensus review. No change to policy statements. References updated. Added Rationale section. Changed Medicare variation to reference Noridian Administrative Services, LLC LCD L33541 Molecular Diagnostic Tests (MDT) due to carrier change in area of manufacture.
	CAC 11/25/14. Consensus review. References and rationale updated. Policy statement unchanged but wording modified to clarify that GES is investigational "for all indications, including but not limited to prediction of CAD likelihood in stable, nondiabetic patients. Coding reviewed, no changes.
	CAC 11/24/15 Consensus review. No change to policy statements. References and rationale updated. Changed LCD number from L33541 to L35160 due to Noridian update. Coding updated with new code from 2016**.**
	CAC 11/29/16 Consensus review. No change to the policy statements. No new references added. Medicare variation revised to refer to Novitas LCD L36713 Corus CAD Test. Variations reformatted. Appendix added. Coding reviewed.
	12/19/17 Consensus review. Policy title change to "Gene Expression Testing in Patients with Stable Ischemic Heart Disease" to be consistent with current guideline statements. No change to the policy statement**.** Background, rationale and references updated.
	10/31/18 Consensus review. No change to policy statements. Rationale condensed. References updated.
	7/17/19 Consensus review. No change to policy statements. References updated.
	6/4/20 Policy retired.

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