BLUE CROSS OF NORTHEASTERN PA "BCNEPA" MEDICAL POLICY BULLETIN	**MANUAL:** MEDICAL POLICY
	REFERENCE NO.: MPO-083-0037
EFFECTIVE DATE October 1, 2014	**SUBJECT:** Gene Expression Testing to Predict Coronary Artery Disease

Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

DESCRIPTION:

The 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.

BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

BACKGROUND:

Heart disease is the leading cause of death in the U.S. and, together with cerebrovascular disease, accounted for 31% of deaths in 2007. (1) Patients with signs and symptoms of obstructive 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 (CTA), 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 1 to 40, with higher values associated with a higher likelihood of obstructive CAD. The test is marketed as Corus CAD™ (CardioDx, Inc.; Palo Alto, California). 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.

MEDICAL POLICY STATEMENT:

BCNEPA will not provide coverage for gene expression testing to predict coronary artery disease (CAD) as it is considered investigational for all indications, including but not limited to prediction of the likelihood of CAD in stable, nondiabetic patients.

GUIDELINES:

The Corus CAD™ test is not a manufactured test kit and has not been reviewed by the U.S. Food and Drug Administration. Rather, it is a laboratory-developed test, offered by the Clinical Laboratory Improvement Act-licensed CardioDx Commercial Laboratory.

RATIONALE:

Gene expression assays to predict the likelihood of obstructive coronary artery disease (CAD) 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. The 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 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 forego 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. Currently, there is no convincing evidence that the use of GES can reduce unnecessary coronary angiography. As a result, the use of gene expression scores for predicting CAD is considered investigational.

Practice Guidelines and Position Statements

American Heart Association

In 2012, AHA released a policy statement on genetics and cardiovascular disease. (15) Gene expression testing is not specifically mentioned. Generally, the writing committee supported recommendations issued in 2000 by a now defunct Advisory Committee to the Department of Health and Human Services, which stated, “No test should be introduced in the market before it is established that it can be used to diagnose and/or predict a health-related condition in an appropriate way.” (16)

Medicare National Coverage

There are no Medicare National Coverage Determinations for GES testing to predict CAD. In July 2013, Palmetto GBA, the Medicare contractor in California, issued a positive local coverage decision for the CorusCAD® test in patients who have typical symptoms of CAD or atypical symptoms and 1 or more CAD risk factors. Because all CorusCAD® tests are processed in California, the test will be covered for Medicare patients in the United States.

DEFINITIONS:

N/A

CODING:

- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

PROCEDURE CODES

81599 84999

SOURCES:

1. Xu J, Kochanek KD, Sherry L. Murphy SL et al. Deaths: Final Data for 2007. Natl Vital Stat Rep 2010; 58(19).
2. Anderson JL, Adams CD, Antman EM et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/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 2007; 116(7):e148-304.
3. Patel MR, Peterson ED, Dai D et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010; 362(10):886-95.
4. Wingrove JA, Daniels SE, Sehnert AJ et al. Correlation of peripheral-blood gene expression with the extent of coronary artery stenosis. Circ Cardiovasc Genet 2008; 1(1):31-8.
5. 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(1):26.
6. 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):425-34.
7. Rosenberg S, Elashoff MR, Lieu HD et al. 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):366-74.
8. Lansky A, Elashoff MR, Ng V et al. A gender-specific blood-based gene expression score for assessing obstructive coronary artery disease in nondiabetic patients: results of the Personalized Risk Evaluation and Diagnosis in the Coronary Tree (PREDICT) trial. Am Heart J 2012; 164(3):320- 6.
9. 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):154-62.
10. 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):284-90.
11. Klocke FJ, Baird MG, Lorell BH et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American

Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). Circulation 2003; 108(11):1404-18.
12. McPherson JA, Davis K, Yau M 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 Pathw Cardiol 2013; 12(2):37-42.
13. 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):258-67.
14. Ladapo JA, Lyons H, Yau M et al. Enhanced Assessment of Chest Pain and Related Symptoms in the Primary Care Setting Through the Use of a Novel Personalized Medicine Genomic Test: Results From a Prospective Registry Study. Am J Med Qual 2014.
15. Ashley EA, Hershberger RE, Caleshu C et al. Genetics and cardiovascular disease: a policy statement from the American Heart Association. Circulation 2012; 126(1):142-57.
16. National Institutes of Health. Office of Science Policy. Enhancing the oversight of genetic tests: recommendations of the Secretary's Advisory Committee on Genetic Testing (SACGT), July 2000. Available online at: http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/genetics-health-and-society-secretarys-advisory-committee-genetic-testing/enhancing-oversight-genetic-tests-recommendations-sacgt. Last accessed May 2014.

APPROVALS:

Approved by Vice President, Clinical Operations & Chief Medical Officer:

Signature:_____
(Nina M. Taggart, MA, MD, MBA)

Date of Approval: September 17, 2014

HISTORY:

Original Development Date: (10/01/14)

Policy developed by: Medical Policy Department