

Policy: MP 279

Section: Medical Benefit Policy

Subject: Gene Expression Testing to Predict Coronary Artery Disease

Applicable line of business:

Commercial	x	Medicaid	x
Medicare	x	ACA	x
CHIP	x		

I. Policy: Gene Expression Testing to Predict Coronary Artery Disease

II. Purpose/Objective:

To provide a policy of coverage regarding Gene Expression Testing to Predict Coronary Artery Disease

III. Responsibility:

- A. Medical Directors
- B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

Commercial

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicare

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

CHIP

Geisinger Health Plan Kids (GHP Kids) is a Children’s Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicaid

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

DESCRIPTION:

The Corus® CAD (coronary artery disease) test (CardioDx, Inc., Palo Alto, CA) is a genetic test which analyzes 23 genes that are involved in the development or response to atherosclerosis. Using an algorithm, a quantitative score is then generated which predicts the likelihood of developing obstructive coronary artery disease.

FOR MEDICARE and MEDICAID BUSINESS SEGMENT:

Palmetto GBA, a national contractor that administers Medicare benefits has determined that the Corus® CAD (coronary artery disease) test (CardioDx, Inc., Palo Alto, CA) is considered reasonable and necessary for the evaluation of members with stable symptoms that have a history of chest pain, suspected anginal equivalent to chest pain, or a high risk of CAD, but no known prior myocardial infarction or revascularization procedures.

LIMITATIONS:

Per the Novitas Solutions LCD Corus® CAD Test (L36713), the following limitations apply:

1. The Corus® CAD test is considered not reasonable and necessary for members who are currently taking steroids, immunosuppressive agents, or chemotherapeutic agents or for members with:

- acute or previous myocardial infarction;
- high-risk unstable angina;
- a history of obstructive CAD;
- a previous revascularization procedure;
- a history of a previous invasive procedure to open a blocked or narrow artery;
- systemic infectious or systemic inflammatory conditions; or
- diabetes.

2. The Corus® CAD test is considered not reasonable and necessary when used for **any of the following**:

- to be used to screen for stenosis among members 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 members.

SEE ALSO: MPA G2050 Cardiovascular Disease Risk Assessment

EXCLUSIONS:

Unless mandated by state or federal regulation, the Plan does **NOT** provide coverage for Gene Expression Testing to Predict Coronary Artery Disease because it is considered **unproven**. The Geisinger Technology Assessment Committee evaluated this technology and concluded that there is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

Unless mandated by state or federal regulation, the Plan does **NOT** provide coverage for multi-gene next generation panels, (i.e. CardioNext, Familion, RhythmFirst) because they are considered **unproven**. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of these tests on health outcomes when compared to established tests or technologies.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven services is outlined in **MP 15 - Experimental Investigational or Unproven Services or Treatment**.

Medicaid Business Segment:

Any requests for services that do not meet criteria set in the PARP may be evaluated on a case by case basis

CODING ASSOCIATED WITH: Gene Expression Testing to Predict Coronary Artery Disease

The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services.

- 84999 Unlisted chemistry procedure
- 81493 Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score [*Corus CAD*]
- 0377U Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables) [*LipoScale*]
- 0415U Cardiovascular disease (acute coronary syndrome [ACS]), IL-16, FAS, FASLigand, HGF, CTACK, EOTAXIN, and MCP-3 by immunoassay combined with age, sex, family history, and personal history of diabetes, blood, algorithm reported as a 5-year (deleted risk) score for ACS {*SmartHealth Vascular Dx*}
- 0439U Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD [*Epi+Gen CHD*]
- 0440U Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1], cg04988978 [MPO], cg17901584 [DHCR24-DT], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD [*PrecisionCHD*]
- 0466U Cardiology (coronary artery disease [CAD]), DNA, genome-wide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease [*CardioRisk+*]

Current Procedural Terminology (CPT®) © American Medical Association: Chicago, IL

LINE OF BUSINESS:

Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

REFERENCES:

Wingrove JA, Daniels SE, Sehnert AJ, Tingley W, Elashoff MR, Rosenberg S, Buellesfeld L, Grube E, Newby LK, Ginsburg GS, Kraus WE. Correlation of peripheral-blood gene expression with the extent of coronary artery stenosis. *Circ Cardiovasc Genet*. 2008 Oct;1(1):31-8

Rosenberg S, Elashoff MR, Beineke P, Daniels SE, Wingrove JA, Tingley WG, Sager PT, Sehnert AJ, Yau M, Kraus WE, Newby LK, Schwartz RS, Voros S, Ellis SG, Tahirkheli N, Waksman R, McPherson J, Lansky A, Winn ME, Schork NJ, Topol EJ; PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) Investigators. 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 Oct 5;153(7):425-34.

Rosenberg S, Elashoff MR, Lieu HD, Brown BO, Kraus WE, Schwartz RS, Voros S, Ellis SG, Waksman R, McPherson JA, Lansky AJ, Topol EJ; PREDICT Investigators. 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 Jun;5(3):366-74

Elashoff MR, Wingrove JA, Beineke P, Daniels SE, Tingley WG, Rosenberg S, Voros S, Kraus WE, Ginsburg GS, Schwartz RS, Ellis SG, Tahirkheli N, Waksman R, McPherson J, Lansky AJ, Topol EJ. Development of a blood-based gene expression algorithm for assessment of obstructive coronary artery disease in non-diabetic patients. *BMC Med Genomics.* 2011 Mar 28;4:26.

Winifred S. Hayes- GTE Report- Corus® CAD (CardioDx Inc.). October 3, 2012

ECRI Target Databas. Corus CAD (CardioDx, Inc.) for Genomic Testing of Obstructive Coronary Artery Disease. September 25,2012.

Hochheiser LI, Juusola JL, Monane M, Ladapo JA. Economic utility of a blood-based genomic test for the assessment of patients with symptoms suggestive of obstructive coronary artery disease. *Popul Health Manag.* 2014 Feb 25.

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):154-162

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

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):258-267

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):284-290

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 May 5.

Geisinger Technology Assessment Committee. Corus CAD (CardioDx, Inc.), October 2015

Ladapo, J. A., Herman, L., Weiner, B. H., Rhees, B., Castle, L., Monane, M., et al. (2015). Use of a blood test incorporating age, sex and gene expression influences medical decision-making in the evaluation of women presenting with symptoms suggestive of obstructive coronary artery disease: summary results from two ambulatory care studies in primary care. *Menopause: The Journal of the North American Menopause Society*, 22 (11), 1-7.

Schwartz PJ, Ackerman MJ, George AL Jr, Wilde AA. Impact of genetics on the clinical management of channelopathies. *J Am Coll Cardiol.* 2013 Jul 16;62(3):169-80

Bennett MT, Sanatani S, Chakrabarti S et al. Assessment of genetic causes of cardiac arrest. *Can J Cardiol* 2013; 29(1):100-10

Ackerman MJ, Marcou CA, Tester DJ. Personalized medicine: genetic diagnosis for inherited cardiomyopathies/channelopathies. *Rev Esp Cardiol* 2013; 66(4):298-307

Elashoff MR, Wingrove JA, Beineke P, Daniels SE, Tingley WG, Rosenberg S, Voros S, Kraus WE, Ginsburg GS, Schwartz RS, Ellis SG, Tahirkheli N, Waksman R, McPherson J, Lansky AJ, Topol EJ. Development of a blood-based gene expression algorithm for assessment of obstructive coronary artery disease in non-diabetic patients. *BMC Med Genomics.* 2011 Mar 28;4:26

Voros, S, Elashoff, MR, Wingrove, JA, Budoff, MJ, Thomas, GS, Rosenberg, S. 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 Mar;233(1):284-90.

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. Journal of the American Board of Family Medicine : JABFM. 2014 Mar-Apr;27(2):258-67.

Ladapo, JA, Budoff, M, Sharp, D, et al. Clinical Utility of a Precision Medicine Test Evaluating Outpatients with Suspected Obstructive Coronary Artery Disease. The American journal of medicine. 2016 Dec 16.

Musunuru K, Ingelsson E, Fornage M, et al. The expressed genome in cardiovascular diseases and stroke: refinement, diagnosis, and prediction: a scientific statement from the American Heart Association. Circ Cardiovasc Genet. Aug 2017;10(4).

Novitas Solutions. Local Coverage Determination (LCD): Corus® CAD Test (L36713)

Kashyap S, Kumar S, Agarwal V, et al. Gene expression profiling of coronary artery disease and its relation with different severities. J Genet. 2018; 97(4):853-867.

Gul B, Lansky A, Budoff MJ et al The clinical utility of a precision medicine blood test incorporating age, sex, and gene expression for evaluating women with stable symptoms suggestive of obstructive coronary artery disease: Analysis from the PRESET Registry. J Womens Health (Larchmt). 2019; 28(5): 728-735

This policy will be revised as necessary and reviewed no less than annually.

Devised: 8/13

Revised: 8/14 (added Medicare coverage), 7/15 (added Limitation), 7/16 (added exclusion) 7/19 (revise criteria per LCD L36713) , 6/25 (Update Unproven Language)

Reviewed: 6/17, 6/18, 6/19, 7/20, 7/21, 7/22, 7/23, 7/24

CMS UM Oversight Committee Approval: 12/23, 7/24, 8/25

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

Please be advised that the use of the logos, service marks or names of Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company on a marketing, press releases or any communication piece regarding the contents of this medical policy is strictly prohibited without the prior written consent of Geisinger Health Plan. Additionally, the above medical policy does not confer any endorsement by Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company regarding the medical service, medical device or medical lab test described under this medical policy.