Priority Health

MEDICAL POLICY
No. 91559-R6

CARDIOVASCULAR RISK MARKERS

Effective Date: February 24, 2021

Review Dates: 12/08, 12/09, 12/10, 12/11, 12/12, 12/13, 11/14, 2/15, 2/16, 2/17, 2/18, 2/19, 2/20, 2/21, 2/22, 2/23, 2/24, 2/25

Date of Origin: December 10, 2008

Status: Current

I. POLICY/CRITERIA

A. In addition to traditional risk assessment, the following **cardiovascular disease (CVD)** risk markers are considered medically necessary:

1. Lipoprotein-associated phospholipase A2 (Lp-PLA_2) (PLAC), limited to one test per year.
2. High-sensitivity C-reactive protein (hs-CRP) if both of the following:

   a. Using the 10-year risk assessment tool recommended by the NCEP, the patient is at intermediate risk of developing CHD (i.e.10-year risk of 10–20%).
   b. The patient is metabolically stable without obvious inflammatory or infectious conditions.

3. Apolipoprotein B (apo B)
4. Lipoprotein(a) enzyme immunoassay

B. The medical literature does not support the utility of the following tests for screening, diagnosis, or management of CVD and they are therefore considered not medically necessary:

1. Apolipoprotein A-I (apo AI)
2. Apolipoprotein E (apo E)
3. Homocysteine testing
4. LDL gradient gel electrophoresis
5. Angiotensin gene (CardiaRisk™ AGT)
6. Measurement of long chain omega-3 fatty acids
7. Interleukin 6 -174 g/c promoter polymorphism
8. Carotid intimal-media thickness
9. LipiScan IVUS Coronary Imaging System (fat composition of plaque)
10. Prothrombotic factors (e.g., plasminogen activator inhibitor [PAI–1], activated factor VII, tissue plasminogen activator [tPA], von Willebrand factor, factor V Leiden, protein C, antithrombin III, fibrinogen)
11. Skin cholesterol test (PREVU Point of Care (POC) Skin Sterol Test, PreMD Inc.)

12. Lipoprotein particle size and concentration/density measurement (e.g., NMR LipoProfile® test)
13. Natriuretic peptides
14. Peripheral arterial tonometry, endothelial function test (e.g. EndoPAT™)
15. Gene expression analysis (e.g. Corus® CAD)
16. Secretory type II phospholipase A2 (sPLA2-IIA)
17. Singulex SMC™ testing for risk of cardiac dysfunction and vascular inflammation (e.g. SMC Endothelin, SMC IL-6, SMC IL 17A, SMC c TnI and SMC TNF-α).

II. MEDICAL NECESSITY REVIEW

Prior authorization for certain drug, services, and procedures may or may not be required. In cases where prior authorization is required, providers will submit a request demonstrating that a drug, service, or procedure is medically necessary. For more information, please refer to the Priority Health Provider Manual.

III. APPLICATION TO PRODUCTS

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

- **HMO/EPO:** ***This policy applies to insured HMO/EPO plans.***
- **POS:** ***This policy applies to insured POS plans.***
- **PPO:** ***This policy applies to insured PPO plans. Consult individual plan documents as state mandated benefits may apply. If there is a conflict between this policy and a plan document, the provisions of the plan document will govern.***
- **ASO:** ***For self-funded plans, consult individual plan documents. If there is a conflict between this policy and a self-funded plan document, the provisions of the plan document will govern.***
- **INDIVIDUAL:** ***For individual policies, consult the individual insurance policy. If there is a conflict between this medical policy and the individual insurance policy document, the provisions of the individual insurance policy will govern.***
- **MEDICARE:** ***Coverage is determined by the Centers for Medicare and Medicaid Services (CMS) and/or the Evidence of Coverage (EOC); if a coverage determination has not been adopted by CMS, this policy applies.***
- **MEDICAID/HEALTHY MICHIGAN PLAN:** ***For Medicaid/Healthy Michigan Plan members, this policy will apply. Coverage is based on medical necessity criteria being met and the appropriate code(s) from the coding section of this policy being included on the Michigan Medicaid Fee Schedule located at: http://www.michigan.gov/mdch/0,1607,7-132-2945_42542_42543_42546_42551-159815--,00.html. If there is a discrepancy between this policy and the Michigan Medicaid Provider Manual located at: http://www.michigan.gov/mdch/0,1607,7-132-2945_5100-87572--,00.html, the Michigan Medicaid Provider Manual will govern. For Medical Supplies/DME/Prosthetics and Orthotics, please refer to the Michigan Medicaid Fee Schedule to verify coverage.***

IV. DESCRIPTION

Determination of **cardiovascular disease (CVD)** risk is based on standard, accepted risk-stratification approaches. These approaches are based on global assessment and traditional risk factor assessment including cholesterol/**low density lipoprotein levels (LDL)**, diet, smoking, diabetes and family and personal medical history. The **National Cholesterol Education Program (NCEP)** utilizes the Framingham risk scoring calculation, endorsed by the **National Heart Lung and Blood Institute (NHLBI)** and the AHA for determining 10-year **coronary heart disease (CHD)** risk.

Newer generation cardiovascular risk markers are developed and proposed to enhance the prediction of cardiovascular disease. Evaluation of the potential clinical utility of these emerging tests includes the following:

- Does the test better identify those at higher risk than the current risk scores (Framingham risk score)?
- Does treatment differ for those at highest risk?
- Does treatment improve clinical outcomes?

V. CODING INFORMATION

ICD-10 Codes that may support medical necessity:

E71.30	Disorder of fatty-acid metabolism, unspecified
E75.21	Fabry (-Anderson) disease
E75.22	Gaucher disease
E75.240	Niemann-Pick disease type A
E75.241	Niemann-Pick disease type B
E75.242	Niemann-Pick disease type C
E75.243	Niemann-Pick disease type D
E75.248	Other Niemann-Pick disease
E75.249	Niemann-Pick disease, unspecified
E75.3	Sphingolipidosis, unspecified
E75.5	Other lipid storage disorders
E75.6	Lipid storage disorder, unspecified
E77.0–E77.9	Disorders of glycoprotein metabolism
E78.00–E78.9	Disorders of lipoprotein metabolism and other lipidemias
E88.1	Lipodystrophy, not elsewhere classified
E88.2	Lipomatosis, not elsewhere classified
E88.89	Other specified metabolic disorders
F17.200–F17.299	Nicotine dependence
I10	Essential (primary) hypertension
I11.0–I11.9	Hypertensive heart disease
I12.0–I12.9	Hypertensive chronic kidney disease
I16.0 – I16.9	Hypertensive crisis

Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system

May be preventive:

Z00.00-Z00.01	Encounter for general adult medical examination
Z00.121-Z00.129	Encounter for routine child health examination
Z13.220	Encounter for screening for lipoid disorders
Z01.411-Z01.419	Encounter for gynecological examination
Z13.6	Encounter for screening for cardiovascular disorders

CPT/HCPCS Codes:
See criteria above for coverage information.

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 *(PA required)*
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
83719	Lipoprotein, direct measurement; VLDL cholesterol
83722	Lipoprotein, direct measurement; small dense LDL cholesterol
86141	C-reactive protein; high sensitivity (hsCRP)
83695	Lipoprotein (a)
82172	Apolipoprotein, each
84999	Unlisted chemistry procedure

(Explanatory notes must accompany claims billed with unlisted codes.)

May be preventive

80061	Lipid panel Lipid panel This panel must include the following: Cholesterol, serum, total (82465) Lipoprotein, direct measurement, high density cholesterol (HDL cholesterol) (83718) Triglycerides (84478)
82465	Cholesterol, serum or whole blood, total
83718	Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)
83721	Lipoprotein, direct measurement; LDL cholesterol
84478	Triglycerides

Not covered for screening

See also Policy# 91540 Genetics: Counseling, Testing and Screening

81240	F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant
82615	Cystine and homocystine, urine, qualitative
83090	Homocysteine
85300	Clotting inhibitors or anticoagulants; antithrombin III, activity
85303	Clotting inhibitors or anticoagulants; protein C, activity
85384	Fibrinogen; activity
85385	Fibrinogen; antigen
85415	Fibrinolytic factors and inhibitors; plasminogen activator

85420 Fibrinolytic factors and inhibitors; plasminogen, except antigenic assay
85421 Fibrinolytic factors and inhibitors; plasminogen, antigenic assay
83700 Lipoprotein, blood; electrophoretic separation and quantitation
83701 Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (e.g., electrophoresis, ultracentrifugation)
83704 Lipoprotein, blood; quantitation of lipoprotein particle number(s) (e.g., by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass (es), when performed
83880 Natriuretic peptide

Not covered for any dx
0052U Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation
0308U Cardiology (coronary artery disease [CAD]), analysis of 3 proteins (high sensitivity [hs] troponin, adiponectin, and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for obstructive CAD
0309U Cardiology (cardiovascular disease), analysis of 4 proteins (NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 [TIMP-1], and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for major adverse cardiac event
81400* Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) *(when billed for evaluation of angiotensin gene)*
81479* Unlisted molecular pathology procedure – *when billed for any test not described as covered. (Explanatory notes must accompany claim)*
82777 Galectin-3
83006 Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)

VI. REFERENCES

1. Advances in the Detection of Rupture-Prone Plaque: The Role of Lipoprotein-Associated Phospholipase A2 in Cardiovascular Risk Assessment. The American Journal of Cardiology Supplement, June 16, 2008.
2. Blue Cross, Shield, Care Network of MI. Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease. Medical Policy.
3. Bots, M.L., et.al. Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? *European Heart Journal* (2007), 398-406.
4. Chow SL, Maisel AS, Anand I, et al. Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the American Heart Association [published correction appears in Circulation. 2017 Nov 7;136(19):e345]. Circulation. 2017;135(22):e1054-e1091. doi:10.1161/CIR.0000000000000490

5. Contois JH, Langlois MR, Cobbaert C, Sniderman AD. Standardization of Apolipoprotein B, LDL-Cholesterol, and Non-HDL-Cholesterol. J Am Heart Assoc. 2023;12(15):e030405. doi:10.1161/JAHA.123.030405
6. De Oliveira-Gomes D, Joshi PH, Peterson ED, Rohatgi A, Khera A, Navar AM. Apolipoprotein B: Bridging the Gap Between Evidence and Clinical Practice. Circulation. 2024;150(1):62-79. doi:10.1161/CIRCULATIONAHA.124.068885
7. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JMcB, Kushner FG, Lauer MS, Shaw LJ, Smith SC, Jr., Taylor AJ, Weintraub WS, Wenger NK. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010; 56:2182–99.
8. Harchaoui, K. E., et.al. Value of Low-Density Lipoprotein Particle Number and Size as Predictors of Coronary Artery Disease in Apparently Health Men and Women, The EPIC-Norfolk Prospective Population Study. Journal of the American College of Cardiology, Vol. 49, No. 5, 2007.
9. Hayes, Inc. Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) Test (PLAC Test; diaDexus) for Prediction of Coronary Heart Disease, January 2007.
10. Hayes, Inc. Lipoprotein Subclass Quantification Using NMR LipoProfile® Test for Atherosclerosis/Coronary Heart disease (CHD), Brief, and April 7, 2007.
11. Hayes, Inc Measurement of Carotid Intima-Media Thickening (IMT) for Detection of Atherosclerosis, August 2007.
12. Hayes, Inc. Noninvasive Peripheral Arterial Tonometry, December 11, 2014
13. Hayes, Inc. Skin Cholesterol Test Using the PREVU* Point of Care (POC) Skin Sterol Test (PreMD Inc.) for Prediction of Coronary Artery Disease Risk, Health Technology Brief. October 30, 2008.
14. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association [published correction appears in Circulation. 2009 Jun 30;119(25):e606. Hong, Yuling [added]]. Circulation. 2009;119(17):2408-2416. doi:10.1161/CIRCULATIONAHA.109.192278
15. Koschinsky ML, Bajaj A, Boffa MB, et al. A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. J Clin Lipidol. 2024;18(3):e308-e319. doi:10.1016/j.jacl.2024.03.001
16. Lorenz, M. W., et. al. Prediction of Clinical Cardiovascular Events with Carotid Intima-Media Thickness: A Systematic Review and Meta-Analysis. Circulation, January 30, 2007.
17. Otvos, J.D. et.al. Low-Density Lipoprotein and High-Density Lipoprotein Particle Subclasses Predict Coronary Events and are Favorably Changed by

Gemfibrozil Therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trail (VA-HIT). *Circulation*, March 28, 2006.

18. Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2022;42(1):e48-e60. doi:10.1161/ATV.0000000000000147
19. Rosenson RS, Stein JH, Durrington P. Lipoprotein(a). In: UpToDate, Freeman MW (Section Editor), Botkin NF (Deputy Editor), UpToDate, Waltham, MA, 2024.
20. Soffer DE, Marston NA, Maki KC, et al. Role of apolipoprotein B in the clinical management of cardiovascular risk in adults: An Expert Clinical Consensus from the National Lipid Association. J Clin Lipidol. 2024;18(5):e647-e663. doi:10.1016/j.jacl.2024.08.013
21. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), September 2002, Updated 2004.
22. Mietus-Snyder M, Perak AM, Cheng S, et al. Next Generation, Modifiable Cardiometabolic Biomarkers: Mitochondrial Adaptation and Metabolic Resilience: A Scientific Statement From the American Heart Association. Circulation. 2023;148(22):1827-1845. doi:10.1161/CIR.0000000000001185
