Medical Coverage Policy | Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

EFFECTIVE DATE: 04|01|2024
POLICY LAST REVIEWED: 12|20|2023

OVERVIEW

Numerous lipid and nonlipid biomarkers have been proposed as potential risk markers for cardiovascular disease. Biomarkers assessed here are those that have the most evidence in support of their use in clinical care, including high-density lipoprotein (HDL) subclass, low-density lipoprotein (LDL) subclass, lipoprotein (a), B-type natriuretic peptide, cystatin C, and fibrinogen. These biomarkers have been studied as alternatives or additions to standard lipid panels for risk stratification in cardiovascular disease or as treatment targets for lipid-lowering therapy.

For coverage of tests filed with PLA codes (0052U-VAP Cholesterol Test), please refer to the related policy "Proprietary Laboratory Analyses (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)"

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Measurement of the following novel lipid and non-lipid risk factors are medically necessary for Commercial products when filed with a covered diagnosis. See the Coding section for details.

- Lipoprotein, blood; electrophoretic separation and quantitation
- Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation)
- Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed

All other measurements of novel lipid and non-lipid risk factors (ie, cystatin C, fibrinogen, lipoprotein[a]) are not covered for Medicare Advantage Plans and not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare Advantage Plans and Commercial Products

B type natriuretic peptide testing is covered but not separately reimbursed when used in conjunction with standard diagnostic tests, medical history and clinical findings during an evaluation of heart failure in an acute care setting or other setting (i.e. emergency department) where test results are immediately determined.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. **§27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

BACKGROUND

Low-density lipoproteins (LDLs) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project as the primary target of cholesterol-lowering therapy. An LDL particle consists of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as LDL cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with" normal" levels of total and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Other non-lipid markers have been identified as being associated with cardiovascular disease (CVD), including B-type natriuretic peptide, cystatin C, and fibrinogen. These biomarkers may have a predictive role in identifying CVD risk or in targeting therapy.

Lipid Markers

High-Density Lipoprotein Subclass

High-density lipoprotein particles exhibit considerable heterogeneity, and it has been proposed that various subclasses of HDL may have a greater role in protection from atherosclerosis. Particles of HDL can be characterized based on size or density and/or on apolipoprotein composition. Using size or density, HDL can be classified into HDL_2, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL_3, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (eg, HDL_2, HDL_3) is a direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance spectroscopy or by gradient-gel electrophoresis. High-density lipoprotein particle numbers can be measured by nuclear magnetic resonance spectroscopy. Several commercial labs offer these measurements of HDL particle size and number. Measurement of apo AI has used HDL particle number as a surrogate, based on the premise that each HDL particle contains a single apo AI molecule.

LDL Subclass

Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a common inherited disorder associated with a more atherogenic lipoprotein profile, also termed "atherogenic dyslipidemia." In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apo B, and low levels of HDL. This lipid profile is commonly seen in type 2 diabetes and is a component of the "metabolic syndrome," defined by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein, and a prothrombotic state. The presence of the metabolic syndrome is considered by Adult Treatment Panel III to be a substantial risk-enhancing factor for CAD.

Low-density lipoprotein size has also been proposed as a potentially useful measure of treatment response. Lipid-lowering treatment decreases total LDL and may also induce a shift in the type of LDL, from smaller, dense particles to larger particles. It has been proposed that this shift in lipid profile may be beneficial in reducing the risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in

lipid profiles than others. Niacin and/or fibrates may cause a greater shift from small to large LDL size than statins. Therefore, measurement of LDL size may potentially play a role in drug selection or may be useful in deciding whether to use a combination of drugs rather than a statin alone.

In addition to the size of LDL particles, interest has been shown in assessing the concentration of LDL particles as a distinct cardiac risk factor. For example, the commonly performed test for LDL-C is not a direct measure of LDL, but, chosen for its convenience, measures the amount of cholesterol incorporated into LDL particles. Because LDL particles carry much of the cholesterol in the bloodstream, the concentration of cholesterol in LDL correlates reasonably well with the number of LDL particles when examined in large populations. However, for an individual patient, the LDL-C level may not reflect the number of particles due to varying levels of cholesterol in different sized particles. It is proposed that the discrepancy between the number of LDL particles and the serum level of LDL-C represents a significant source of unrecognized atherogenic risk. The size and number of particles are interrelated. For example, all LDL particles can invade the arterial wall and initiate atherosclerosis. However, small, dense particles are thought to be more atherogenic than larger particles. Therefore, for patients with elevated numbers of LDL particles, the cardiac risk may be further enhanced when the particles are smaller versus larger.

Lipoprotein (a)
Lipoprotein (Lp) (a) is a lipid-rich particle similar to LDL. The major apolipoprotein associated with LDL is Apo B; in Lp(a), however, there is an additional apo A covalently linked to apo B. The apo A molecule is structurally similar to plasminogen, suggesting that Lp(a) may contribute to the thrombotic and atherogenic basis of CVD. Levels of Lp(a) are relatively stable in individuals over time but vary up to 1000-fold between individuals, presumably on a genetic basis. The similarity between Lp(a) and fibrinogen has stimulated intense interest in Lp(a) as a link between atherosclerosis and thrombosis. In addition, approximately 20% of patients with CAD have elevated Lp(a) levels. Therefore, it has been proposed that levels of Lp(a) may be an independent risk factor for CAD.

Non–Lipid Markers

B-Type or Brain Natriuretic Peptide
Brain natriuretic peptide (BNP) is an amino acid polypeptide secreted primarily by the ventricles of the heart when the pressure to the cardiac muscles increases or there is myocardial ischemia. Elevations in BNP levels reflect deterioration in cardiac loading levels and may predict adverse events. Brain natriuretic peptide has been studied as a biomarker for managing heart failure and predicting cardiovascular and heart failure risk.

Cystatin C
Cystatin C is a small serine protease inhibitor protein secreted from all functional cells in the body. It has primarily been used as a biomarker of kidney function. Cystatin C has also been studied to determine whether it may serve as a biomarker for predicting cardiovascular risk. Cystatin C is encoded by the *CST3* gene.

Fibrinogen
Fibrinogen is a circulating clotting factor and precursor of fibrin. It is important in platelet aggregation and a determinant of blood viscosity. Fibrinogen levels have been shown to be associated with future risk of CVD and all-cause mortality.

For individuals who are asymptomatic with risk of cardiovascular disease who receive novel cardiac biomarker testing (eg, apo B, apo AI, apo E, lipoprotein[a], B-type natriuretic peptide, cystatin C, fibrinogen, leptin), the evidence includes systematic reviews, meta-analyses, and large, prospective cohort studies. Relevant outcomes are overall survival, other test performance measures, change in disease status, morbid events, and medication use. The evidence from cohort studies and meta-analyses of these studies has suggested that some of these markers are associated with increased cardiovascular risk and may provide incremental accuracy in risk prediction. In particular, apo B and apo AI have been identified as adding some incremental predictive value. However, it has not been established whether the incremental accuracy provides

clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with hyperlipidemia managed with lipid-lowering therapy who receive novel cardiac biomarker testing (eg, apo B, apo AI, apo E, apo E, lipoprotein[a], B-type natriuretic peptide, cystatin C, fibrinogen), the evidence includes analyses of the intervention arm(s) of lipid-lowering medication trials. Relevant outcomes are overall survival, change in disease status, morbid events, and medication use. In particular, apo B, apo AI, and apo E have been evaluated as markers of lipid-lowering treatment success, and evidence from the intervention arms of several randomized controlled trials has suggested that these markers are associated with treatment success. However, there is no direct evidence that using markers other than LDL and HDL as a lipid-lowering treatment target leads to improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes. Therefore, these services are considered not medically necessary for Commercial products.

There is a Local Coverage Determination (LCD) for B-type Natriuretic Peptide (BNP) Testing that indicates: BNP measurements may be considered reasonable and necessary when used in combination with other medical data such as medical history, physical examination, laboratory studies, chest x-ray, and electrocardiography:

- To distinguish cardiac cause of acute dyspnea from pulmonary or other non-cardiac causes. Plasma BNP levels are significantly increased in patients with CHF (Congestive Heart Failure) presenting with acute dyspnea compared with patients presenting with acute dyspnea due to other causes.
- To distinguish decompensated CHF from exacerbated chronic obstructive pulmonary disease (COPD) in a symptomatic patient with combined chronic CHF and COPD. Plasma BNP levels are significantly increased in patients with CHF with or without concurrent lung disease compared with patients who have primary lung disease.
- To establish prognosis or disease severity in chronic CHF when needed to guide therapy
- To achieve optimal dosing of guideline-directed medical therapy (GDMT) in select clinically euvolemic patients followed in a well-structured heart failure (HF) disease management program
- To guide therapeutic decision-making in individuals who have amyloidosis

BNP measurements must be analyzed in conjunction with standard diagnostic tests, medical history and clinical findings. The efficacy of BNP measurement as a stand-alone test has not yet been established. Clinicians should be aware that certain conditions such as ischemia, infarction and renal insufficiency, may cause elevation of circulating BNP concentration and require alterations of the interpretation of BNP results. Therefore, B type natriuretic peptide testing is covered but not separately reimbursed when used in conjunction with standard diagnostic tests, medical history and clinical findings during an evaluation of heart failure in an acute care setting or other setting (i.e. emergency department) where test results are immediately determined.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT codes are medically necessary when filed with one of the covered ICD-10-CM codes, below:

83700 Lipoprotein, blood; electrophoretic separation and quantitation

83701 Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation)

83704 Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed

Covered ICD-10-CM

The following CPT codes are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:
82610 Cystatin C
83695 Lipoprotein (a)
83722 Lipoprotein, Direct Measurement; Small Dense LDL Cholesterol
85384 Fibrinogen; activity
85385 Fibrinogen; antigen

Medicare Advantage Plans and Commercial Products:
The following CPT code is covered but not separately reimbursed for Medicare Advantage Plans and Commercial Products:
83880 Natriuretic peptide

RELATED POLICIES
Biomarker Testing Mandate
Medicare Advantage Plans National and Local Coverage Determinations Policy
Measurement of Lipoprotein-Associated Phospholipase A2 in the Assessment of Cardiovascular Risk
Non-Reimbursable Health Service Codes

PUBLISHED
Provider Update: February 2024
Provider Update, March 2023, November 2023
Provider Update, April 2022
Provider Update, April 2021
Provider Update, April 2020
Provider Update, July 2019

REFERENCES
1. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* May 16 2001;285(19):2486-2497. PMID 11368702
2. Di Angelantonio E, Gao P, Pennells L, et al. Lipid-related markers and cardiovascular disease prediction. JAMA. Jun 20 2012; 307(23): 2499-506. PMID 22797450
3. Perera R, McFadden E, McLellan J, et al. Optimal strategies for monitoring lipid levels in patients at risk or with cardiovascular disease: a systematic review with statistical and cost-effectiveness modelling. *Health Technol Assess.* Dec 2015;19(100):1-401, vii-viii. PMID 26680162
4. Thanassoulis G, Williams K, Ye K, et al. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. *J Am Heart Assoc.* Apr 14 2014;3(2):e000759. PMID 24732920
5. van Holten TC, Waanders LF, de Groot PG, et al. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. *PLoS One.* May 2013;8(4):e62080. PMID 23630624
6. Tzoulaki I, Siontis KC, Evangelou E, et al. Bias in associations of emerging biomarkers with cardiovascular disease. *JAMA Intern Med.* Apr 22 2013;173(8):664-671. PMID 23529078
7. Willis A, Davies M, Yates T, et al. Primary prevention of cardiovascular disease using validated risk scores: a systematic review. *J R Soc Med.* Aug 2012;105(8):348-356. PMID 22907552
10.Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med. Oct 06 2009; 151(7): 496-507. PMID 19805772
13. Ridker PM, Rifai N, Cook NR, et al. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA.* Jul 20 2005;294(3):326-333. PMID 16030277

15. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* Sep 4 2001;104(10):1108-1113. PMID 11535564
19. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA.* Feb 14 2007;297(6):611-619. PMID 17299196
20. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA.* Aug 15 2007;298(7):776-785. PMID 17699011
22. Campos H, Moye LA, Glasser SP, et al. Low-density lipoprotein size, pravastatin treatment, and coronary events. *JAMA.* Sep 26 2001;286(12):1468-1474. PMID 11572739
23. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA.* Nov 10 1993;270(18):2195-2199. PMID 8411602
24.Suk Danik J, Rifai N, Buring JE, et al. Lipoprotein(a), hormone replacement therapy, and risk of future cardiovascular events. *J Am Coll Cardiol.* Jul 8 2008; 52(2):124-131. PMID 18598891
25. Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med.* Mar 24 2008; 168(6):598-608. PMID 18362252
26. Smolders B, Lemmens R, Thijs V. Lipoprotein (a) and stroke: a meta-analysis of observational studies. *Stroke.* Jun 2007;38(6):1959-1966. PMID 17478739
27. CMS.gov, Centers for Medicare and Medicaid Services Local Coverage Determination (LCD): B-type Natriuretic Peptide (BNP) Testing (L33573)
https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33573&ContrId=275&ver=24&ContrVer=1&CntrctrSelected=275*1&Cntrctr=275&s=57&DocType=2&bc=AAgAAACAAAAA&