BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.65 Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

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Related Policies:

2.04.100 - Cardiovascular Risk Panels
2.04.13 - Genetic Testing for Alzheimer Disease
2.04.32 - Measurement of Lipoprotein-Associated Phospholipase A2 in the Assessment of Cardiovascular Risk

Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

Description

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Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease. Biomarkers assessed herein are those that have the most evidence in support of their use in clinical care, including apolipoprotein B (apo B), apolipoprotein AI (apo AI), apolipoprotein E (apo E), high-density lipoprotein (HDL) subclass, low-density lipoprotein (LDL) subclass, lipoprotein(a), B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. 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.

OBJECTIVE

The objective of this evidence review is to determine whether novel cardiac biomarker testing in asymptomatic patients or patients with hyperlipidemia improves the net health outcome.

POLICY STATEMENT

Measurement of novel lipid and non-lipid biomarkers (ie, apolipoprotein B, apolipoprotein AI, apolipoprotein E, low-density lipoprotein subclass, high-density lipoprotein subclass, lipoprotein [a], B-type natriuretic peptide, cystatin C, fibrinogen, leptin) is considered **investigational** as an adjunct to low-density lipoprotein cholesterol in the risk assessment and management of cardiovascular disease.

POLICY GUIDELINES

For testing performed as a panel, see evidence review 2.04.100.

Genetic Counseling

Experts recommend formal genetic counseling for individuals patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some individuals patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Some Plans may have contract or benefit exclusions for genetic testing.

FDA 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 (CLIA). Lipid and non-lipid biomarker tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who are asymptomatic with risk of cardiovascular disease who receive novel cardiac biomarker testing (eg, apo B, apo AI, apolipoprotein E (apo E), high-density lipoprotein (HDL) subclass, low-density lipoprotein (LDL) subclass, 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, apolipoprotein B (apo B) and apo apolipoprotein AI (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 outcome.

For individuals with hyperlipidemia managed with lipid-lowering therapy who receive novel cardiac biomarker testing (eg, apo B, apo AI, apo E, HDL subclass, LDL subclass, lipoprotein[a], B-type natriuretic peptide, cystatin C, fibrinogen, leptin), 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 outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Heart, Lung, and Blood Institute

In 2001, the National Heart, Lung, and Blood Institute's National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) issued a position statement.[2,] Apolipoprotein B (apo B), apolipoprotein AI (apo AI), lipid subclass, and lipoprotein(a) (Lp[a]) were listed as "emerging risk factors" for cardiovascular risk assessment, without specific recommendations for how these measures should be used in clinical practice. A 2004 update to these guidelines discussed the result of clinical trials of statin therapy.[112,]

In 2013, the Institute published a systematic evidence review on managing blood cholesterol in adults.[113,] The review was used to develop joint guidelines by the American College of Cardiology (ACC) and American Heart Association (AHA) on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (see below).[114,]

American College of Cardiology and American Heart Association

In 2013, the ACC and the AHA published guidelines for the assessment of cardiovascular risk.[114,] Pooled cohort equations for estimating arteriosclerotic cardiovascular disease (ASCVD) were developed from sex- and race-specific proportional hazards models that included covariates of age, treated or untreated systolic blood pressure level, total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels, current smoking status, and history of diabetes. Additional risk factors evaluated included diastolic blood pressure, family history of ASCVD, moderate or severe chronic kidney disease, and body mass index. None of the variables significantly improved discrimination for 10-year hard ASCVD risk prediction. The ACC and AHA recommended that further research using state-of-the-art statistical techniques (including net reclassification improvement and integrative discrimination index) examine the utility of novel biomarkers when added to these new pooled cohort equations in different populations and patient subgroups. The guidelines stated that future updates might include guidance on whether on-treatment markers such as apo B, Lp(a), or low-density lipoprotein (LDL) particles are useful for guiding treatment decisions.

The ACC/AHA (2019) guidelines on primary prevention of cardiovascular disease include information on appropriateness of Lp(a) level measurement stating "a relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a)."[115,] The guidelines also include recommendations for apo B measurement stating, "a relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor."

American Diabetes Association and American College of Cardiology Foundation

In 2008, a consensus statement from the American Diabetes Association and the ACC Foundation addressed lipoprotein management in patients with cardiometabolic risk.[116,] This statement included specific recommendations for incorporating apo B testing into clinical care for high-risk patients and recommended that, for patients with metabolic syndrome being treated with statins, both LDL-C and apo B should be used as treatment targets, with an apo B target of less than 90 mg/dL, even if target LDL has been achieved.

This consensus statement also commented on the use of LDL particle number in patients with cardiometabolic risk and on the limitations of the clinical utility of nuclear magnetic resonance measurement of LDL particle number or size, including lack of widespread availability. The statement also noted that there is a need for more independent data confirming the accuracy of the method and whether its predictive power is consistent across various patient populations.

The American Diabetes Association 2022 Standards of Care do not discuss the use of specific novel biomarkers for cardiovascular disease and risk management.[117,]

American Association of Clinical Endocrinologists and the American College of Endocrinology

In 2017, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published joint guidelines on the management of dyslipidemia and the prevention of cardiovascular diseases.[118,] The guidelines recommended that, among patients with "triglyceride (TG) concentration of greater than 150 mg/dL or HDL-C concentration of less than 40 mg/dL, the apo B or the apo B to apo AI ratio may be useful in assessing residual risk in individuals at risk for ASCVD (even when the LDL-C levels are controlled)."

In 2020, the AACE published an updated consensus statement on dyslipidemia and prevention of cardiovascular disease.[119,] They recommended measurement of Lp(a) in several patient populations including those with ASCVD, those with a family history of premature ASCVD and/or increased Lp(a), and individuals with a 10-year ASCVD risk of 10% of greater. Recommendations also included consideration of apo B or LDL particle measurement "based on individual patient clinical circumstances."

National Lipid Association

National Lipid Association (NLA) recommendations for patient-centered management of dyslipidemia were published in 2015.[120,] These recommendations stated that non-HDL-C and LDL-C should be primary targets for therapy and that apo B is an optional, secondary target for therapy. The Association favored non-HDL-C over apo B because the former is universally available and because apo B has not consistently shown superiority in predicting ASCVD risk.

In 2018, the NLA published a guideline on the management of blood cholesterol in conjunction with 11 other organizations, which discussed the measurement of apo B and Lp(a).[121,] A triglyceride level ≥200 mg/dL was mentioned as a relative indication of apo B measurement. Relative indications for measurement of Lp(a) include family history of premature ASCVD or ASCVD without traditional risk factors.

In 2019, the NLA issued a scientific statement on the use of Lp(a), which notes that Lp(a) measurement "is reasonable" to refine risk assessment for ASCVD events in the following populations: patients with first-degree relatives with premature ASCVD (<55 years of age for men; <65 years of age for women), patients with premature ASCVD without traditional risk factors, patients with severe hypercholesterolemia (LDL-C ≥190 mg/dL) or familial hypercholesterolemia, and patients with very-high risk of ASCVD that may be candidates for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy.[122,] Additionally Lp(a) "may be reasonable" to measure in patients with the following: intermediate (7.5 to 19.9%) or borderline (5 to 7.4%) ASCVD risk when statin initiation is uncertain for primary prevention, inadequate response to LDL-C lowering therapy despite adherence, family history of elevated Lp(a), calcific valvular aortic stenosis, or recurrent or progressive ASCVD despite lipid-lowering therapy.

In 2021, the NLA issued a scientific statement on lipid measurements in cardiovascular disease including information on apo B, small dense LDL, and Lp(a).[123,] The authors refer to the 2019 statement for information on Lp(a), and they recommend that measurements of apo B and small dense LDL "may be reasonable at initial evaluation." Additionally, apo B measurement "is reasonable" for patients receiving lipid lowering therapy while small dense LDL measurement is "not recommended" for these patients.

National Institute for Health and Care Excellence

In 2016, the National Institute for Health and Care Excellence updated its guidance on risk assessment and reduction, including lipid modification of CVD.[124,] The guidance recommended measuring a full lipid profile including total cholesterol, HDL, non-HDL, and triglycerides before starting lipid-lowering therapy for primary prevention of CVD. The guidance also recommended measurement of total cholesterol, HDL, non-HDL, and triglycerides for primary and secondary prevention in people on high-intensity statins at 3 months of treatment, aiming for a 40% reduction in non-HDL. Nontraditional risk factors, including apo B , were not discussed as part of risk assessment or treatment targets.

U.S. Preventive Services Task Force Recommendations

The **U.S. Preventive Services Task Force (2009) issued recommendations on the use of nontraditional risk factors for the assessment of coronary heart disease (CHD).[125,]** The **Task Force included Lp(a) in its summary statement: "The evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of CHD to prevent CHD events."**

The recommendation was updated in 2018 and came to the same conclusion: evidence is insufficient to assess the benefits and harms of novel testing methods to diagnose CVD. However, the nontraditional risk factors included in this recommendation were different than those in this evidence review.[126,]

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy-FEP	Policy updated with literature review through November 9, 2022; references added. Policy statement unchanged. FEP Benefit change, New FEP Policy