MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**CARDIOVASCULAR DISEASE RISK ASSESSMENT - LABORATORY EVALUATION OF LIPIDS**
Policy Number	**2.02.29**
Category	**Laboratory Test**
Effective Date	**09/15/05**
Revised Date	**07/20/06, 05/17/07, 07/17/08, 07/16/09, 10/28/10, 10/20/11, 10/18/12, 10/17/13, 10/16/14, 12/17/15, 11/17/16, 12/21/17, 12/20/18, 11/21/19**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

I. Based on our criteria and review of the peer-reviewed literature, use of the following laboratory tests in the assessment of cardiovascular disease risk have not been proven to improve health outcomes and are considered **investigational**:
   A. Apolipoprotein A-I;
   B. Apolipoprotein B;
   C. Apolipoprotein E;
   D. High density lipoprotein subclasses;
   E. Intermediate density lipoprotein (remnant-like particles);
   F. Low density small lipoprotein; and
   G. Lipoprotein(a) enzyme immunoassay.

II. Based on our criteria and review of the peer-reviewed literature, gene expression testing to predict coronary artery disease (CAD) is considered **investigational** for all indications, including but not limited to prediction of the likelihood of CAD in stable, nondiabetic patients.

Refer to Corporate Medical Policy # 2.02.15 regarding Inflammatory Markers of Coronary Artery Disease Risk.

Refer to Corporate Medical Policy # 11.01.03 regarding Experimental or Investigational Services.

POLICY GUIDELINES

I. This policy applies only to routine coronary artery disease risk assessment and does not apply to the evaluation of possible familial lipid disorders or other dyslipidemias.

II. The Federal Employees Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Cardiovascular disease (CVD), defined as coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease is the major cause of morbidity and mortality in the Western world. Most patients with CVD have at least one major risk factor, however the same can be said for most middle-aged and elderly people without CVD. Therefore, risk factors cannot account for all incident cardiovascular events. Although low-density lipoproteins (LDL) and high-density lipoproteins (HDL) are considered the major lipid risk factors for CVD, they do not completely predict risk of disease. 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 occur in subjects with normal levels of total and LDL cholesterol. There is interest in determining whether lipid subclasses, including concentration and size of LDL and HDL particles, may further stratify risk for CVD above traditional risk factor measurement.

Apolipoprotein A- I (apo A- I) is a lipid-binding protein that forms complexes with other proteins and lipids to form HDL particles. It is the major protein component of HDL and is usually reduced when the HDL level is low. Low levels of apo A-1 may be associated with an increased risk for cardiovascular disease. Direct measurement of apo A- I has been proposed as more accurate than the traditional use of HDL level in evaluation of the cardioprotective, or 'good', cholesterol. In addition, the ratio of apo B/apo A- I has been proposed as a superior measure of the ratio of pro-atherogenic (e.g., "bad") cholesterol to anti-atherogenic (e.g., "good") cholesterol. Some, but not all, epidemiologic studies have reported that the apo B/apo A-I ratio is superior to other ratios, such as TC/HDL-C, or non-HDL chol/HDL-C.

Apolipoprotein B (apo B) is the major protein of all lipoproteins except for high-density lipoprotein (HDL). The most abundant form of apo B, large B or B-100, constitutes the apo B found in low-density and very low-density lipoproteins. It has been proposed that apo B is a better marker of cardiovascular risk than total LDL. Some experts feel using apo B as a measure of the number of atherogenic particles may be useful to monitor statin and niacin therapy.

Apolipoprotein E (apo E) is the primary apolipoprotein found in very low-density lipoproteins. It is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. The genotype of apo E can be assessed by gene amplification techniques. The apo E phenotype can be assessed by measuring plasma levels of apo E. It has been proposed that various genotypes are more atherogenic than others, and that apo E measurement may provide information on risk of coronary artery disease above traditional risk factor measurement. It has also been proposed that the apo E genotype may be useful in selection of specific components of lipid-lowering therapy, such as drug selection. Some experts feel that measurement of apo E may be useful in patients with elevated triglycerides and elevated total cholesterol, especially in the presence of palmar crease or tuboeruptive xanthomas. Apolipoprotein E isoforms have also been investigated as a risk factor for Alzheimer's disease.

High Density Lipoprotein (HDL) subclass (lipoprotein AI (LpAI) and lipoprotein AI/AII (LpAI/AII) and/or HDL3 and HDL2) may have a protective role against cardiovascular disease. A large body of epidemiologic literature has demonstrated an inverse relationship between HDL levels and cardiovascular risk. It has been proposed that various subclasses of HDL may have a greater role in protection from atherosclerosis. Particles can be characterized based on size/density, and/or on the lipoprotein composition. Using size/density, HDL can be classified into HDL2, the larger less dense particles that may have the greatest degree of cardioprotection, and HDL3, the smaller more dense particles. HDL contains two associated lipoproteins, LpA-I and A-II. HDL particles can also be classified on whether they contain apolipoprotein A-1(apo A-1). There has been substantial interest in determining whether subclasses of HDL can be used to provide additional information on cardiovascular risk compared to HDL alone. More recently, measurement of apo A-I has become the preferred surrogate method for HDL subclass type.

Intermediate Density Lipoprotein (remnant-like particles). Triglyceride-rich proteins (TRL) consist of a great variety of lipoproteins differing in size, density, and apolipoprotein content. Based on their size and ability to enter the arterial wall, certain TRLs are considered atherogenic while others are not. Remnant lipoproteins, which are considered atherogenic, consist of low-density lipoproteins that are reduced in size, partially depleted of triglycerides, and enriched with cholesteryl esters. Remnant lipoproteins are also referred to as intermediate density lipoproteins based on how they separate on ultracentrifugation. Measurement of intermediate density lipoproteins has been investigated as a tool for risk assessment for coronary heart disease and as a technique to diagnose type III hyperlipoproteinemia.

Low Density (Small) Lipoprotein (LDL) particle size has been hypothesized to be a risk factor for coronary heart disease. The National Cholesterol Education Program (NCEP) has designated total LDL as the primary target of therapy in the Adult Treatment Panel (ATP III) recommendations. However, LDL particles are not uniform in size or density, and particle size/density has been proposed as a technique to further stratify patient risk beyond total LDL. LDL 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 small, dense particles to larger particles. It has been proposed that this

shift in lipid profile may be beneficial in reducing risk for coronary artery disease (CAD) independent of the total LDL level.

There are two main subclass patterns of LDL. Subclass pattern A particles have a diameter larger than 25 nm and are less dense. Subclass pattern B particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a commonly inherited disorder associated with a more atherogenic lipoprotein profile.

Lipoprotein(a) Enzyme Immunoassay (Lp[a]) is a low-density, lipoprotein-like, lipid-rich particle similar to LDL. Apolipoprotein B is the major apolipoprotein associated with LDL; in Lp(a), however, there is an additional apolipoprotein A linked to apolipoprotein B. The apolipoprotein (a) molecule is structurally similar to plasminogen, suggesting that Lp(a) may contribute to the thrombotic and atherogenic basis of cardiovascular disease. The similarity between apolipoprotein (a) and fibrinogen has stimulated interest in Lp(a) as a link between atherosclerosis and thrombosis. Approximately 20% of patients with coronary artery disease (CAD) have elevated levels of Lp(a). Therefore, it has been proposed the levels of Lp(a) may be an independent risk factor for CAD. Some experts feel Lp(a) may be useful as a determinant of CHD onset in familial hypercholesterolemia patients, in patients with early CHD and no risk factors, and in those with a significant family history.

Gene Express Assays consist of expression levels of various genes in circulating white blood cell or whole blood samples and 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. These tests 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 Corus CAD™ test was 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. According to the CardioDx® website, the Corus CAD test is intended for use in patients who present with stable symptoms suggestive of obstructive CAD such as, chest discomfort, tightness, pain, or pressure, and shortness of breath. The Corus CAD test is not intended for patients who have a history of obstructive CAD, or have had a prior myocardial infarction or revascularization procedure, or are diabetic, or are currently taking steroids, immunosuppressive agents, or chemotherapeutic agents.

RATIONALE

Improved ability to predict risk and/or treatment response does not by itself result in better health outcomes. To improve health outcomes, clinicians must have the tools to incorporate emerging risk factors into existing risk prediction models that have been demonstrated to classify patients into risk categories with greater accuracy. Such tools are currently not available. Predictive models also need to be accompanied by treatment guidelines that target intervention toward patients who will get the most benefit. The Adult Treatment Panel (ATP III) practice guidelines from the report of the National Cholesterol Education Program continues to tie clinical decision making to conventional lipid measures, such as total cholesterol, LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C).

Apolipoprotein A-I. Literature continues to focus on the utility of apo A-I and the apo B/apo A-I ratio as additional predictors of cardiovascular risk, and on the relationship of these apolipoprotein measures to traditional lipid risk factors. Clinical evidence indicates inconsistent findings regarding the predictive value of apo A-I for future cardiovascular events. The Air Force/Texas Atherosclerosis Prevention Study (AFCAPS/TexCAPS) found that apo A-I at baseline and at one year was predictive of future cardiovascular events. The Physicians Health Survey found apo A-I had little or no predictive value after adjustment for other risk factors. In the Atherosclerosis Risk in Communities (ARIC) study, apo A-I was also found to have little or no predictive value in assessing patients at risk for cardiovascular disease.

Apolipoprotein B. Some experts continue to argue that apo B is superior to LDL cholesterol, and that the apo B/apo A-I ratio is superior to the LDL/HDL ratio, as predictors of cardiovascular risk, and that these apolipoprotein measures should supplement or replace traditional lipid measures. Furthermore, a publication from a recent consensus conference from the American Diabetes Association and the American College of Cardiology Foundation included specific recommendations for incorporating apo B testing into clinical care for high-risk patients. This expert panel stated, “ApoB and LDL particle

number also appear to be more discriminating measures of the adequacy of LDL lowering therapy than are LDL cholesterol or non-HDL cholesterol." They therefore recommend that for patients with metabolic syndrome who are being treated with statins, both LDL cholesterol and apo B should be used as treatment targets, with an apo B target of less than 90mg/dl. Treatment should be intensified for patients with apoB above this level even if target LDL has been achieved. The current evidence does in general support the contention that apo B and apo B/apo A-I are as good as or better than currently used lipid measures as predictors of cardiovascular risk. Also, tools for assisting clinicians in applying apo B measurements to clinical care are being developed. However, it is not yet possible to conclude that the use of apo B levels will improve outcomes when used in routine clinical care. First, the evidence suggests that any incremental improvement in predictive ability over traditional measures is likely to be small and of uncertain clinical significance. Second, none of the major lipid treatment guidelines, such as The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), have yet to formally incorporate the measurement of apolipoproteins into their recommendations. This creates difficulties in interpreting and applying the results of apo B and/or apo B/apo A-I measurements to routine clinical care. As a result, it does not appear likely that in the near future, apolipoprotein measures will replace traditional lipid measurements for cardiovascular risk prediction in routine clinical care.

Apolipoprotein E genotype or phenotype. A large body of research has focused on the correlation between lipid levels and the underlying apolipoprotein E (apo E) genotype. Other studies have focused on the relationship between genotype and clinical disease. Clinical evidence suggests that apo E is not clinically useful in providing additional information on risk for CAD when compared with other established and emerging risk factors. None of the studies reviewed provide adequate data to suggest that apo E genotype improves outcomes when used in clinical care.

High density lipoprotein subclass (HDL). Retrospective cross-sectional studies have suggested that the protective effect of HDL was associated primarily with the HDL-2 subclass. However, these studies could not determine whether decreased HDL-2 preceded the development of cardiovascular disease or was its result. A number of large, prospective studies designed to answer this question have reported mixed results. While a number of studies suggest the HDL subclassification provides independent information on risk assessment for CAD, this finding has not been reported consistently in all studies. HDL subclassification has not been incorporate into quantitative risk assessment models or treatment guidelines, such as the Adult Treatment Panel (ATP III) that can be used in clinical practice.

Intermediate density lipoprotein (remnant-like particles). An immunoseparation assay has received approval from the U.S. Food and Drug Administration (FDA) for the direct measurement of intermediate density lipoprotein. While measurement of intermediate-density lipoproteins (IDLs) has emerged as an important research tool in evaluating cardiac risk factors and understanding how different components of plasma triglycerides contribute to cardiac risk, it is unclear how the management of IDLs can be used in the management of the patient. The majority of publications focus on the pathophysiology and basic science aspects of IDL, with a smaller number of research studies reporting data with potential clinical relevance. There are no prospective, large-scale cohort studies that evaluated IDLs as a predictor of cardiovascular risk, nor are there any large diagnostic studies that evaluated the utility of IDLs in diagnosing type III hyperlipidemia. None of the available studies provide guidance on the clinical use of IDL measurements, nor does this evidence suggest that health outcomes are improved as a result of measuring IDL level.

Low density (small) lipoprotein particle size. Small LDL size is one component of an atherogenic lipid profile that also includes increased triglycerides, increased apolipoprotein B, and decreased HDL. Some studies have reported that LDL size is an independent risk factor for CAD, and others have reported that a shift in LDL size may be useful marker of treatment response. A relatively small number of published articles contain clinically relevant evidence on the utility of measuring the concentration of small, dense LDL (or LDL particle size). The available publications primarily focus either on the use of these measures as a predictor of cardiovascular risk, or the effect of pharmacologic treatment on small, dense LDL. Studies predicting cardiac risk were cross-sectional studies that evaluated the association of small, dense LDL with a variety of cardiovascular outcomes. There are no large, prospective cohort studies that evaluate the predictive ability of small, dense LDL for future cardiovascular events. The studies of treatment effect examined the impact of diet and/or pharmacologic agents on small, dense LDL and other LDL subclasses. These studies generally confirmed that small, dense LDL is impacted preferentially by fibrate treatment, and possibly also by statin therapy. However, none of the studies demonstrate that preferentially targeting small, dense LDL leads to improved outcomes, as compared to using the standard LDL targets that are widespread in clinical care. These newly published studies do not provide evidence that

measurement of small, dense LDL leads to improved clinical outcomes. Tools for linking concentration of LDL particles to clinical decision making, both in risk assessment and treatment response, are currently not available.

Lipoprotein(a) enzyme immunoassay [Lp(a)]. Numerous studies evaluate Lp(a) as a cardiovascular risk factor. A large number of retrospective studies suggest that elevated levels of Lp(a) are associated with CVD. However they could not determine whether the elevation of Lp(a) preceded the development of CVD or was a result of CVD. Prospective studies have produced mixed results. A meta-analysis (Smolders B, et al. 2007) summarized evidence from observational studies of the relationship between lp(a) and stroke. There were 5 prospective cohort studies and 23 case-control studies included in this analysis. From prospective cohort studies, Lp(a) added a modest amount of incremental predictive information (combined RR for the highest one-third of Lp(a) 1.22, 95% CI: 1.04-1.43). From case-control studies, an elevated Lp(a) level was also associated with an increased risk of stroke (combined OR 2.39, 95% CI: 1.57-3.63). The authors concluded that this meta-analysis suggests that elevated Lp(a) is a risk factor for incident stroke. The authors noted however, that the use of formal meta-analytic methods to observational studies is controversial, because weaknesses implicit in the study design of case-control studies and cohort studies may bias the strength of associations within the data. Evaluation of Lp(a) as a risk factor is complicated by the lack of a standardized assay, different study methodologies, the variation of Lp(a) levels in different races and ethnic groups, and the complicated interplay of various lipid cardiovascular risks associated with other lipid parameters. The Adult Treatment Panel (ATP) III identified Lp(a) as an "emerging risk factor," however improved risk prediction does not by itself result in better health outcomes. Tools for linking Lp(a) to clinical decision making, both in risk assessment and treatment response, are currently not available.

Gene expression tests. The evidence for gene expression testing for coronary artery disease (CAD) prediction in nondiabetic patients with increased CAD risk (due to suggestive symptoms or elevated predicted risk) includes retrospective case-control and prospective cohort studies. Relevant outcomes are test accuracy, test validity, change in disease status (CAD detected on angiography), morbid events (cardiac events), and resource utilization (rates of coronary angiography). The prospective 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 Gene Expression Score (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 forgo further testing based on a low GES. Clinical utility of GES has not been demonstrated. Several studies with methodologic limitations reported management changes as a result of the test, but the effect of these management changes is uncertain. Evidence for a significant incremental improvement in outcomes when gene expression testing is added to standard clinical evaluation is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
82172 **(E/I)**	Apolipoprotein, each
83695 **(E/I)**	Lipoprotein (a)
83700	Lipoprotein, blood; electrophoretic separation and quantitation

Code	Description
83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (e.g, electrophoresis, ultracentrifugation)
83704 **(E/I)**	Lipoprotein, blood: quantitation of lipoprotein particle numbers and lipoprotein particle subclass(es) (e.g. by nuclear magnetic resonance spectroscopy)
83722 **(E/I)**	Lipoprotein, direct measurement; small dense LDL cholesterol

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HCPCS Codes

Code	Description
No specific codes	

ICD10 Codes

Code	Description
E71.30	Disorder of fatty-acid metabolism, unspecified
E75.21	Fabry (-Anderson) disease
E75.22	Gaucher disease
E75.240-E75.249	Niemann-Pick disease (code range)
E75.3	Sphingolipidosis, unspecified
E75.5-E75.6	Other lipid storage disorders (code range)
E77.0-E77.9	Disorders of glycoprotein metabolism
E78.0-E78.6	Disorders of lipoprotein metabolism and other lipidemias
E78.70	Disorder of bile acid and cholesterol metabolism, unspecified
E78.79	Other disorders of bile acid and cholesterol metabolism
E78.81-E78.9	Other disorders of lipoprotein metabolism
E88.1-E88.2	Other and unspecified metabolic disorders (code range)
E88.89	Other specified metabolic disorders
I20.0-I20.9	Angina pectoris (code range)
I21.01-I21.4	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (code range)
I22.0-I22.8	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (code range**)**
I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site
I24.0	Acute coronary thrombosis not resulting in myocardial infarction
I24.1	Dressler's syndrome
I24.8	Other forms of acute ischemic heart disease
I24.9	Acute ischemic heart disease, unspecified
I25.10-I25.9	Chronic ischemic heart disease (code range)
I70.0-I70.92	Atherosclerosis (code range)
Z82.41	Family history of sudden cardiac death
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system

Code	Description
Z86.711	Personal history of pulmonary embolism
Z86.718	Personal history of other venous thrombosis and embolism
Z86.72	Personal history of thrombophlebitis
Z86.73	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits
Z86.74	Personal history of sudden cardiac arrest
Z86.79	Personal history of other diseases of the circulatory system

REFERENCES

Acevedo M, et al. Comparison of lipoprotein-associated phospholipase A2 and high sensitive c-reactive protein as determinants of metabolic syndrome in subjects without coronary heart disease: in search of the best predictor. Int J Endocrinol 2015;2015:934681.

*ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA 2002 Dec 18;288(23):2998-3007.

*Arsenault BJ, et al. Cholesterol levels in small LDL particles predict the risk of coronary heart disease in the EPIC-Norfolk prospective population study. Eur Heart J 2007 Nov;28(22):2770-7.

*Barter PJ, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: a report of the thirty-person/ten-country panel. J Intern Med 2006 Mar;259(3):247-58.

*Benn M, et al. Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B: the Copenhagen City Heart Study. Arterioscler Thromb Vasc Biol 2007 Mar;27(3):661-70.

*Bennet AM, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA 2007 Sep 19;298(11):1300-11.

Boekholdt SM, et al. Levels and changes of HDL cholesterol and apolipoprotein A-1 in relation to risk of cardiovascular events among statin-treated patients: a meta-analysis. Circulation 2013 Oct 1;128(14):1504-12.

BlueCross BlueShield Association. Gene expression testing in the Evaluation of Patient with Stable Ischemic Heart Disease. Medical Policy Reference Manual. Policy #2.04.72. 2019 Mar 14.

BlueCross BlueShield Association. Measurement of lipoprotein-associated phospholipase A2 in the assessment of cardiovascular risk. Medical Policy Reference Manual. Policy #2.04.32. 2018 Dec 13.

BlueCross BlueShield Association. Measurement of serum intermediate density lipoproteins (remnant-like particles). Medical Policy Reference Manual. Policy #2.04.31. Archived. 2009 Dec 03.

BlueCross BlueShield Association. Novel lipid risk factors in risk assessment and management of cardiovascular disease. Medical Policy Reference Manual Policy #2.04.65. 2018 Dec 13.

Daniels SE, et al. Biological and analytical stability of a peripheral blood gene expression score for obstructive coronary artery disease in the PREDICT and COMPASS studies. J Cardiovasc Transl Res Oct 2014;7(7):615-22.

*Davidson MH, et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists. J Clin Lipidol 2011 Sep-Oct;5(5):338-67.

*De Graaf J, et al. High plasma level of remnant-like particles cholesterol in familial combined hyperlipidemia. J Clin Endocrinol Metab 2007 Apr;92(4):1269-75.

*Di Angelantonio E GP, et al. Lipid-related markers and cardiovascular disease prevention. JAMA 2012; 307(23):2499-506.

Doliner B, et al. Apoliprotein E gene polymorphism and subclinical carotid atherosclerosis: the Northern Manhattan Study. J Stroke Cerebrovasc Dis 2018 Mar;27(3):645-652.

Elashoff MR, 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.

*El Harchaoui K, et al. Value of low-density lipoprotein particle number and size as predictors of coronary artery disease in apparently healthy men and women: the EPIC-Norfolk Prospective Population study. J Am Coll Cardiol 2007 Feb 6;49(5):547-53.

Emoto T, et al. The apolipoprotein B/A1 ratio is associated with reactive oxygen metabolites and endothelial dysfunction in statin-treated patients with coronary artery disease. J Atheroscler Thromb 2013 Jul 30;20(7):623-9.

*Expert Panel of Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. 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 2001 May 16; 285(19):2468-97.

Garg PK, et al. Lipoprotein-associated phospholipase A2 and risk of incident cardiovascular disease in a multi-ethnic cohort: the multi ethnic study of atherosclerosis. Atherosclerosis 2015 Jul;241(1):176-82.

*Greenland P, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2010;56:e50-e103.

*Goldstein LB, et al. Primary prevention of ischemic stroke. A guideline from the American Heart Association/American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circ 2006 Jun 20;113(24):e873-923.

*Gotto AM, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas coronary atherosclerosis prevention (AFCAP/TexCAPS). Circ 2000 Feb 8;101(5):477-84.

*Hayashi Y, et al. Impact of low-density lipoprotein particle size on carotid intima-media thickness in patients with type 2 diabetes mellitus. Metabolism 2007;56(5):608-13.

*Ingelsson E, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA 2007 Aug 15;298(7):776-85.

Kappelle, PJWH, et al. Apolipoprotein B/A-1 and total cholesterol/high-density lipoprotein cholesterol ratios both predict cardiovascular events in the general population independently of nonlipid risk factors, albuminuria and C-reactive protein. J Int Med 2010;269:232-42.

Kim SH, et al. The association between the apolipoprotein B/A-I ratio and coronary calcification may differ depending on the kidney function in a healthy population. PLoS One 2017 Sep 28:12(9):e0185522.

Kouvari M, et al. Lipoprotein (a) and 10-year cardiovascular disease incidence in apparently healthy individuals: a sex-based sensitivity analysis from ATTICA cohort study. Angiology 2019 Oct;7099):819-829.

Martin SS, et al. HDL cholesterol subclasses, myocardial infarction, and mortality in secondary prevention: the lipoprotein investigators collaborative. Eur Heart J 2015 Jan1;36(1):22-30.

Mora S, et al. On-treatment non-high-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and lipid ratios in relation to residual vascular risk after treatment with potent statin therapy: JUPITER (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin). J Am Coll Cardiol 2012 Apr 24:59(17):1521-8.

*Kulminski AM, et al. Health-protective and adverse effects of the apolipoprotein E epsilon2 allele in older men. J Am Geriatr Soc 2008;56(3):478-83.

Lansky A, 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 Sep;164(3):320-6.

Mani P, et al. Relation of high-density lipoprotein cholesterol: apolipoprotein A-1 ratio to progression of coronary atherosclerosis in statin-treated patients. Am J Cardiol 2014 Sep 1;114(5):681-5.

*Ridker PM, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007 Feb 14;297(6):611-9.

Rosenberg S, 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 Jun;5(3):366-74.

Rosenberg S, 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 Oct 5;153(7):425-34.

Schmidt C, et al. Apolipoprotein B and Apolipoprotein A-I in vascular risk prediction – a review. Curr Pharm Des 2014;20(40):6289-98.

*Smith SC Jr, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circ 2006 May 16;113(19):2363-72.

Sniderman AD, et al. Age and cardiovascular risk attributable to apolipoprotein B, low-density lipoprotein cholesterol or non-high-density lipoprotein cholesterol. J Am Heart Assoc 2016 Oct 13;5(10).

Sturm AC, et al. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol 2018 Aug 7;72(6):662-680.

Tonkin AM, et al. Biomarkers in stable coronary heart disease, their modulation and cardiovascular risk: the LIPID biomarker study. Int J Cardiol 2015 Aug 16;201:499-507.

*US Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: US Preventive Services Task Force recommendation statement. Ann Int Med 2009 Oct 6;151(7):474-82.

van Capelleveen JC, et al. Association of high-density lipoprotein-cholesterol versus apolipoprotein A-I with risk of coronary heart disease: The European Prospective Investigation Into Cancer-Norfolk Prospective Population Study, the Atherosclerosis Risk in Communities Study, and the Women's Health Study. J Am Heart Assoc. 2017 Aug 3;6(8). pii: e006636.

*Van der Steeg WA, et al. Role of the apolipoprotein B-apolipoprotein A-I ratio in cardiovascular risk assessment: a case-control analysis in EPIC-Norfolk. Ann Intern Med 2007 May 1;146(9):640-8.

*Volcik KA, et al. Apolipoprotein E polymorphisms predict low density lipoprotein cholesterol levels and carotid artery wall thickness but not incident coronary heart disease in 12,491 ARIC study participants. Am J Epidemiol 2006 Aug 15;164(4):342-8.

Voros S, 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 Mar;233(1):284-290.

Welsh C, et al. Comparison of conventional lipoprotein tests and apolipoproteins in the prediction of cardiovascular diseases. Circulation 2019 Aug 13;140(7):542-5523.

Zhu YM, et al. Association of apolipoproteins B and A-1with markers of vascular health or cardiovascular events. Can J Cardiol. 2017 Oct;33(10):1305-1311.

*Key Article

KEY WORDS

Apolipoprotein A-I, Apolipoprotein B, Apolipoprotein E, Lipoprotein(a) enzyme immunoassay.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Determination (NCD) for Lipid Testing. Please refer to the following NCD website for Medicare Members: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=102&ncdver=2&bc=AgAAgAAAAAAA&

CMS covers tests for cardiac risk factors (total cholesterol, cholesterol high density lipoproteins, triglycerides) but does not provide specific language regarding the lipid subclass tests addressed in this policy.

However, CPT code 83704 - Lipoprotein, blood: quantitation of lipoprotein particle numbers and lipoprotein particle subclasses (e.g. by nuclear magnetic resonance spectroscopy) is listed as a covered code.