

## Evidence Based Guideline

### Novel Lipid Risk Factors in Risk Assessment of Cardiovascular Disease

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#### Description of Procedure or Service

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Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease. This policy will focus on those lipid markers that have the most evidence in support of their use in clinical care. The lipid markers assessed here are apolipoprotein B, apolipoprotein A-1, HDL subclass, LDL subclass, apolipoprotein E, and lipoprotein A.

#### Background

Low-density lipoproteins (LDL) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) as the primary target of cholesterol-lowering therapy. LDL particles consist 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-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 occur in subjects with 'normal' levels of total and LDL cholesterol. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Apolipoprotein B: Apolipoprotein B (apo B) is the major protein moiety 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 LDL and very-low-density lipoproteins (VLDL). Since both LDL and VLDL each contain 1 molecule of apolipoprotein B, measurement of apo B reflects the total number of these atherogenic particles, 90% of which are LDL. Since LDL particles can vary both in size and in cholesterol content, for a given concentration of LDL-C, there can be a wide variety of both size and numbers of LDL particles. Thus, it has been postulated that apo B is a better measure of the atherogenic potential of serum LDL than is LDL concentration.

Two basic techniques are used for measuring LDL particle concentration. Particle size can be determined by gradient gel electrophoresis, or direct measurement of the number of LDL particles can be performed using nuclear magnetic spectroscopy. Nuclear resonance spectroscopy (NMR) is based on the fact that lipoprotein subclasses of different size broadcast distinguishable NMR signals. Thus NMR can quantify the number of LDL particles of a specific size (i.e., small dense LDL) and can provide a measurement of the total number of particles.

Apolipoprotein A-I: HDL contains two associated apolipoproteins, i.e., A-I and A-II. HDL particles can also be classified by whether they contain apolipoprotein A-I (apo A-I) only or whether they contain both apo A-I and A-II. All lipoproteins contain apo A-I and some also contain apo A-II. Since all HDL particles contain apo A-I, this lipid marker can be used as an approximation for HDL number, similar to the way apo B has been proposed as an approximation of the LDL number.

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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 proatherogenic (i.e., “bad”) cholesterol to anti-atherogenic (i.e., “good”) cholesterol.

Apolipoprotein E: Apolipoprotein E (apo E) is the primary apolipoprotein found in very-low-density lipoproteins and chylomicrons. Apo E is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. The apo E gene is polymorphic, consisting of 3 alleles (e2, e3, and e4) that code for 3 protein isoforms, known as E2, E3, and E4, which differ from one another by one amino acid. These molecules mediate lipid metabolism through their different interactions with the LDL receptors. The genotype of apo E alleles can be assessed by gene amplification techniques, or the apo E phenotype can be assessed by measuring plasma levels of apolipoprotein E.

It has been proposed that various apo E 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 the selection of specific components of lipid-lowering therapy, such as drug selection. In the major lipid-lowering intervention trials, including trials of statin therapy, there is considerable variability in response to therapy that cannot be explained by factors such as compliance. Apo E genotype may be one factor that determines an individual’s degree of response to interventions such as statin therapy.

LDL subclass: Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, the particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, the 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, also termed “atherogenic dyslipidemia.” In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apolipoprotein B, and low levels of HDL. This lipid profile is commonly seen in type II diabetes and is one 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; ATP III) to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein (CRP), and a prothrombotic state. Presence of the metabolic syndrome is considered by ATP III to be a substantial risk-enhancing factor for coronary artery disease (CAD).

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 smaller, dense particles to larger particles. It has been proposed that this shift in lipid profile may be beneficial in reducing risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profile 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 to use a combination of 2 or more 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, LDL-C is not a direct measure of LDL but, chosen for its convenience, measures the amount of cholesterol incorporated into LDL particles. Since 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 compared to larger particles. Therefore, for patients with elevated numbers of LDL particles, cardiac risk may be further enhanced when the particles are smaller versus larger.

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Two techniques are most commonly used for measuring LDL particle concentration, the surrogate measurement of apo B or direct measurement of the number of particles using nuclear magnetic spectroscopy (NMR). NMR is used based on the fact that lipoprotein subclasses of different size broadcast distinguishable NMR signals. Thus NMR can directly measure the number of LDL particles of a specific size (i.e., small dense LDL) and can provide a measurement of the total number of particles. Thus, NMR is proposed as an additional technique to assess cardiac risk.

**HDL subclass:** HDL 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/density and/or on the apolipoprotein 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, which are smaller, more dense particles. HDL contains two associated apolipoproteins, i.e., A-I and A-II. HDL particles can also be classified by whether they contain apolipoprotein A-I (apo A-I) only or whether they contain both apo A-I and A-II. 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.

An alternative to measuring the concentration of subclasses of HDL, such as HDL2 and HDL3, is direct measurement of HDL particle size and/or number. Particle size can be measured by NMR spectroscopy or by gradient-gel electrophoresis. HDL particle numbers can be measured by NMR spectroscopy. Several commercial labs offer these measurements of HDL particle size and number. Measurement of apo A-I has used measurement of HDL particle number as a surrogate, based on the premise that each HDL particle contains one apo A-I molecule.

**Lipoprotein A:** Lipoprotein(a) (lp[a]) is a 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 covalently linked to the 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. Levels of lp(a) are relatively stable in individuals over time, but vary up to 1,000-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 levels of lp(a). Therefore, it has been proposed that levels of lp(a) may be an independent risk factor for CAD.

**\*\*\*Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Evidence Based Guideline for Novel Risk Factors in Risk Assessment of Cardiovascular Disease

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Measurement of novel risk factors may not be appropriate in the risk assessment and management of cardiovascular disease.

## Medical Evidence regarding Novel Risk Factors in Risk Assessment of Cardiovascular Disease indicates it is not recommended in the following situations

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It is not yet possible to conclude that the measurements of novel risk factors such as Apolipoprotein B, Apolipoprotein A-I, Apolipoprotein E, LDL Subclass, HDL Subclass or Lipoprotein A will improve outcomes when used in routine clinical care. Improved ability to predict risk and/or treatment response does not by itself result in better health outcomes. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. No studies have demonstrated improved health outcomes for either risk assessment and/or treatment response.

# Novel Lipid Risk Factors in Risk Assessment of Cardiovascular Disease

The most widely used risk assessment models, such as the Framingham prediction model, and the most widely used treatment guidelines, the ATP III guidelines, do not provide the tools necessary for clinicians to incorporate novel risk factors measurements into routine assessment and management of hyperlipidemic patients. This lack creates difficulties in interpreting and applying the results of novel risk factors measurements to routine clinical care.

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## Billing/Coding/Physician Documentation Information

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This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 83704, 83700, 83701*

*There is no specific CPT code for measurement of apolipoprotein B. CPT code 82172 might be used.*

*There is no CPT code for subclassification that is specific to high-density lipoprotein (HDL). CPT code 82664 or 83701 may be used.*

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.65, 6/10/10

Senior Medical Director review 7/2010

Specialty Matched Consultant Advisory Panel review 4/2011

Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the US Preventive Services Task Force. *Ann Intern Med* 2009; 151:496–507. Retrieved on March 10, 2011 from <http://www.annals.org/content/151/7/496.full.pdf+html>

U.S. Preventive Services Task Force (USPSTF). Using Nontraditional Risk Factors in Coronary Heart Disease Risk Assessment: U.S. Preventive Services Task Force Recommendation Statement. October 6, 2009 vol. 151 no. 7 474-482. Retrieved on March 10, 2011 from <http://www.annals.org/content/151/7/474.full.pdf+html>

## Policy Implementation/Update Information

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8/31/10 New Evidenced Based Guideline created by consolidating the following policies: “Apolipoprotein B in Cardiac Disease Risk Assessment”, “Lipoprotein(a) Enzyme Immunoassay in Cardiac Disease Risk Assessment”, “High-Density Lipoprotein Subclass Testing in Cardiac Disease Risk Assessment”, and “Apolipoprotein E Genotype or Phenotype in Cardiac Disease Risk Assessment”. Novel lipid risk factor measurements are not

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recommended for risk assessment of cardiovascular disease. (mco)

5/10/11 Specialty Matched Consultant Advisory Panel review 4/2011. References updated. (mco)

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