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<b>Medical Benefit</b>		<b>Effective Date:</b> 07/01/14	<b>Next Review Date:</b> 03/19
<b>Preauthorization</b>	No	<b>Review Dates:</b> 09/09, 09/10, 09/11, 09/12, 09/13, 03/14, 03/15, 03/16, 03/17, 03/18	

***This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.***

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>Who are asymptomatic with risk of cardiovascular disease</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Novel cardiac biomarkers testing</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Routine care without biomarker testing</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Other test performance measures</li> <li>Change in disease status</li> <li>Morbid events</li> <li>Medication use</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With hyperlipidemia managed with lipid-lowering therapy</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Novel cardiac biomarkers testing</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Routine care without biomarker testing</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Change in disease status</li> <li>Morbid events</li> <li>Medication use</li> </ul>

### Description

Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease (CVD). 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), B-type natriuretic peptide, cystatin C, fibrinogen, high-density lipoprotein (HDL) subclass, low-density lipoprotein (LDL) subclass, and 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 CVD or as treatment targets for lipid-lowering therapy.

### Summary of Evidence

For individuals who are asymptomatic with risk of CVD who receive novel cardiac biomarker testing (e.g., apo B, apo AI, apo E, HDL subclass, LDL subclass, Lp[a], BNP, 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 the effects of the technology on health outcomes.

For individuals with hyperlipidemia managed with lipid-lowering therapy who receive novel cardiac biomarker testing (e.g., apo B, apo AI, apo E, apo E, HDL subclass, LDL subclass, Lp[a], BNP, 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 the effects of the technology on health outcomes.

### Policy

Measurement of novel lipid and non-lipid risk factors (i.e., 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 the Cardiovascular Risk Panels Protocol.

#### *Genetic Counseling*

Experts recommend formal genetic counseling for 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 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.

### Medicare Advantage

For Medicare Advantage this is considered **not medically necessary**.

### Background

#### *Low-Density Lipoproteins and Cardiovascular Disease*

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. 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 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 CVD, including B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers may have a predictive role in identifying CVD risk or in targeting for therapy,

### Lipid Markers

#### APOLIPOPROTEIN B

Apolipoprotein B (apo B) is the major protein moiety of all lipoproteins, except for HDL. The most abundant form of apo B, large B or B<sub>100</sub>, constitutes the apo B found in LDL and very-low-density lipoproteins (VLDL). Because LDL and VLDL each contains one molecule of apo B, measurement of apo B reflects the total number of these atherogenic particles, 90% of which are LDL. Because LDL particles can vary in size and in cholesterol content, for a given concentration of LDL-C, there can be a wide variety in 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 LDL concentration.

#### APOLIPOPROTEIN AI

HDL contains two associated apolipoproteins (i.e., AI, AII). HDL particles can also be classified by whether they contain apo AI only or whether they contain apo AI and apo AII. All lipoproteins contain apo AI, and some also contain apo AII. Because all HDL particles contain apo AI, 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.

Direct measurement of apo AI has been proposed as more accurate than the traditional use of HDL level in the evaluation of the cardioprotective, or "good," cholesterol. In addition, the ratio of apo B/apo AI 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 VLDLs 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 apolipoprotein E (APOE) is polymorphic, consisting of three epsilon alleles (e2, e3, e4) that code for three 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 LDL receptors. The genotype of apo E alleles can be assessed by gene amplification techniques, or the APOE phenotype can be assessed by measuring plasma levels of apo E.

It has been proposed that various APOE genotypes are more atherogenic than others, and that APOE measurement may provide information on risk of CAD above traditional risk factor measurement. It has also been proposed that the APOE 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. APOE genotype may be one factor that determines an individual's degree of response to interventions such as statin therapy.

#### 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 or density and/or on apolipoprotein composition. Using size or density, HDL can be classified into HDL<sub>2</sub>, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL<sub>3</sub>, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (e.g., HDL<sub>2</sub>, HDL<sub>3</sub>) is direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance spectroscopy (NMRS) or by gradient-gel electrophoresis. HDL particle numbers can be measured by NMRS. 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 one 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 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 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 [ATP III]) to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein, and a prothrombotic state. Presence of the metabolic syndrome is considered by ATP III to be a substantial risk-enhancing factor for 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 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, cardiac risk may be further enhanced when the particles are smaller versus larger.

#### LIPOPROTEIN (A)

Lipoprotein (a) (Lp[a]) is a lipid-rich particle similar to LDL. Apo B is the major apolipoprotein associated with LDL; in Lp (a), however, there is an additional apo A covalently linked to the apo B. The apo A molecule is struc-

turally 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

##### BRAIN NATRIURETIC PEPTIDE

BNP is an amino acid polypeptide secreted primarily by the ventricles of the heart when 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. BNP 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.

##### LEPTIN

Leptin is a protein secreted by fat cells that has been found to be elevated in heart disease. Leptin has been studied to determine if it has any relation to the development of CVD.

#### **Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) 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 CLIA. Laboratories that offer LDTs must be licensed by 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.

#### **Related Protocols**

Cardiovascular Risk Panels

Genetic Testing for Alzheimer Disease

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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