Cardiovascular Disease Risk Tests

**Background**

Novel cardiovascular disease risk tests are developed with the expectation that more extensive testing will enhance disease risk stratification, encourage patient compliance and help predict response to medical therapy. These tests include novel lipid factors, genetic variant testing and other independent laboratory tests, such as fibrinogen and Cystatin-C.

**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 low-density lipoprotein (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 LDL concentration.

**Apolipoprotein AI:** HDL contains two associated apolipoproteins, i.e., AI and AII. HDL particles can also be classified by whether they contain apolipoprotein AI (apo AI) only or whether they contain both apo AI and AII. All lipoproteins contain apo AI and some also contain apo AII. Since 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 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 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 apolipoprotein E (APOE) gene is polymorphic, consisting of 3 epsilon 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 (APOE) phenotype can be assessed by measuring plasma levels of apolipoprotein E.

It has been proposed that various (APOE) genotypes are more atherogenic than others and that (APOE) measurement may provide information on risk of coronary artery disease above traditional risk factor measurement. It has also been proposed that the (APOE) genotype may be useful in the selection of specific
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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.

**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 whether 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.

**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.

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 AI has used measurement of HDL particle number as a surrogate, based on the premise that each HDL particle contains one apo AI 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.
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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. Patients with a positive test for the LPA genetic variant rs3798220 have a higher risk for thrombosis and therefore may derive greater benefit from the anti-thrombotic properties of aspirin. As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment.

**Long Chain Fatty Acids:** Long chain Omega-3 fatty acids can be measured in the blood and have been promoted as a cardiac disease risk factor. Ingestion of Omega-3 fatty acids has been shown to be beneficial in decreasing the growth rate of atherosclerotic plaque. Consumption of omega-3 fatty acids, either by eating fish or taking fish oil supplements, has also been studied as a factor in stroke, arrhythmias and sudden death.

**Fibrinogen:** Fibrinogen is the most abundant clotting protein in circulation. It is a 300-kDa glycoprotein synthesized in the liver and is a precursor of fibrin. It is important in platelet aggregation and a determinant of blood viscosity. Serum fibrinogen levels increase during periods of inflammation. Fibrinogen has been used as an inflammatory marker and has been studied as a cardiovascular disease risk factor.

**Cystatin C:** Cystatin C or cystatin 3 is a small protein encoded by the CST3 gene and is typically used as a biomarker of kidney function. Because of the relationship between renal disease and cardiovascular disease, Cystatin C has been recently studied for its role in predicting the risk of new-onset cardiovascular disease.

**Lipoprotein-Associated Phospholipase A2:** Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with low-density lipoproteins. Accumulating evidence has suggested that Lp-PLA2 is a biomarker of coronary artery disease and may have a pro-inflammatory role in the progression of atherosclerosis.

**Genotyping for 9p21 Single Nucleotide Polymorphisms:** A number of highly correlated single nucleotide polymorphisms (SNPs) found in the chromosome 9 region p21 locus (9p21) have been significantly associated with myocardial infarction (MI), particularly early onset MI, and other manifestations of cardiovascular disease (CVD). Associations with abdominal aortic aneurysm and with intracranial aneurysm have also been reported. Genotyping for 9p21 SNPs may be offered as an approach to identify patients who may be at increased risk of some of these outcomes.

**KIF6 Genotyping:** Genetic testing to determine the KIF6 Trp719Arg variant status has been evaluated as a prognostic test to predict risk of future cardiovascular events and/or as a pharmacogenetic test to predict response to statin therapy, particularly in high-risk patients.

**Hereditary Hypercoagulability Factors:** Hereditary hypercoagulability factors such as factor V Leiden and prothrombin, coagulation factor II have been proposed as risk factors of cardiovascular disease. It has been reported that thrombosis plays a role in acute coronary syndromes involving both platelets and coagulation factors.

**B-Type or Brain Natriuretic Peptide (BNP):** BNP is an amino acid polypeptide which is 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 congestive heart failure and predicting cardiovascular and heart failure risk.

**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 relationship with the development of cardiovascular disease.
**Cardiovascular Disease Risk Panels**

Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate risk of cardiovascular (CV) disease. There are numerous commercially available risk panels that include different combinations of lipids, non-cardiac biomarkers, measures of inflammation, metabolic parameters, and/or genetic markers. Risk panels report the results of multiple individual tests, as distinguished from quantitative risk scores that combine the results of multiple markers into one score.

Numerous biomarkers, genetic factors and radiologic measures have been associated with increased risk of CV disease. Over 100 emerging risk factors have been proposed as useful for refining estimates of cardiovascular risk. Some general categories of these potential risk factors are as follows:

**Lipid markers.** In addition to LDL and HDL, other lipid markers may have predictive ability, including the apolipoproteins, Lipoprotein (a), lipid subfractions, and/or other measures.

**Inflammatory markers.** Many measures of inflammation have been linked to the likelihood of CV disease. High-sensitivity C-reactive protein (hs-CRP) is one example of an inflammatory marker, others include fibrinogen, interleukins, and tumor necrosis factor.

**Metabolic syndrome biomarkers.** Measures associated with metabolic syndrome, such as specific dyslipidemic profiles or serum insulin levels, have been associated with increased risk of CV disease.

**Genetic markers.** A number of mutations associated with increased thrombosis risk, such as the MTHFR mutation or the prothrombin gene mutations, have been associated with increased CV risk. In addition, numerous single-nucleotide polymorphisms (SNPs) have been associated with CV disease in large genome-wide studies.

CV risk panels may contain measures from one or all of the above categories, and may include additional measures not listed above such as radiologic markers (carotid CMT, calcium score). Some cardiovascular risk panels are relatively limited, including a few markers in addition to standard lipids. Others include a wide variety of potential risk factors from a number of different categories, often including both genetic and non-genetic risk factors. Other panels are composed entirely of genetic markers.

*Some examples of commercially available CV risk panels are as follows:*

**Health Diagnostics Cardiac Risk Panel:** MTHFR gene analysis, common variants; vitamin D, 1,25 dihydroxy; BNP; A2 (Lp-PLA2); myeloperoxidase; apolipoprotein; immune complex assay; lipoprotein, blood; electrophoretic separation and quantitation; very long chain fatty acids; total cholesterol; HDL; LDL; triglycerides; high-sensitivity CRP(hsCRP); lipoprotein (a); insulin, total; fibrinogen; apolipoprotein analysis; multiple SNPs associated with coronary artery disease (CAD)

**Genova Diagnostics CV Health Plus Genomics™ Panel:** apo E; prothrombin; factor V leiden; fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; lipoprotein (a); LP-PLA2; MTHFR gene; triglycerides, very low-density lipoprotein (VLDL); VLDL size; vitamin D; hs-CRP

**Genova Diagnostics CV Health Plus™ Panel:** fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; lipid panel; lipoprotein (a); LP-PLA2; triglycerides; VLDL; VLDL size; vitamin D; hs-CRP.

**Cleveland HeartLab CVD Inflammatory Profile:** hs-CRP, urinary microalbumin, myeloperoxidase, Lp-PLA2, F2-isoprostanes
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*Applied Genetics Cardiac Panel:* genetic mutations associated with: coronary artery disease, cytochrome p450 mutations associated with metabolism of clopidogrel, ticagrelor, warfarin, beta blockers, rivaroxaban, and prasugrel (2C19, 2C9/VKORC1, 2D6, 3A4/3A5), factor V leiden, prothrombin gene, MTHFR gene, apo-E gene

*Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel:* factor V leiden, factor V R2, Prothrombin gene, factor XIII, fibrinogen -455, PAI-1, GPIIIis (HPA-1), MTHFR, ACE I/D, Apo B, Apo E.

*Singulex® cardiac-related test panels:* Several panels of markers related to cardiac dysfunction, vascular inflammation and dysfunction, dyslipidemia, and cardiometabolic status are offered by Singulex (Alameda, CA). Some of these panels are offered in conjunction with a CV disease testing and wellness management service. The test panels use an immunoassay method referred to as “Proprietary high-precision Single Molecule Counting [SMC] technology.”

- **Cardiac Dysfunction panel:** SMC™ cTnl (high-sensitivity troponin), NT-proBNP
- **Vascular Inflammation and Dysfunction panel:** SMC™ IL-6, SMC™ IL-17A, SMC™ TNFα, SMC™ Endothelin, Lp-PLA2, hs-CRP, homocysteine, vitamin B12, folate.
- **Dyslipidemia panel:** Total Cholesterol, LDL-C (direct), apo B, sdLDL, HDL-C, apo A-1, HDL2b, triglycerides, Lp(a)
- **Cardiometabolic panel:** parathyroid, vitamin D, calcium, magnesium, leptin, adiponectin, ferritin, cortisol, cystatin C, hemoglobin A1c, glucose, insulin, thyroid-stimulating hormone (TSH), T3 and free T4, uric acid, liver panel, renal panel, thyroid peroxidase antibody, thyroglobulin antibody.

In addition to panels that are specifically focused on CV risk, a number of commercially available panels include markers associated with CV health, along with a range of other markers that have been associated with inflammation, thyroid disorders and other hormonal deficiencies, and other disorders. Examples of these panels include:

- **Singulex Cardiometabolic Panel:** described above.
- **WellnessFX (San Francisco, CA) Premium:** total cholesterol, HDL, LDL, triglycerides, Apo AI, Apo B, LP(a), Lp-PLA2, omega-3 fatty acids, free fatty acids, lipid particle numbers, lipid particle sizes, blood urea nitrogen/creatinine, aspartate aminotransferase and alanine aminotransferase, total bilirubin, albumin, total protein, dehydroepiandrostosterone, free testosterone, total testosterone, estradiol, sex hormone binding globulin, cortisol, insulin-like growth factor 1, insulin, glucose, hemoglobin A1c, total T4, T3 uptake, free T4 index, TSH, total T3, free T3, reverse T3, free T4, hs-CRP, fibrinogen, homocysteine, complete blood count with differential, calcium, electrolytes, bicarbonate, ferritin, total iron binding capacity, vitamin B12, red blood cell magnesium, 25-hydroxy vitamin D, progesterone, follicle-stimulating hormone, luteinizing hormone.

**Related Policies:**
Carotid Intimal-Medial Thickness
Computed Tomography to Detect Coronary Artery Calcification
Gene Expression Testing to Predict Coronary Artery Disease
ST2 Assay for Chronic Heart Failure

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

**Policy**
Measurement of cardiovascular disease risk factors (i.e., apolipoprotein B, apolipoprotein AI, apolipoprotein E, LDL subclass, HDL subclass, lipoprotein[a], lipoprotein-associated
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phospholipase A2 [Lp-PLA2], genomic markers including genotyping for 9p21 SNPs, rs3798220 allele, and KIF6, hereditary hypercoagulability factors, long chain fatty acids, fibrinogen, cystatin C, leptin, Brain Natriuretic Peptide) is considered investigational as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease. BCBSNC does not provide coverage for investigational services or procedures.

Cardiovascular disease risk panels are considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

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.

When Cardiovascular Disease Risk Tests are covered

Not Applicable.

When Cardiovascular Disease Risk Tests are not covered

Measurement of cardiovascular risk factors (i.e., apolipoprotein B, apolipoprotein A1, apolipoprotein E, LDL subclass, HDL subclass, lipoprotein[a], long chain fatty acids, fibrinogen, genomic markers, cystatin C) is considered investigational as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease.

Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) in the assessment of cardiovascular risk is considered investigational.

The use of genotyping for 9p21 single nucleotide polymorphisms is considered investigational, including but not limited to, identification of patients who may be at increased risk of cardiovascular disease or its manifestations (e.g., MI, ischemic stroke, peripheral arterial disease, coronary artery calcification), or identification of patients who may be at increased risk for aneurysmal disease (abdominal aortic aneurysms, intracranial aneurysms, polypoidal choroidal vasculopathy).

The use of genetic testing for the rs3798220 allele (LPA-Aspirin Check®) is considered investigational in patients who are being considered for treatment with aspirin to reduce risk of cardiovascular events.

KIF6 Genotyping is considered investigational for predicting cardiovascular risk and/or the effectiveness of statin therapy.

Measurement of hereditary hypercoagulability factors is considered investigational for predicting cardiovascular disease risk.

Measurement of Brain Natriuretic Peptide (BNP) is considered investigational for predicting cardiovascular disease risk.

Measurement of leptin is considered investigational for predicting cardiovascular disease risk.

Cardiovascular risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk, are considered investigational.

Policy Guidelines

Numerous non-traditional lipid and other biomarker measurements have been proposed for use in
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improving risk prediction for cardiovascular disease, including apo B, apo A-1, the ratio of apo B/apo A-1, apo E, lipoprotein A, and subclasses of LDL and HDL, B-type natriuretic peptide cystatin C, fibrinogen and leptin. In general, there is evidence that some of these markers may provide some incremental accuracy in risk prediction. However, it has not been established that 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.

Some markers, e.g. apo B, have also been proposed as treatment targets for lipid-lowering therapy. While some evidence supports that they may be accurate in predicting residual risk for patients on lipid lowering therapy, there is no high-quality evidence that these markers lead to health outcome improvements when used in place of traditional lipid targets, such as LDL. Because of the deficiencies in the literature around these issues, the use of these novel lipid risk markers remains investigational.

There is a large body of literature evaluating Lp-PLA2 as a predictor of cardiovascular risk. These studies demonstrate that Lp-PLA2 is an independent predictor of cardiovascular disease. To improve outcomes, clinicians must have the tools to incorporate emerging risk factors into existing risk prediction models, and these models should demonstrate improved classification into risk categories that will lead to more appropriate treatment. Although Lp-PLA2 levels have been shown to be associated with cardiovascular disease risk, the changes in patient management that would occur as a result of obtaining Lp-PLA2 levels in practice are not well-defined. The available evidence is insufficient to determine that the use of Lp-PLA2 for risk stratification for cardiovascular disease improves the net health outcome.

The Berkeley HeartLab offers the 9p21-EarlyMICheck™ Genotype Test, which detects the rs10757278 A>G and rs1333049 G>C SNPs within the 9p21 locus of chromosome. It is suggested that the test may help identify patients at increased risk for early onset myocardial infarction, for abdominal aortic aneurysm, and for myocardial infarction / coronary heart disease in general, allowing providers to characterize and reduce other contributing risk factors.

Cardiac risk genotyping panels offered by other laboratories may include and individually report 9p21 SNP results. For example, the deCODE MI™ test genotypes 9p21.3 rs10757278 in addition to 7 other SNPs from other chromosomal loci to estimate the risk of coronary heart disease and MI.

LPA-Aspirin Check® is a commercially available genetic test (Berkeley HeartLab, a Genetic Diagnostics service) that detects the presence of the rs3798220 allele. Patients with a positive test for rs3798220 have a higher risk for thrombosis, and therefore may derive more benefit from the anti-thrombotic properties of ASA. It has been proposed that the additional information obtained from the LAP-Aspirin Check® test may aid physicians in better estimating the benefit/risk of ASA therapy, and therefore may aid in deciding whether to prescribe ASA for individual patients. The LPA-Aspirin Check® test has not been cleared or approved by the U.S. Food and Drug Administration (FDA).

The data supporting the association of the KIF6 rs20455 single nucleotide polymorphism (SNP), corresponding to an arginine-to-tryptophan substitution at position 719 (Trp719Arg), with CAD outcomes are contradictory. The most recent evidence from large populations at different levels of vascular risk do not support a significant association with future CAD outcomes. Moreover, the biologic function of the KIF6 gene product protein is currently unknown. Thus, the clinical validity for the KIF6 genotyping test has not been shown. Celera Corporation, now a wholly owned subsidiary of Quest Diagnostics, Inc., holds a U.S. patent relating to methods of determining heart attack risk by detecting the KIF6 gene variant and reduction of such increased risk by statin therapy, and offers the “Cardio IQ™ KIF6 Genotype”. Celera's Berkeley HeartLab (BHL) subsidiary has been offering KIF6 genotyping (KIF6-StatinCheck™ Genotype Test) since July 2008.

In 2010, the independent Evaluation of Genomic Applications in Practice and Prevention (EGAPP™) Working Group determined that there was not enough evidence to indicate whether cardiogenomic profiles should or should not be used in the general population to determine people’s risk for...
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developing cardiovascular disease. The EGAPP Working Group discouraged the use of these profiles except in research settings. There was no definite demonstration that the tests were useful for medical or personal decision-making.

The EGAPP recommendation statement was based on the following key points:

- Using genomic markers in combination with traditional risk factors was not found to lead to improved outcomes for the treatment of cardiovascular disease.
- Health improvements could theoretically be made with preventive medical or behavior changes (such as screening, change of diet, increase of exercise, weight loss, and smoking cessation), but none of the evidence showed health improvements as a direct result of using these tests.
- Further development and evaluation of these technologies and evidence that supports added value in predicting clinical outcomes from these tests is needed.

Despite a correlation with cardiac risk, there is insufficient scientific evidence in the published literature regarding how measurements of omega-3 fatty acid composition would affect management and improve clinical outcomes of individuals at risk for or patients with CHD.

The evidence for the use of cardiovascular (CV) risk panels in individuals who have risk factors for CV disease includes multiple cohort and case-control studies and systematic reviews of these studies. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in CV risk panels are associated with increased risk of CV disease. However, it is not clear how the results of individual risk factors impact management changes, so it is also uncertain how the panels will impact management decisions. Given the lack of evidence for clinical utility of any individual risk factor beyond simple lipid measures, it is unlikely that the use of CV risk panels improves outcome. Studies that have evaluated the clinical validity of panels of multiple markers have not assessed management changes that would occur as a result of testing, or demonstrated improvements in outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy 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. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81105, 81106, 81107, 81108, 81109, 81110, 81111, 81112, 81240, 81241, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 82172, 82610, 82726, 83695, 83698, 83880, 83700, 83701, 83704, 85384, 0111T, 0423T, 0024U

Codes 82172, 83701, 83704 are always investigational.

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.

There is no specific code for genotyping for 9p21 single nucleotide polymorphisms. The unlisted code 81479 may be used.

There is no specific code for genetic testing for the rs3798220 allele. The unlisted code 81479 may be used.
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There is no specific code for genetic testing for KIF6 genotyping. The unlisted code 81479 may be used.

There is no specific CPT code for Leptin. CPT code 83520 or 82397 may be used.

Diagnosis codes: 250, 250.0, 250.00, 250.01, 250.02, 250.03, 250.1, 250.10, 250.11, 250.12, 250.13,250.2, 250.20, 250.21, 250.22, 268.9, 272, 272.0, 272.1, 272.2, 272.3, 272.4, 272.5, 272.6, 272.7, 272.8, 272.9, 278, 278.0, 278.00, 278.01, 278.02, 278.03, 278.1, 278.2, 401, 401.0, 401.1, 401.9, 402, 402.1, 402.10, 402.11, 402.9, 402.90, 402.91, V70.0, V12.5, V12.50, V12.51, V12.52, V12.53, V12.54, V12.55, V12.59, V17.2, V17.4, V17.41, V17.49, V17.6, V17.60, V17.62, V17.69, V17.7, V17.71, V17.78, V17.9, V77.91, V77.99, V81, V81.0, V81.1, V81.2

ICD-10 diagnosis codes: E78.00, E78.01, E78.1, E78.2, E78.3, E78.4, E78.5, E78.6, E88.1, E75.21, E75.22, E75.240, E75.241, E75.242, E75.243, E75.248, E75.249, E77.0, E77.1, E78.81, E78.89, E88.89, E78.9, E66.9, E66.01, E66.3, E66.2, E65, E67.0, I110, I10, I10, Z00.00, Z00.01, Z86.79, Z86.711, Z86.711, Z86.79

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For policy titled, “Novel Lipid Risk Factors in Risk Assessment of Cardiovascular Disease”


Senior Medical Director review 7/2010


Specialty Matched Consultant Advisory Panel review 4/2012

For policy re-titled, “Cardiovascular Disease Risk Tests”


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Medical Director review 8/2012


Specialty Matched Consultant Advisory Panel review 4/2013


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Medical Director review 5/2013


Medical Director review 11/2013


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Medical Director review 4/2017

Policy Implementation/Update Information

For policy titled, “Novel Lipid Risk Factors in Risk Assessment of Cardiovascular Disease”

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 recommended for risk assessment of cardiovascular disease. (mco)


For policy re-titled, “Cardiovascular Disease Risk Tests”

10/1/12  Evidence Based Guideline converted to Corporate Medical Policy. Policy re-titled from “Novel Lipid Risk Factors in Risk Assessment of Cardiovascular Disease” to “Cardiovascular Disease Risk Tests.” Measurement of cardiovascular risk factors, (i.e., apolipoprotein B, apolipoprotein A-I, apolipoprotein E, LDL subclass, HDL subclass, lipoprotein[a], long chain fatty acids,) is considered investigational as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease. References updated. Description and Policy Guidelines sections updated. Medical Director review 8/2012. Notification given 10/1/12 for effective date 1/1/2013. (mco)

1/29/13  Policy Statement revised from “Measurement of cardiovascular risk factors for assessment of cardiovascular risk is considered investigational.” to “Measurement of cardiovascular risk factors (i.e., apolipoprotein B, apolipoprotein A-I, apolipoprotein E, LDL subclass, HDL subclass, lipoprotein[a], long chain fatty acids, fibrinogen, cystatin C) is considered investigational as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease. BCBSNC does not provide coverage for investigational services or procedures.” Added the following codes to the Billing/Coding section: 278.01, 278.02, 278.03, V12.50, V12.51, V12.52, V12.53, V12.54, V12.55 and V12.59. (mco)

5/14/13  Specialty Matched Consultant Advisory Panel review 4/2013. This policy now consolidates the following policies: “Lipoprotein-associated Phospholipase A2”, “Genotyping for 9p21 Genetic Polymorphisms to Predict Cardiovascular Disease Risk”, “Genetic Testing for Lipoprotein (a) as a Decision Aid for Aspirin Treatment”, and “KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy.” Added information regarding Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2), genotyping for 9p21 SNPs, testing for rs3798220 allele and KIF6 Trp719Arg variant to Description and Policy Guidelines. Added the following statements to the “When not Covered” section: “Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2)in the assessment of cardiovascular risk is considered investigational.”; “The use of genotyping for 9p21 single nucleotide polymorphisms is considered investigational, including but not limited to, identification of patients who may be at increased risk of cardiovascular disease or its manifestations (e.g., MI, ischemic stroke, peripheral arterial disease, coronary artery calcification), or identification of patients who may be at increased risk for aneurysmal disease (abdominal aortic aneurysms, intracranial aneurysms, polypoidal choroidal
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vasculopathy).”; “The use of genetic testing for the rs3798220 allele (LPA-Aspirin Check®) is considered investigational in patients who are being considered for treatment with aspirin to reduce risk of cardiovascular events.”; “KIF6 Genotyping is considered investigational for predicting cardiovascular risk and/or the effectiveness of statin therapy.”

6/11/13 Policy statement revised to state: “Measurement of cardiovascular risk factors (i.e., apolipoprotein B, apolipoprotein A-I, apolipoprotein E, LDL subclass, HDL subclass, lipoprotein[a], lipoprotein-associated phospholipase A2 [Lp-PLA2], genomic markers including genotyping for 9p21 SNPs, rs3798220 allele, and KIF6, hereditary hypercoagulability factors, long chain fatty acids, fibrinogen, cystatin C) is considered investigational as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease. BCBSNC does not provide coverage for investigational services or procedures.” “When not Covered” section updated to include the following statements: “Measurement of cardiovascular risk factors (i.e., apolipoprotein B, apolipoprotein A-I, apolipoprotein E, LDL subclass, HDL subclass, lipoprotein[a], long chain fatty acids, fibrinogen, genomic markers, cystatin C) is considered investigational as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease.” and “Measurement of hereditary hypercoagulability factors is considered investigational for predicting cardiovascular disease risk.” Description section updated. Policy Guidelines updated. Added the following CPT codes to the Billing/Coding section: 81250, 81241, 81240, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408. Medical Director review 5/2013. Notification given June 11, 2013 for effective date August 13, 2013. (mco)

7/1/13 ICD-10 diagnosis codes added to “Billing/Coding” section. Policy remains on notification for effective date August 13, 2013. (mco)

12/10/13 Description section updated. Added the following Policy Statements: “Cardiovascular disease risk panels are considered investigational. BCBSNC does not provide coverage for investigational services or procedures.” Added the following tests as investigational: Brain Natriuretic Peptide and Leptin. Added the following statements to the “When not Covered” section: “Measurement of Brain Natriuretic Peptide (BNP) is considered investigational for predicting cardiovascular disease risk. Measurement of leptin is considered investigational for predicting cardiovascular disease risk. Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk, are considered investigational.” Policy Guidelines updated. References updated. Added the following codes to the “Billing/Coding” section: Diagnosis codes 250, 250.0, 250.00, 250.01, 250.02, 250.03, 250.1, 250.10, 250.11, 250.12, 250.13, 250.2, 250.20, 250.21, 250.22, 268.9, 402, 402.1, 402.10, 402.11, 402.9, 402.90, 402.91, V17.2, V17.4, V17.41, V17.49, V72.6, V72.60, V72.62, V72.69, V77, V77.1, V77.8, V77.9, V77.91, V77.99, V81, V81.0, V81.1, V81.2. Added CPT code 83880. Added the following statement: “There is no specific CPT code for Leptin. CPT code 83520 or 82397 may be used.” Medical Director review 11/2013. Policy noticed 12/10/13 for effective date 2/11/14. (mco)

4/1/14 Policy Guidelines updated. References updated. No changes to Policy Statements. (mco)


6/10/14 Added the following statement to Policy Guidelines: “The LPA-Aspirin Check® test has not been cleared or approved by the U.S. Food and Drug Administration (FDA).” References updated. Removed effective date for ICD-10 codes from Billing/Coding section. (mco)

11/25/14 References updated. No changes to Policy Statement. (td)
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12/30/14 Code 83006 to the Billing/Coding section effective 1/1/15. (td)


7/28/15 References updated. (td)

10/30/15 Billing/Coding section updated to reorder codes for clarity. Codes 82172, 83701, 83704 are always investigational. Policy Guidelines section updated. References updated. Policy noticed 10/30/15 for effective date 12/30/15. (td)

12/30/15 Billing/Coding section updated to add code 0423T; effective 1/1/16. (td)

1/26/16 References updated. (td)


9/30/16 Under “Billing/Coding” section, deleted ICD-10 code E.78.0 and added the following ICD-10 codes for effective date 10/1/16: E78.00, E78.01. (jd)

1/27/17 References updated. Medical Director review 12/2016. (jd)


12/29/17 Codes 81105, 81106, 81107, 81108, 81109, 81110, 81111, 81112, 0024U added to code section, effective 1/1/18. (jd)

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