BlueCross BlueShield Nebraska

CARDIOVASCULAR RISK PANELS AND BIOMARKERS (RECOMMEND PREAUTHORIZATION)

V.19

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DESCRIPTION

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, noncardiac 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 1 score.

The evidence for the use of 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.

Accumulating evidence has suggested that Lp-PLA_2 is a biomarker of coronary artery

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

Dates

Original Effective
09-24-2014
Last Review
08-07-2024
Next Review
08-11-2025

POLICY

I. Cardiovascular risk panels* and biomarkers (see guidelines below), for the risk assessment and management of cardiovascular disease, including but not limited to, measurement of novel lipid and non-lipid biomarkers (i.e., apolipoprotein B, apolipoprotein AI, apolipoprotein I, low-density lipoprotein subclass, high-density lipoprotein subclass, cystatin C, fibrinogen, leptin) is considered **investigational** as an adjunct to low-density lipoprotein cholesterol.
II. Measurement of lipoprotein-associated phospholipase A2 (83698, 0052U) is considered **investigational**.

GUIDELINES

A simple lipid panel (80061) is generally composed of the following lipid measures:

- Total cholesterol (82465)
- LDL cholesterol (83721)
- HDL cholesterol (83718)

reported as part of a simple lipid panel.

Other types of lipid testing, ie, apolipoproteins, lipid particle number or particle size, lipoprotein (a), etc., are not considered to be components of a simple lipid profile.

This policy does not address the use of panels of biomarkers in the diagnosis of acute myocardial infarction.

*Some examples (not all inclusive) of commercially available Cardiovascular risk panels are as follows:

- Advanced Lipid Panel
- Algorithmically scored multi-protein biomarker panels
- Applied Genetics Cardiac Panel
- Applied Genetics Cardiac Panel
- Atherotech® Diagnostics Lab CVD Risk Panel and VAP Lipid Panel
- Berkeley Heart Lab Cardio IQ™
- Boston Heart Advanced Risk Markers Panel
- Boston Heart Cholesterol Balance Test
- Boston Heart HDL Map panel
- Cleveland HeartLab CVD Inflammatory Profile
- CV Health Plus Genomics Panel
- CV Health Plus Panel
- CVD Inflammatory Profile
- Genetiks Genetics Diagnosis and Research Center Cardiovascular Risk Panel
- Genova Diagnostic CV Health Plus Genomics™ Panel
- Health Diagnostics Cardiac Risk Panel
- Metametrix Cardiovascular Health Profile
- OmegaCheck Panel
- Singulex
- True Health Diagnostics

BACKGROUND

Cardiovascular disease (CVD) remains the single largest cause of morbidity and mortality in the developed world. Mortality from CVD has accounted for 1 in 4 deaths in the United States, and there are numerous socio-economic factors that affect CVD mortality rates.[1,] Lower-income, race, age, and behavioral factors all have a significant impact on health outcome disparities associated with CVD.

As a result, accurate prediction of CVD risk is a component of medical care that has the potential to focus on and direct preventive and diagnostic activities. Current methods of risk prediction in use in general clinical care

Components of CVD risk include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. Also, numerous laboratory tests have been associated with CVD risk, most prominently lipids such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL). These clinical and lipid factors are often combined into simple risk prediction instruments, such as the Framingham Risk Score.[1] The Framingham Risk Score provides an estimate of the 10-year risk for developing cardiac disease and is currently used in clinical care to determine the aggressiveness of risk factor intervention, such as the decision to treat hyperlipidemia with statins.

Many additional biomarkers, genetic factors, and radiologic measures have been associated with an increased risk of CVD. Over 100 emerging risk factors have been proposed as useful for refining estimates of CVD 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) (Lp[a]), lipid subfractions, and/or other measures.
- **Inflammatory markers.** Many measures of inflammation have been linked to the likelihood of CVD. High-sensitivity C-reactive protein (hs-CRP) is an example of an inflammatory marker; others include fibrinogen, interleukins, and tumor necrosis factor.
- **Metabolic syndrome biomarkers.** Measures associated with metabolic syndromes, such as specific dyslipidemic profiles or serum insulin levels, have been associated with an increased risk of CVD.
- **Genetic markers.** A number of variants associated with increased thrombosis risk, such as the 5,10-methylene tetrahydrofolate reductase (MTHFR) variant or the prothrombin gene variants, have been associated with increased CVD risk. Also, numerous single nucleotide variants have been associated with CVD in large genome-wide studies.

Risk Panel Testing

Cardiovascular disease risk panels may contain measures from 1 or all of the previous categories and may include other measures not previously listed such as radiologic markers (carotid medial thickness, coronary artery calcium score). Some CVD 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 nongenetic risk factors. Other panels are composed entirely of genetic markers.

Low-density lipoproteins (LDLs) have been identified as 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 low-density lipoprotein cholesterol, 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 low-density lipoprotein cholesterol.

Other non-lipid markers have been identified as being associated with cardiovascular disease (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 therapy. In the United States, social, biological, and environmental disparities exist in the prevalence, morbidity, and mortality rates that are associated with CVD.[1,] Population subgroups that are most significantly adversely affected by such disparities included Black and Hispanic Americans, individuals with low socioeconomic status, and individuals who live in rural settings.

Treatment

Although treatment for elevated coronary disease risk with statins targets cholesterol levels, selection for treatment involves estimation of future CAD risk using well-validated prediction models that use additional variables.

Lipid Markers

Apolipoprotein B

Apolipoprotein (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 LDL. Because LDL and very-low density LDL each contain 1 molecule of apo B, the 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

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 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 (ie, “bad”) cholesterol to anti-atherogenic (ie, “good”) cholesterol.

Apolipoprotein E

Apolipoprotein E is the primary apolipoprotein found in very-low density LDLs and chylomicrons. Apolipoprotein 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, 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 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 the risk of CAD beyond 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. The *APOE* genotype may be a factor that determines an individual’s degree of response to interventions such as statin therapy.

High-Density Lipoprotein Subclass

High-density lipoprotein 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_2, the larger, less dense particles that may have the greatest degree of cardio protection, and HDL_3, which are smaller, denser particles.

or by gradient-gel electrophoresis. High-density lipoprotein particle numbers can be measured by nuclear magnetic resonance spectroscopy. 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 a single apo AI molecule.

Low-Density Lipoprotein 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 common 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) to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein, and a prothrombotic state. The presence of the metabolic syndrome is considered by Adult Treatment Panel III to be a substantial risk-enhancing factor for CAD.

Low-density lipoprotein 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 the risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profiles 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

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, the cardiac risk may be further enhanced when the particles are smaller versus larger.

Lipoprotein (a)

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with LDLs. Accumulating evidence has suggested that Lp-PLA_2 is a biomarker of CAD and may have a proinflammatory role in the progression of atherosclerosis. Recognition that atherosclerosis represents, in part, an inflammatory process has created considerable interest in the measurement of pro-inflammatory factors as part of cardiovascular disease risk assessment.

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

Interest in Lp-PLA_2 as a possible causal risk factor for CAD has generated the development and testing of Lp-PLA_2 inhibitors as a new class of drugs to reduce the risk of CAD. However, clinical trials of Lp-PLA_2 inhibitors have not shown significant reductions in CAD endpoints. Furthermore, assessment of Lp-PLA_2 levels has not been used in the selection or management of subjects in the clinical trials.

Non-Lipid Markers

Brain Natriuretic Peptide

Brain natriuretic peptide (BNP) is an amino acid polypeptide secreted primarily by the ventricles of the heart when the 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

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 have been found to be elevated in heart disease. Leptin has been studied to determine if it has any relation to the development of CVD.

Quick Code Search

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+ **CPT-PLA**

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REVISIONS

08-15-2024

Removed 83880 from policy

02-01-2024

0119U moved to policy V.74

12-01-2023

Policy title updated - Cardiovascular Risk Panels and Biomarker

Codes updated - added: 83090, 83698, 83880, 83876, 0052U, 0119U, 82610, 82664, 83695, 83700, 83701, 83704, 85384, 85385, 82163, 84206, 84681, 83719

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Added new 2019 code 83722