Cardiovascular Disease Risk Tests

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DESCRIPTION

Cardiovascular disease (CVD) remains the single largest cause of morbidity and mortality. As a result, accurate prediction of CVD risk is a component of medical care that has the potential to focus and direct preventative and diagnostic activities. Current methods of risk prediction in use in general clinical care are not highly accurate and, as a result, there is a potential unmet need for improved risk prediction instruments.

Components of cardiovascular disease (CVD) risk include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. Numerous laboratory tests have been proposed as potential risk markers for CVD to include lipid and non-lipid biomarkers (inflammatory markers and metabolic markers). These biomarkers include but are not limited to 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, homocysteine, 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. Also, these biomarkers are utilized in

different combinations in cardiovascular risk panels to evaluate the risk of CVD. The cardiovascular risk panel's report the results of multiple individual tests (lipid markers, inflammatory markers, metabolic syndrome markers and genetic markers) as distinguished from quantitative risk scores that combine the results of multiple markers into a single score.

Clinical risk factors and biomarkers such as lipid markers are often combined into simple risk prediction instruments, such as Framingham Risk Score. 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.

There is a large amount of literature on the association of individual risk factors with cardiovascular disease (CVD). Most of this literature evaluates correlations between individual biomarkers and the presence of, or future development of, CVD. A framework for the evaluation of the clinical utility of risk factor assessment includes the following steps:

1. Standardization of the measurement of the risk factor.
2. Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor independently contributes to risk assessment compared with established risk factors. Also, because there are many potential novel risk factors that could be incorporated into existing CVD risk panels, it is important to understand the relation between each risk factor and other risk factors.
3. Determination of how the novel risk assessment will be used in the management of the patient, compared with standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

Novel Biomarkers in Asymptomatic Individuals with Risk of Cardiovascular Disease

Low-density lipoproteins (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.

Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease (CVD). 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.

A large body of literature has accumulated on the utility of novel lipid risk factors in the prediction of future cardiac events. The evidence reviewed herein consists of systematic reviews, meta-analyses, and large, prospective cohort studies that have evaluated the association between these lipid markers and cardiovascular outcomes. A smaller amount of literature is available on the utility of these markers as a marker of treatment response. Data on treatment response are taken from RCTs that use one or more novel lipid markers as a target of lipid-lowering therapy.

The Adult Treatment Panel III (ATP III) guidelines noted that, to determine their clinical significance, emerging risk factors should be evaluated against the following criteria:

- Significant predictive power that is independent of other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk.

Clinical Context and Test Purpose
The purpose of novel cardiac biomarker testing is to provide an alternative or superior method for diagnosing cardiovascular disease (CVD) to inform a decision to proceed with appropriate treatment for patients who are asymptomatic with a risk of CVD.

Populations
The relevant population of interest are individuals who are asymptomatic with a risk of cardiovascular disease (CVD).

Interventions
The intervention being considered is novel cardiac biomarker testing, which would be managed by cardiologists and primary care providers in an outpatient clinical setting.

Comparators
Comparators of interest include routine care without biomarker testing.

Patients who are asymptomatic with a risk of cardiovascular disease (CVD) are actively managed by cardiologists and primary care providers in an outpatient setting.

Outcomes
The general outcomes of interest are overall survival (OS), other test performance measures, change in disease status, morbid events, and medication use.

Follow-up at 1 and 6 years are of interest for novel cardiac biomarker testing for OS, other test performance measures, change in disease status, morbid events, and medication use.

Lipid Markers

Lipid Marker	Description
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-LDL. Because LDL and very-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	High-density lipoprotein contains 2 associated apolipoproteins (ie, AI, AII). High-density lipoprotein particles can also be classified by whether they contain apo AI only or 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 (ie, "bad") cholesterol to anti-atherogenic (ie, "good") cholesterol.
Apolipoprotein E	Apolipoprotein E is the primary apolipoprotein found in very-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 1 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 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. 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 cardioprotection, and HDL_3, which are smaller, denser particles. An alternative to measuring the concentration of subclasses of HDL (eg, HDL_2, HDL_3) is a direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance spectroscopy 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 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, the cardiac risk may be further enhanced when the particles are smaller versus larger.
Lipoprotein (a)	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 the 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.

Apolipoprotein B (apo B)
The evidence has suggested that apo B provides independent information on risk assessment for CVD and that apo B may be superior to LDL-C in predicting cardiovascular risk. Numerous large prospective cohort studies and nested case-control studies have compared these measures, and most have concluded that apo B is a better predictor of cardiac risk than LDL-C. However, some meta-analyses have concluded that apo B is not a better predictor of cardiac risk than HDL or non-HDL combined with LDL. There is also greater uncertainty about the degree of improvement in risk prediction and whether the magnitude of improvement is clinically significant. While there have been attempts to incorporate apo B into multivariate risk prediction models, at present, apo B is not included in the models most commonly used in routine clinical care, such as the Framingham risk model and the Prospective Cardiovascular Munster Study Score.

As a marker of response to cholesterol-lowering treatment, apo B may be more accurate than LDL-C and may provide a better measure of the adequacy of anti-lipid therapy than LDL-C. Post hoc analyses of RCTs of statin treatment have reported that on-treatment levels of apo B are more highly correlated with clinical outcomes than standard lipid measures. Whether the degree of improvement in assessing treatment response is clinically significant has yet to be determined.

Currently, it is not possible to conclude that the use of apo B levels will improve outcomes 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 by using apo B in place of LDL-C for risk assessment and/or treatment response. The most widely used risk assessment models (e.g., the Framingham prediction model) and the most widely used treatment guidelines (e.g., the ATP III guidelines) do not provide the tools necessary for clinicians to incorporate apo B measurements into routine assessment and management of hyperlipidemic patients. This lack creates difficulties in interpreting and applying the results of apo B and/or apo B/apo AI measurements to routine clinical care.

Apolipoprotein A-I
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 ration 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.

The current evidence has generally indicated that measurement of apo AI and the apo B/apo AI ratio are as good as or better than currently used lipid measures such as LDL and HDL. Some experts have argued that the apo B/apo AI ratio is superior to the LDL/HDL ratio as a predictor of cardiovascular risk and should supplement or replace traditional lipid measures as both a risk marker and a treatment target. However, there is substantial uncertainty regarding the degree of improvement that these measures provide.

The evidence suggests that any incremental improvement in predictive ability over traditional measures is likely to be small and of uncertain clinical significance.

The use of apo AI and the apo B/apo AI ratio as a target of treatment response to statins may also be as good as or better than the traditional measure of LDL. However, to improve outcomes, clinicians must have the tools to translate this information into clinical practice. Such tools for linking apo AI to clinical decision making, both in risk assessment and treatment response, are currently not available. Apo AI has not been incorporated into quantitative risk assessment models or treatment guidelines that can be used in clinical practice (e.g., the ATP III). The ATP III practice guidelines continue to tie clinical decision making to conventional lipid measures, such as TC, LDL-C, and HDL-C. Therefore, it is not yet possible to conclude that these measures improve outcomes or that they should be adopted in routine clinical care. There is continued interest in developing new therapeutic agents that raise HDL, and apo AI mimetics are currently in development for this purpose.

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 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 a factor that determines an individual's degree of response to interventions such as statin therapy.

The evidence has suggested that APOE genotype may be associated with lipid levels and CAD but is probably not useful in providing additional clinically relevant information beyond established risk factors. Apo E is considered a relatively poor predictor of CAD, especially compared with other established and emerging clinical variables, and does not explain a large percentage of the interindividual variation in TC and LDL levels. Moreover, apo E has not been incorporated into standardized cardiac risk assessment models and was not identified as an important "emerging risk factor" in the most recent ATP III recommendations.

The evidence on response to treatment indicates that APOE genotype may be a predictor of response to statins and may allow clinicians to better gage a patient's chance of successful treatment, although not all studies have consistently reported this relation. At present, it is unclear how this type of information would change clinical management. Dietary modifications are a universal recommendation for those with elevated cholesterol or LDL levels, and statin drugs are the overwhelmingly preferred agents for lipid-lowering therapy. It is unlikely that a clinician would choose alternative therapies, even in the presence of an APOE phenotype that indicates diminished response.

None of the available evidence has provided adequate data to establish that APOE genotype or phenotype improves outcomes when used in clinical care.

Low-Density Lipoprotein (LDL) Subclass and Low-Density Lipoprotein Particle Size and Concentration

LDL particles are not uniform in size or density, and 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 include 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. 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.

LDL Gradient Gel Electrophoresis
LDL particle diameter can be measured using nuclear magnetic resonance or ultracentrifugation while particle density can be measured by gradient gel electrophoresis (GGE). GGE is the most commonly used lab technique.

LDL gradient gel electrophoresis (GGE) has been promoted as an important determinant of coronary heart disease (CHD) risk, and as a guide to drug and diet therapy in patients with established coronary artery disease (CAD). The measurement of LDL subclass patterns may be useful in elucidating possible atherogenic dyslipidemia in patients who have no abnormalities in conventional measurement (total cholesterol, HDL, LDL and triglycerides). However, the therapeutic usefulness of discovering such subclass abnormalities has not been substantiated.

Small LDL size is a component of an atherogenic lipid profile; other components include increased triglycerides, increased apo B, and decreased HDL. Some studies have reported that LDL size is an independent risk factor for CAD, while others have reported that a shift in LDL size may be a useful marker of treatment response.

A relatively small number of studies have evaluated the predictive ability of LDL particle size and number as measured by NMR. These studies do not demonstrate that NMR-measured particle size and/or number offer predictive ability beyond that provided by traditional lipid measures. NMR measures have been proposed as indicators of residual cardiovascular risk in patients treated with statins who have met LDL goals, but there is no evidence that these measures improve health outcomes when used for this purpose.

The direct clinical application of measuring small, dense lipoprotein particles is still unclear. To improve outcomes, clinicians must have tools to translate this information into clinical practice. Such tools for linking levels of small, dense LDL to clinical decision making are currently not available. Published data are inadequate to determine how such measurements should guide treatment decisions and whether these treatment decisions result in beneficial patient outcomes.

Lipoprotein (a)
A large amount of epidemiologic evidence has determined that Lp(a) is an independent risk factor for CVD. The overall degree of risk associated with Lp(a) levels appears to be modest, and the degree of risk may be mediated by other factors such as LDL levels and/or hormonal status.

There is considerable uncertainty regarding the clinical utility of measuring Lp(a), specifically how knowledge of Lp(a) levels can be used in clinical care of patients being evaluated for lipid disorders. There is scant evidence on the use of Lp(a) as a treatment target for patients with hyperlipidemia. The available evidence is insufficient related to impact on clinical outcomes

High Density Lipoprotein (HDL) Subclass and High-Density Particle Size and Concentration

HDL comprises several components and subclasses that also have been related to CHD risk. While HDL cholesterol is the risk indicator most often used, HDL subclasses (HDL_2 and HDL_3) have also been used for risk prediction. 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_2, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL_3, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL is direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance (NMR) spectroscopy or by gradient-gel electrophoresis. HDL particle numbers can be measured by NMR spectroscopy. Several commercial labs offer these measurements by 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 1 apo AI molecule.

One RCT has evaluated the association of HDL particle size and number as measured by NMR with residual CVD risk. While this study found an association with HDL particle (but not HDL size) and CVD, it is uncertain how NMR-measured HDL particle number would be used to change clinical management beyond information provided by traditional lipid measures.

MI-Heart Ceramides – Mayo Clinic

MI-HEART ceramides is a blood test that measures the risk of adverse cardiovascular events and quantifies plasma ceramides, which are clinically shown to be novel biomarkers of unstable atherosclerotic cardiovascular disease.

Ceramides are complex lipids that play a central role in cell membrane integrity, cellular stress response, inflammatory signaling, and apoptosis. Synthesis of ceramides from saturated fats and sphingosine occurs in all tissues. Metabolic dysfunction and dyslipidemia results in accumulation of ceramides in tissues not suited for lipid storage. Elevated concentrations of circulating ceramides are associated with atherosclerotic plaque formation, ischemic heart disease, myocardial infarction, hypertension, stroke, type 2 diabetes mellitus, insulin resistance, and obesity.

Individuals with elevated plasma ceramides are at higher risk of major adverse cardiovascular events even after adjusting for age, gender, smoking status, and serum biomarkers such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, c-reactive protein (CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2).

MI-Heart Ceramide Risk Score:

0-2 Lower risk

3-6 Moderate risk

7-9 Increased risk

10-12 Higher risk

Summary of Evidence
For individuals who are asymptomatic with risk of cardiovascular disease (CVD) who receive novel cardiac biomarker testing (e.g., apo B, apo AI, apo E, HDL subclass, LDL subclass, Lp[a], heart ceramides), the evidence includes systematic reviews, meta-analyses, and large, prospective cohort studies. 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, lipoprotein [a], heart ceramides), the evidence includes analyses of the intervention arm(s) of lipid-lowering medication trials. In particular, apo B, apo AI, apo E, and heart ceramides) 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.

Non-Lipid Markers
Note: This testing has been proposed for the determination of CVD risk and may be included in CVD risk panel testing, see information below regarding CVD risk panel testing.

Laboratory Test	Description
Albumin	Albumin is traditionally regarded as a biomarker for risk prediction in various clinical setting, such as a low albumin associated with cardiovascular mortality. Although albumin does not have specific binding sites for cholesterol, it is considered to be a regulator of cholesterol transport.

	Albumin and coronary heart events in the general population: whether albumin concentration can predict nonfatal coronary heart events is interesting but controversial issue. In the Atherosclerosis Risk in Communities (ARIC) Study, low serum albumin (SA) concentration was only associated with incident MI in individuals who were current smokers. Moreover, low SA did not provide adequate predictive power for incident coronary heart events in the older populations (aged 65–74 years). From a prospective study on the elderly (aged 65 years and older), low SA concentration was identified with a high risk for coronary heart events in women but not in men. In Zutphen Elderly Study, SA only predicted the incidences of coronary heart events among men with elevated total cholesterol. Therefore, the risk discrimination of incident coronary heart events using SA concentration is not consistent and varies with different designs of studies. It is possible that low SA concentration does have a direct causative role for incident coronary heart events but could be an indicator of an underlying condition. The measurement of albumin is widely available and popular in current medical institutes because of its perceived reliability and low cost. While studies have shown the application of albumin in comprehensive cardiovascular fields, tailored therapies such as nutritional intervention and direct albumin administration in individuals with low albumin considered as high-risk groups should be investigated with randomized controlled trials (RCTs) to understand its clinical efficacy and safety. The current evidence is insufficient in demonstrating that the use of albumin testing in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
Brain Natriuretic Peptide (BNP)	Brain natriuretic peptide (BNP) is an amino acid polypeptide that is secreted primarily by the ventricles of the heart when pressure to

	the cardiac muscles increase 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. BNP levels appear to be associated with cardiovascular risks. However, the current evidence is insufficient in demonstrating that the use of BNP testing in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
Calcium	Calcium plays a number of critically important roles in physiology and pathology, in addition to its most widely recognized function as a critical structural component of bone. Many cells have calcium-sensing receptors, with evidence that the concentrations of calcium ions in the extracellular fluid directly regulate cell function (e.g., parathyroid, renal tubule, and many more). Extracellular calcium concentration directly impacts on cell membrane potentials, and so impacts on function of all excitable tissues, particularly the nervous system and the heart. Calcium is a key messenger in the contraction of muscle, including the myocardium. There has been a large number of observational studies on the influence of dietary calcium intake on cardiovascular risk, the results were conflicting and insufficient. The general consensus is there is currently no good evidence to support calcium intake for reasons of cardiovascular safety.
CBC with differential	All blood cells (white blood cells [WBC], red blood cells [RBC] and platelets) can play a role in atherosclerosis. Complete blood count (CBC) is widely available in clinical practice but utility as potential risk factors for cardiovascular disease (CVD) is uncertain. Most studies focused on patient populations with pre-existing CVD or looked at mortality

	rather than incidence of CVD. Therefore, further studies are needed to help clarify the potential role of blood count components as an inexpensive and routinely assessed set of biomarkers of CVD risk in the healthy populations.
Coenzyme Q10 (CoQ10)	A fat-soluble, vitamin-like substance required for normal mitochondrial function that occurs naturally in the body. Used to produce energy to fuel cell growth and maintenance. CoQ10 is also an antioxidant sold in the United States (US) as a dietary supplement. A deficiency of CoQ10 is associated with a number of diseases such as mitochondrial disease, heart failure and hypertension. Testing CoQ10 levels has been proposed for determining CVD risk. The current evidence is insufficient in demonstrating that the use of testing CoQ10 levels in the assessment cardiovascular disease risk changes patient management or improves net health outcomes.
Cortisol	The hormone cortisol is released in response to stress and studies suggest that high levels of cortisol from long term stress can increase blood cholesterol, triglycerides, blood sugar and blood pressure. These are common risk factors of heart disease and cortisol has been proposed to indicate CVD risk possibly as a response to increased mental stress. The current evidence is insufficient in demonstrating that the use of testing cortisol levels in the assessment cardiovascular disease risk changes patient management or improves net health outcomes.
Cyanocobalmin/Vitamin B-12	Vitamin B-12 and folate are cofactors of homocysteine metabolism, and lower intake of these nutrients are associated with high blood homocysteine levels a potential risk for cardiovascular disease (CVD). The evidence regarding the association of dietary intake of Vitamin B-12 and folate and the risk of CVD remains limited.

	The current evidence is insufficient regarding the association of vitamin B-12 and folate and their association in lowering risk of CVD. Further randomized prospective randomized controlled trials are needed regarding the relationship between vitamin B-12 and folate for lowering CVD risk.
Cystatin C	Cystatin C is a small serine protease inhibitor protein that is secreted from all functional cells in the body. It has primarily been used as a biomarker for 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. Several meta-analyses have reported that higher levels of cystatin C are associated with higher cardiovascular risk and higher risk of cardiovascular death. In contrast, in a large cohort, cystatin C did not improve risk prediction of CVD. The current evidence is insufficient in demonstrating that the use of cystatin C testing in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
Ferritin	Elevated ferritin levels have been reported as a risk factor for cardiovascular disease risk (CVD), however, the current evidence is insufficient regarding the association between ferritin and cardiovascular risk. Further studies are needed to clarify the prognostic role of ferritin.
Folate/folic acid	Vitamin B-12 and folate are cofactors of homocysteine metabolism, and lower intake of these nutrients are associated with high blood homocysteine levels a potential risk for cardiovascular disease (CVD). The evidence regarding the association of dietary intake of Vitamin B-12 and folate and the risk of CVD remains limited. The current evidence is insufficient regarding the association of vitamin B-12 and folate and their association in lowering risk of CVD. Further randomized prospective randomized

	controlled trials are needed regarding the relationship between vitamin B-12 and folate for lowering CVD risk.
Glucose	Some speculate that low glycemic values are associated with increased glycemic variability, which is in turn associated with higher CVD risk. It has also been suggested that fasting glucose and hemoglobin A1c (HbA1c) in the lower ranges have a different relationship with CVD and mortality. In the general population studies there is little evidence that a low fasting glucose is associated with Cardiovascular disease (CVD) risk. The current evidence is insufficient in demonstrating that the use of glucose testing in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
Hemoglobin A1c (HbA1c)	Biomarker such as hemoglobin A1c has been proposed for identifying people with increased risk of cardiovascular disease (CVD). However, the association between hemoglobin A1c levels and CVD risk is not well understood. Although a possible increased CVD risk or low HbA1c levels among the general population without known diabetes has been suggested, most studies did not find a statistically significant association. The current evidence is insufficient in demonstrating that the use of hemoglobin A1c testing in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
Homocysteine	Homocysteine (Hcy) is an amino acid that has been evaluated as a potential marker of cardiovascular disease (CVD). The association between homocysteine-lowering interventions and risk of CVD has been examined. Homocysteine is a sulfur-containing amino acid that is rapidly oxidized in plasma into

	homocysteine and cysteine-homocysteine disulfide. Measurement of total plasma homocysteine is the sum of homocysteine and its oxidized forms. Plasma levels of homocysteine have been actively researched as a risk factor for cardiovascular disease (CVD), initially based on the observation that patients with hereditary homocystinuria, an inborn error of metabolism associated with high plasma levels of homocysteine, had a markedly increased risk of CVD. Subsequently, prospective epidemiologic studies were conducted to determine if an elevated plasma level of homocysteine were an independent risk factor for CVD and could be used to improve current risk prediction models. Interest in homocysteine as a potentially modifiable risk factor has been stimulated by the epidemiologic finding that levels of homocysteine inversely correlate with levels of folate. This finding has raised the possibility that treatment with folic acid might lower homocysteine levels and, in turn, reduce the risk of CVD. Therefore, homocysteine has potential utility both as a risk predictor and as a target of treatment. Determination of homocysteine concentration may be offered as a component of a comprehensive cardiovascular risk assessment that may include evaluation of small-density lipoproteins, subclassification of high-density lipoproteins, evaluation of lipoprotein (a), high-sensitivity C-reactive protein, and genotyping of apolipoprotein E. The purpose of testing homocysteine levels in asymptomatic patients at risk of cardiovascular disease (CVD) or in patients who have CVD is to inform management decisions such as whether to lower homocysteine levels. The evidence is insufficient in demonstrating that the use of homocysteine testing in assessing cardiovascular disease risk changes

	patient management or improves net health outcomes.
Insulin	Insulin is a key hormone that functions as a regulator of cellular metabolism. Insulin resistance is defined as a decrease in tissue response to insulin stimulation thus insulin resistance is characterized by defects in uptake and oxidation of glucose, a decrease in glycogen synthesis, and, to a lesser extent, the ability to suppress lipid oxidation. Insulin resistance can alter systemic lipid metabolism which then leads to the development of dyslipidemia and the well-known lipid triad: (1) high levels of plasma triglycerides, (2) low levels of high-density lipoprotein, and (3) the appearance of small dense low-density lipoproteins. This triad, along with endothelial dysfunction, which can also be induced by aberrant insulin signaling, contribute to atherosclerotic plaque formation. New therapies are focusing on decreasing insulin resistance and the development of CVD and atherosclerotic plaque generation. The current evidence shows that the insulin assay is a weak indicator for the occurrence of CVD. The current evidence is insufficient in demonstrating that the use of insulin testing in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
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. Two meta-analyses have suggested that leptin levels are associated with CHD and stroke, although this association may depend on BMI. Another meta-analysis suggested no significant association between leptin concentration and CHD risk. The evidence is insufficient in demonstrating that the use of leptin testing in assessing cardiovascular

	disease risk changes patient management or improves net health outcomes.
Long chain omega 3 fatty acids	Higher palmitic and lower long chain omega-3 fatty acids (e.g., alpha-linolenic, eicosapentaenoic and docosahexaenoic acids) in serum are correlated with higher incidence of CHD. It has been proposed that red blood cell (RBC) fatty acids composition, which is an index of long-term intake of eicosapentaenoic plus docosahexaenoic acids, can be considered a new, modifiable, and clinically relevant risk factor for death from CHD. However, there is lack of scientific evidence regarding how measurements of RBC omega-3 fatty acids composition would affect management of individuals at risk for or patients with CHD. Large randomized clinical trials are needed to ascertain the clinical value of RBC omega-3 fatty acids composition in the management of CHD.
Magnesium	Magnesium may have a beneficial effect on CV risk factors by improving glucose and insulin metabolism which may also affect the lipid profile. Studies have focused on the effects of magnesium or circulating magnesium levels on inflammation and/or oxidative process. The current evidence is insufficient regarding the association of magnesium and its association in lowering risk of CVD. Further randomized prospective randomized controlled trials are needed regarding the relationship between magnesium and lipid profile.
Myeloperoxidase (MPO)	Higher levels of the leukocyte enzyme myeloperoxidase (MPO), which is secreted during acute inflammation and promotes oxidation of lipoproteins, are associated with the presence of coronary disease and may be predictive of acute coronary syndrome in patients with chest pain. Although elevated plasma MPO concentration may be associated with a more advance cardiovascular disease risk profile, plasma MPO does not predict mortality independent of other cardiovascular

	disease risk factors in patients with stable coronary artery disease. There is a lack of scientific evidence regarding how measurements of MPO would affect management of individuals at risk for or patients with CHD. Large randomized controlled studies are needed to ascertain the clinical value of MPO in the management of CVD risk.
Renal Function: BUN and creatinine	End stage chronic kidney disease is associated with cardiovascular mortality, but it is uncertain to what extent renal function is related to risk of subsequent coronary heart disease (CHD) in apparently healthy adults. There is lack of evidence related to the association of renal function in the general population for the purposes of CHD prevention. Similar considerations for CHD prevention apply to patients with and without renal dysfunction concerning interventions for cessation of smoking, maintaining ideal body weight and an active lifestyle, and glycemic control. The current evidence is insufficient in demonstrating that the use of renal function testing (BUN and creatinine) in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
Testosterone	Aging is accompanied by reduction in circulating testosterone. There is an intense debate whether low testosterone contributes to ill health as opposed to a biomarker for its presence. Observational studies show lower risk of cardiovascular events in older men with higher testosterone, and lower mortality from ischemic heart disease in men with high concentrations of its more potent androgenic metabolite dihydrotestosterone. However, randomized trials of testosterone supplementation have been underpowered for the outcome of cardiovascular events. Additional randomized controlled trials are needed to clarify the role of testosterone

	levels and testosterone supplementation for this indication. The current evidence is insufficient in demonstrating that the use of testosterone testing in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
Thrombogenic/Hemostatic Factors: fibrinogen, prothrombin coagulation factor II, Factor V Leiden	Thrombosis plays a key role in acute coronary syndromes, including myocardial infarction. Both platelets and coagulation factors are involved in the thrombotic process. Although the precise hemostatic or prothrombotic mechanisms that predispose to myocardial infarction have not been worked out, the evidence that aspirin and other antiplatelet therapy can reduce risk is compelling and suggests a role for platelet hyperaggregability. Another hemostatic factor associated with CHD risk is fibrinogen. A high fibrinogen level associates significantly with increased risk for coronary events, independent of cholesterol level; and conversely, a low fibrinogen level indicates a reduced risk, even in the presence of high total cholesterol levels. Other hemostatic factors that have been found to be associated with increased coronary risk include activated factor VII, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), von Willebrand factor, factor V Leiden, protein C, and antithrombin III. Studies have shown that some of these prothrombotic factors are elevated as a component of the metabolic syndrome. Fibrinogen is a circulating clotting factor that acts at the final step in the coagulation response to vascular and tissue injury, and epidemiological data support an independent association between elevated levels of fibrinogen to be associated with future risk of cardiovascular disease. Reports from a number of cohort studies have suggested that thrombogenic/hemostatic factors are associated with cardiovascular risk. However, the evidence in insufficient in demonstrating that the use of this testing in assessing cardiovascular disease risk changes

	patient management or improves net health outcomes.
Thyroid Function: thyroid stimulating hormone (TSH), T3 and T4	Thyroid status is determined through measurement of thyroid function tests in peripheral blood. Concentrations of thyroid stimulating hormone (TSH), which is produced by the pituitary gland, and the thyroid hormones thyroxine (T4) and triiodothyronine (T3), are easily measured through established assays. The thyroid hormone is one of the key regulators of cardiac function and cardiovascular hemodynamics. There is considerable knowledge about the genomic mechanisms by which thyroid status affects lipid and lipoprotein metabolism. As a result of these actions, hypothyroidism has been associated with higher levels of LDL cholesterol and apolipoprotein B, as well as unfavorable changes in LDL particle number, size, and oxidation. The extent to which CVD mediates the association between elevated serum TSH has not yet been well established or sufficiently quantified. Further studies are needed to examine the association of subclinical hypothyroidism and high-normal TSH concentrations to determine the clinical benefit of thyroid hormone replacement therapy for active CVD screening.
Troponin quantitative	Cardiac troponin (cTn) has been well described as the preferred biomarker for diagnosis of myocardial infarction due to the high sensitivity and specificity for myocardial injury. However, the use of cTn as prognostic biomarker for the primary assessment of cardiovascular risk in asymptomatic patient has only recently been described. While studies may show promise that cardiac troponin (cTn) may have potential in risk prediction tools in asymptomatic individuals, more research is needed to assess how to best

	fit cTn into risk prediction algorithms, whether it predicts risk that is modifiable and whether it has utility including economical cost effectiveness in all those requiring cardiovascular risk assessment. The evidence is insufficient in demonstrating that the use of this testing in assessing cardiovascular disease risk changes patient management or improves net health outcomes.
Vitamin D	Decreased serum level of vitamin D is a purported risk factor for cardiovascular disease (CVD). The association of low vitamin D and cardiovascular diseases (CVD) and risk factors has been explored in many studies. However, studies and trials on the effect of vitamin D supplementation on cardiovascular risk factors and hypertension are conflicting with inconsistent results. Therefore, large, well-powered randomized controlled trials are warranted to explore the benefits of vitamin D supplementation which may reduce the impact of health problems to include CVD. The current evidence is insufficient in demonstrating that the use of Vitamin D testing to assess cardiovascular disease risk changes patient management or improves net health outcomes.

Summary of Evidence

For individuals who are asymptomatic with risk of cardiovascular disease (CVD) who receive cardiac biomarker testing using nonlipid markers (BNP, calcium, CBC with differential, CoQ10, cortisol, vitamin b-12, cystatin C, ferritin, folate, glucose, hemoglobin A1c, homocysteine, insulin, leptin, long chain omega 3 fatty acids, magnesium, MPO, renal function (BUN and creatine), testosterone, fibrinogen, prothrombin coagulation factor II, Factor V Leiden, thyroid function (TSH, T3, T4), troponin, and vitamin D), the evidence includes systematic reviews, meta-analyses, and large, prospective cohort studies. Numerous non-traditional lipid measurements have been proposed for use in improving risk prediction for cardiovascular disease (CVD). 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 these markers leads to changes in management that improve health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Inflammatory Markers of Coronary Artery Disease Risk
Evidence has suggested that there may be certain biomarkers of CAD that may have a pro-inflammatory role in the progression of atherosclerosis. Recognition that atherosclerosis represents, in part, an inflammatory process has created interest in measurement of pro-inflammatory factors as part of cardiovascular disease risk assessment.

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) and Secretory Phospholipase A2 (sPLA2-IIA):
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 (LDLs). Accumulating evidence has suggested that Lp-PLA2 and secretory phospholipase A2 (sPLA2-IIA) are biomarkers of coronary artery disease (CAD) and may have a pro-inflammatory role in the progression of atherosclerosis. Recognition that atherosclerosis represents, in part, an inflammatory process has created considerable interest in the measurement of proinflammatory factors as part of cardiovascular disease risk assessment.

Interest in Lp-PLA2 as a possible causal risk factor for CAD has generated development and testing of Lp-PLA2 inhibitors as a new class of drugs to reduce the risk of CAD. However, clinical trials of Lp-PLA2 inhibitors have not shown significant reductions in CAD end points.

A large body of literature has accumulated on the utility of risk factors in the prediction of future cardiac events. The evidence assessed for this review consists of large, prospective cohort studies that have evaluated the association between lipoprotein-associated phospholipase A2 (Lp-PLA2) and cardiovascular outcomes.

The National Cholesterol Education Program (NCEP) ATP-III guidelines have indicated that to determine the clinical significance of Lp-PLA2, the emerging risk factors should be evaluated against the following criteria4:

- Significant predictive power that is independent of other major risk factors.
- A relatively high prevalence in the population (justifying routine measurement in risk assessment).
- Laboratory or clinical measurement must be widely available, well-standardized, inexpensive, have accepted population reference values, and be relatively stable biologically.
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk.

Clinical Context and Test Purpose
The purpose of Lp-PLA2 testing in patients who have risk of cardiovascular disease (CVD) is to inform, improve patient stratification using risk prediction models that alter management decisions and improve health outcomes.

Populations
The relevant population of interest are individuals at risk for coronary artery disease (CAD).

Interventions
The relevant intervention of interest is testing for Lp-PLA2 as a biomarker of CAD.

Asymptomatic patients are typically evaluated by primary care physicians. Symptomatic patients are referred to cardiology.

Comparators
The following practice is currently being used to manage CAD risk: standard assessment of cardiovascular risk.

Outcomes
The primary outcomes of interest are the development of CVD such as CAD, stroke and mortality.

The development of CVD typically occurs over many years or decades.

Clinically Valid
A large consistent body of evidence has established that Lp-PLA2 level is an independent predictor of CAD. Relatively few studies have examined the degree to which Lp-PLA2 improves on existing CAD prediction models regarding clinically important magnitudes of reclassification.

Levels of Lp-PLA2 decrease substantially after treatment with anti-lipid medications, including statins. However, in treated patients, Lp-PLA2 levels may no longer be associated with risk of CAD, and thus may not be useful as a measure of treatment response.

Clinically Useful
Changes in patient management that could potentially occur with a strategy using Lp-PLA2 levels are not well-established. Studies that directly evaluate patient management changes and/or health outcome improvements are needed to determine whether the use of Lp-PLA2 measurement has efficacy in CVD. Alternatively, robust decision modeling studies may demonstrate clinically important changes in health outcomes by incorporating Lp-PLA2 levels into CAD prediction models. Groups such as the American Heart Association have often incorporated results from decision models to inform their guidelines when the data underlying the models are robust. Incorporation of Lp-PLA2 into decision models is necessary to demonstrate the potential clinical utility of the biomarker.

Summary of Evidence
For individuals who have a risk of cardiovascular disease (CVD) who receive Lp-PLA2 testing and secretory phospholipase A2 (sPLA2-IIA) testing, the studies may have demonstrated that Lp-PLA2 and sPLA2-IIA levels are an independent predictor of

cardiovascular disease, however, the changes in patient management that would occur as a result of obtaining this testing in practice are not well-defined. To demonstrate clinical utility, clinicians must have the tools to incorporate Lp-PLA2 and sPLA2-IIA test results into existing risk prediction models that improve classification into risk categories alter treatment decisions and lead to improved health outcomes. Direct evidence for such improved health outcomes with Lp-PLA2 and sPLA2-IIA testing in clinical practice is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Genetic Markers (Genomic Profiling) to Assess Cardiovascular Risk
Susceptibility of coronary artery disease (CAD) is claimed to be 40% to 60% inherited, but until recently genetic risk factors predisposing to CAD have been elusive. It has been suggested that an improvement in CVD risk classification (adjusting intermediate risk of CVD into high or low risk categories) might lead to management changes (e.g. earlier initiation or higher rates of medical interventions, or targeted recommendations for behavioral change) that improve CVD outcomes.

9p21 Genetic Variant
The evaluation of Genomic Applications in Practice and Prevention Working Group (EWG) (2010) found insufficient evidence to recommend testing for the 9p21 genetic variant or 57 other variants in 28 genes to assess risk for cardiovascular disease (CVD) in the general population, specifically heart disease and stroke. The EWG found that the magnitude of net health benefit from use of any of these tests alone or in combination are negligible. The EWG discourages clinical use unless further evidence supports improved clinical outcomes. Based on the available evidence, the overall certainty of net health benefit is deemed low. The evidence is insufficient to determine the effects of this technology on net health outcomes.

KIF6 Genotyping
Genetic testing to determine KIF6 (Trp719Arg) variant status is being 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 high-risk patients.

The evidence for use of KIF6 genotyping for individuals who are asymptomatic with risk of CVD is limited and it has not been determined whether knowledge of carrier status can be used to improve patient management decisions and improve net health outcomes. The evidence is insufficient to determine the effects of this technology on net health outcomes.

LPA Genetic Variant
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 antithrombotic properties of aspirin. As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment.

The LPA minor allele, rs3798220, is associated with higher levels of LPA and a higher risk of cardiovascular events. This allele is infrequent in the population and is associated with a modest increase in cardiovascular risk in the general population. Testing for this allele is commercially available, but performance characteristics are uncertain, and standardization of testing has not been demonstrated. Several observational studies have reported that this genetic variant is an independent risk factor for cardiovascular disease, but some studies have not reported a significant association. It is unclear whether the information derived from genetic testing leads to changes in management. In particular, it cannot be determined from available evidence whether deviating from current guidelines on aspirin treatment based on LPA genetic testing improves outcomes. The evidence is insufficient to determine the effects of this technology on net health outcomes.

MTHFR

The MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase. This enzyme plays a role in processing amino acids, the building blocks of proteins. Methylenetetrahydrofolate reductase is important for a chemical reaction involving forms of the vitamin folate (also called vitamin B9). Specifically, this enzyme converts a molecule called 5,10-methylenetetrahydrofolate to a molecule called 5-methyltetrahydrofolate. This reaction is required for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds. MTHFR mutation, have been associated with increased cardiovascular risk.

Polymorphisms in the MTHFR gene have also been studied as possible risk factors for a variety of common conditions. These include heart disease, stroke, high blood pressure (hypertension), high blood pressure during pregnancy (preeclampsia), an eye disorder called glaucoma, psychiatric disorders, and certain types of cancer. Research indicates that individuals who have the 677C>T polymorphism on both copies of the MTHFR gene have an increased risk of developing vascular disease, including heart disease and stroke. Many of the MTHFR gene polymorphisms alter or decrease the activity of methylenetetrahydrofolate reductase, leading to an increase of homocysteine in the blood. This increase in homocysteine levels may contribute to the development of many of these conditions.

Studies of MTHFR gene variations in people with these disorders have had mixed results, with associations found in some studies but not in others. Therefore, it remains unclear what role changes in the MTHFR gene play in these disorders. It is likely that additional factors influence the processing of homocysteine and that variations in homocysteine levels play a role in whether a person develops any of these conditions. A large number of genetic and environmental factors, most of which remain unknown, likely determine the risk of developing most common, complex conditions. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Summary of Evidence
There is insufficient evidence to support that genetic markers alters the management or improves net health outcomes in cardiovascular disease risk.

Cardiovascular Disease Risk Testing Panels
Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate risk of cardiovascular disease (CVD). 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 panel's report the results of multiple individual tests, as distinguished from quantitative risk scores that combine the results of multiple markers into a single score.

Cardiovascular risk panels (CVD) may contain measures from one or all the following categories: lipid markers; inflammatory markers; metabolic syndrome biomarkers and genetic markers. The panels may also include other measures such as radiologic markers (carotid medial thickness, coronary artery calcium score). Some CVD 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 cardiovascular disease (CVD) risk panels including but not limited to the following**:**

- **Cardiac Risk Panel (Health Diagnostics):** MTHFR gene analysis, common variants; vitamin D, 1, 25 dihydroxy; B-type natriuretic peptide (BNP); Lp-PLA2; myeloperoxidase; apolipoprotein; immune complex assay; lipoprotein, blood; electrophorectic separation and quantitation; very long chain fatty acids; total cholesterol; HDL; LDL; triglycerides; (high sensitivity CRP, hs-CRP); lipoprotein (a); insulin; total fibrinogen; apolipoprotein analysis; multiple SNPs associated with coronary artery disease (CAD).
- **Boston Heart Diagnostics:** total cholesterol; triglyceride; HDL-C; APO A-1; Boston Heart Lab Mapy; LDL-C; Lp(a); Apo-B; sdLDL-C; Boston Heart Cholesterol Balance; hs-CRP; Lp-PLA2; MPO; Boston Heart Prediabetes Assessment; glucose; insulin; HbA1c; Boston Heart Statin Induced Myopathy (SLCO1B1) Genotype; Apo-E; Factor II/Factor V; NT-proBNP; vitamin D.
- **CV Health Plus Genomics Panel (Genova Diagnostics):** 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
- **CV Health Plus Panel (Genova Diagnostics):** 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.

- **Cardiovascular Health Profile - Metametrix (now part of Genova Diagnostics acquired Metametric, Inc.):** homocysteine; C-reactive protein (hs-CRP); fibrinogen; red blood cell magnesium; coenzyme Q10; vitamin E; lipid peroxides; total testosterone; sex hormone binding globulin; free androgen index (calculation); insulin; ferritin; total cholesterol; HDL cholesterol; LDL cholesterol; triglycerides; lipoprotein (a).
- **CVD Inflammatory Profile (Cleveland Heartlab):** hs-CRP; urinary microalbumin; myeloperoxidase; Lp-PLA2; F2-isoprostanes. _
- **Applied Genetics Cardiac Panel:** genetic mutations associated with CAD; cytochrome p450 mutations associated with metabolism of clopidogrel, ticagrelor, warfarin,B-blockers, rivaroxaban, and prasurgrel (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; GPIIIs (HPA-1); MTHFR; ACE I/D; apo B; apo E.
- **4myheart (Quest Diagnostics) :** lipoprotein subfractionation by ion mobility**;** Apo-B; Lp(a); homocysteine; Lp-PLA2; hs-CRP; fibrinogen; insulin; NT-proBNP; vitamin D; omega 3 and 6; 4q25-AF risk genotype test; 9p21 genotype; Apo-E genotype; CYP2C19 genotype; KIF6 genotype; LPA-aspirin genotype; LPA intron 25 genotype; apolipoprotein A1; hemoglobin A1c.
- **Cardiac Related Test Panels (Singulex):**
    - **Cardiac Dysfunction panel**: SMC™ cTmNI (high sensitivity troponin); NT-proBNP
    - **Vascular Information and Dysfunction panel**: SMC™ IL-6; SMC™ IL-7; SMC™ TNFa; SMC™ Endothelin; Lp-PLA2; hs-CRP; homocysteine; vitamin B12; folate
    - **Dyslipidemia panel**: cholesterol total; LDL-C (direct); APO B; sdLDL; HDL-C; APO A-1; HDL2b; triglycerides; Lp(a)
    - **Cardiometabolic:** Parathyroid hormone; vitamin D; calcium; magnesium; leptin; adiponectin; ferritin; cortisol a.m.; testosterone; cystatin C; glucose; insulin; T4; T3; Free T4; Free T3; TSH; uric acid.

In addition to panels that are specifically focused on CVD risk, a number of commercially available panels include makers associated with cardiovascular 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:

- **Cardiometabolic Panel (Singulex)**: described above
- **Heart Health Testing Profile (Salveo Diagnostics):** Lipid panel; lipoprotein particles; LDL-P, Lp(a)-P, IDL-P, VLDL-P; ApoB; hsCRP; homocysteine; fibrinogen; Lp-PLA_2 Activity; uric acid, CoQ10; creatinine kinase; CMP; magnesium; cystatin C; CBC with differential.
- **Wellness FX Premium (WellnessFX):** 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, dehydroepiandrosterone, 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, thyroid-stimulating hormone, 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.

Clinical Context and Test Purpose
The purpose of cardiovascular (CVD) risk panel testing in patients who have risk factors for CVD is to inform management and treatment decisions.

Ppopulations
The relevant population of interest are individuals with risk factors for cardiovascular disease risk (CVD).

Interventions
The relevant intervention of interest is testing with cardiovascular disease (CVD) risk panels.

Patients who have risk factors for CVD are initially managed in primary care. Patients who have had a cardiovascular (CV) event may be following in specialty clinical by cardiologists or neurologists.

Comparators
The following practice is currently being used to manage those at risk for cardiovascular disease (CVD): management of clinical risk factors with or without simple lipid testing.

Outcomes
The beneficial outcomes of interest are decreased morbidity and mortality from cardiovascular disease (CVD).

The development of cardiovascular disease (CVD) occurs over many years and manifests as coronary heart disease (CHD), CVD, or peripheral arterial disease. The timing for measuring outcomes can range from 5 to 10 years.

While multiple risk factors have been individually associated with CVD, there is no convincing evidence that the addition of any individual risk marker, or combination of risk markers, leads to clinically meaningful changes in management that improve outcomes. In the available studies, improvements in risk prediction have generally been of a small magnitude, and/or have not been found to be associated with clinically meaningful management changes. Because of this uncertain impact on management, the clinical utility for any of the individual risk markers is either low or uncertain.

Moreover, the available evidence on individual risk markers is only of limited value in evaluating CVD risk panels. It is difficult to extrapolate the results of single risk factors to panels, given the variable composition of panels. Ideally, panels should be evaluated individually based on their impact on clinical decision making.

No published studies were identified that evaluated the use of commercially available CVD risk panels as risk prediction instruments in clinical care. Some studies have attempted to incorporate novel risk markers into an overall quantitative risk score, but these risk scores are not the same as CVD risk panels, which report the results of individual risk factors.

Furthermore, there are no standardized methods for combining multiple individual risk factors with each other, or with established risk prediction instruments such as the FRS. Therefore, there is a potential for both overestimation and underestimation of the true cardiac risk. This may lead to management decisions based on an inaccurate risk assessment. As a result of these deficiencies, it is not possible to assess the impact of using CVD risk panels on health outcomes reliably.

Summary of Evidence
For individuals who have risk factors for cardiovascular disease (CVD) who receive CVD risk panels, the evidence includes multiple cohort and case-control studies and systematic reviews of these studies. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in CVD risk panels are associated with increased risk of CVD. 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 the clinical utility beyond simple lipid measurements (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides), it is unlikely that the use of CVD 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 net health outcomes.

Practice Guideline and Position Statements

American Association of Clinical Endocrinologists (AACE)
In 2020, the American Association of Clinical Endocrinologists (AACE) published an updated consensus statement on dyslipidemia and prevention of cardiovascular disease. They recommended measurement of Lp(a) in several patient populations including those with ASCVD, those with a family history of premature ASCVD and/or increased Lp(a), and individuals with a 10-year ASCVD risk of 10% or greater. Recommendations also included consideration of apo B or LDL particle measurement "based on individual patient clinical circumstances."

American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)
In 2013, the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) issued a joint guideline for the assessment of cardiovascular risk. These guidelines recommended that age- and sex-specific pooled cohort equations, which included total cholesterol and high-density lipoprotein to predict the 10-year risk of a first hard atherosclerotic cardiovascular disease event, be used in non-Hispanic blacks and non-Hispanic whites between 40 and 79 years of age (American Heart Association/American College of Cardiology class of recommendation I, American Heart Association/American College of Cardiology level of evidence B). Regarding newer risk markers after quantitative risk assessment, the guidelines stated the following: "If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of ≥1 of the following: family history, hs-CRP [high-sensitivity C-reactive protein], CAC [coronary artery calcium] score, or ABI [ankle-brachial index] may be considered to inform treatment decision-making" (class of recommendation IIb, level of evidence B). The guidelines did not recommend other novel cardiac risk factors or panels of cardiac risk factors.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) testing was not mentioned in this guideline.

American College of Cardiology (ACC) and American Heart Association (AHA)
In 2019, the American College of Cardiology (ACC) and American Heart Association (AHA) issued a joint statement on the primary prevention of cardiovascular disease which states regarding elevated Lp(a) "a relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a)." The guideline further states regarding elevated apo B (≥130 mg/dL) that "a relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor."

Lipoprotein-associated phospholipase A2 (Lp-PLA2) testing was not mentioned in the above 2019 guideline, which was a change from 2010 guidelines. In their prior guideline, Lp-PLA2 was given an IIb recommendation for assessing cardiovascular risk in intermediate-risk asymptomatic adults.

European Society of Cardiology/European Atherosclerosis Society
In 2019, the European Society of Cardiology and European Atherosclerosis Society published a guideline for the management of dyslipidemias: lipid modification to reduce CV risk.[30,] This guideline contains updated recommendations for lipid analyses for CV disease risk estimation. Beyond traditional lipid markers (ie, total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides), the guideline recommends non-HDL-C "for risk assessment, particularly in people with high triglyceride levels, diabetes mellitus, obesity, or very low LDL-C levels" [Class I recommendation; Level C evidence (consensus of opinion of the experts and/or small

studies, retrospective studies, registries)]. Apolipoprotein B is recommended "for risk assessment, particularly in people with high triglyceride levels, diabetes mellitus, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high triglyceride levels, diabetes mellitus, obesity, or very low LDL-C levels" [Class I recommendation; Level C evidence]. Additionally, the guideline states that lipoprotein(a) measurement "should be considered at least once in each adult person's lifetime to identify those with very high inherited lipoprotein(a) levels > 180 mg/dL who may have a lifetime risk of atherosclerotic CVD equivalent to the risk associated with heterozygous familial hypercholesterolemia" and "should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk" [Class I!a recommendation; Level C evidence].

National Institute for Health and Care Excellence (NICE)
In 2016, the National Institute for Health and Care Excellence updated its guidance on risk assessment and reduction, including lipid modification, of CVD. The guidance recommended measuring a full lipid profile including total cholesterol, high-density lipoprotein (HDL), non-HDL, and triglycerides before starting lipid-lowering therapy for primary prevention of CVD. The guidance also recommended measurement of total cholesterol, HDL, non-HDL, and triglycerides for primary and secondary prevention in people on high-intensity statins at 3 months of treatment, aiming for 40% reduction in non-HDL. Apo B and other nontraditional risk factors were not discussed as part of risk assessment or treatment targets.

U.S. Preventative Services Task Force (USPSTF)
In 2018, The USPSTF updated the 2009 recommendation regarding risk assessment using nontraditional risk factors in coronary heart disease risk assessment, the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ankle-index (ABI), high-sensitivity C-reactive protein (hsCRP) level, or coronary artery calcium (CAC) score to traditional risk assessment for cardiovascular disease (CVD) in asymptomatic adults to prevent CVD events.

Regulatory Status
Multiple assay methods for cardiac risk marker components, such as lipid panels and other biochemical assays, have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process.

Other components of testing panels are laboratory-developed tests. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Lipid and non–lipid biomarker tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Several homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process. Food and Drug Administration product code: LPS.

In December 2014, the PLAC® Test (diaDexus, San Francisco, CA), a quantitative enzyme assay, was cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process for Lp-PLA2 activity. It was considered substantially equivalent to a previous version of the PLAC® Test (diaDexus), which was cleared for marketing by the Food and Drug Administration in July 2003. Food and Drug Administration product code: NOE.

PRIOR APPROVAL

Not applicable.

POLICY

Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease
The measurement of lipid and non-lipid biomarkers for cardiovascular disease risk assessment and/or management in ***asymptomatic individuals***, including but not limited to the following is considered **investigational:**

- Albumin
- Apolipoprotein A-I (apo A-I)
- Apolipoprotein B (apo B)
- Apolipoprotein E (apo E)
- B-type natriuretic peptide (BNP) (Brain Natriuretic Peptide)
- Calcium
- CBC with differential
- Coenzyme Q10 (CoQ10)
- Cortisol
- Cyanocobalmin/Vitamin B-12
- Cystatin C
- Ferritin
- Fibrinogen (may also include thrombogenic or hemostatic factors including but not limited to Prothrombin coagulation factor II and Factor V Leiden)

- Folate
- Glucose
- Hemoglobin A1c
- High density lipoprotein subclass, HDL subspecies (HDL_2 and HDL_3)
- Homocysteine
- Insulin
- LDL gradient gel electrophoresis
- Leptin
- Lipoprotein (a) enzyme immunoassay
- Lipoprotein -associate phospholipase A_2 (Lp-PLA2)
- Lipoprotein remnants: intermediate density lipoprotein (IDL)
- Long chain omega-3 fatty acids composition in red blood cell
- Low density lipoprotein (LDL) particles subclass
- Magnesium
- MI-Heart Ceramides
- Myeloperoxidase (MPO)
- Renal function: BUN and creatinine
- Secretory phospholipase A2 (sPLA2-IIA)
- Testosterone
- Thyroid function testing: TSH, T3 and T4
- Troponin
- Vitamin D

Numerous non-traditional lipid measurements and non-lipid biomarkers have been proposed for use in improving risk prediction for cardiovascular disease (CVD). 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 (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides) Furthermore, no studies have provided high-quality evidence that measurement of these markers leads to changes in management that improve net health outcomes. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Measure of Inflammatory Markers in the Assessment of Cardiovascular Risk
The measurement of inflammatory makers including but not limited to lipoprotein-associated phospholipase A2 (Lp-PLA2), other human A2 phospholipase such as secretory phospholipase A2 (sPLA2-IIA) or plasma myeloperoxidase (MPO) in the assessment of cardiovascular risk is considered **investigational**.

For individuals who have a risk of cardiovascular disease (CVD) who receive Lp-PLA2 testing and secretory phospholipase A2 (sPLA2-IIA) testing, the studies may have demonstrated that Lp-PLA2 and sPLA2-IIA levels are an independent predictor of cardiovascular disease, however, the changes in patient management that would occur as

a result of obtaining this testing in practice are not well-defined. To demonstrate clinical utility, clinicians must have the tools to incorporate Lp-PLA2 and sPLA2-IIA test results into existing risk prediction models that improve classification into risk categories alter treatment decisions and lead to improved health outcomes. Direct evidence for such improved health outcomes with Lp-PLA2 and sPLA2-IIA testing in clinical practice is lacking. The evidence is insufficient to determine the effects of the technology on net health outcomes

Cardiovascular Disease Risk Testing Panels
Cardiovascular risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels) in asymptomatic individuals, including but not limited to the following, are considered **investigational.**

- Applied Genetics Cardiac Panel
- Boston Heart Diagnostics
- Cardiac Related Test Panels (Singulex)
    - Cardiac Dysfunction Panel
    - Vascular Information and Dysfunction Panel
    - Dyslipidemia Panel
    - Cardiometabolic Panel
- Cardiac Risk Panel (Health Diagnostics)
- Cardiovascular Health Profile -Metametrix (now part of Genova Diagnostics which acquired Metametrix, Inc)
- CV Health Plus Genomics Panel (Genova Diagnostics)
- CV Health Plus Panel (Genova Diagnostics)
- CVD Inflammatory Profile (Cleveland Heartlab)
- Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel
- Heart Health (Salveo Diagnostics)
- WellnessFX Premium (WellnessFX)
- 4myheart (Quest Diagnostics)

For individuals who have risk factors for cardiovascular disease (CVD) who receive CVD risk panels, the evidence includes multiple cohort and case-control studies and systematic reviews of these studies. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in CVD risk panels are associated with increased risk of CVD. 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 the clinical utility beyond simple lipid measurements (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides), it is unlikely that the use of CVD 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 this testing on net health outcomes.

Genetic Markers (Genotype Testing) for Predicting Cardiovascular Risk
Genetic markers (genotype testing) for predicting cardiovascular disease risk and/or management in asymptomatic individuals is considered **investigational,** including but not limited to the following, as there is insufficient evidence to support that genetic markers alters the management or improves net health outcomes:

- KIF6 genotype
- 9p21 genotype
- CYP2C19 genotype
- 4q25-AF risk genotyping
- LPA –Aspirin genotype
- LPA intron 25 genotype
- Apolipoprotein E genotyping (APO E genotyping)
- MTHFR

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81240 Prothrombin coagulation factor II (see also medical policy 02.04.46)
- 81241 Factor V Leiden (see also medical policy 02.04.46)
- 81225 CYP2C19 (see also medical policy 02.04.67)
- 81291 MTHFR (see also medical policy 02.04.46)
- 81401 Molecular pathology procedure, level 2 (e.g. 2-10 SNPs, 1 methylated variant (typically using non-sequencing target variant analysis), or detection of dynamic mutation disorder/triplet repeat (Apo E, APO B)
- 81479 Unlisted molecular pathology procedure (when utilized with a description of KIF6, 9p21, 4q25-AF, LPA-Aspirin, LPA-Intron 25, this code may also be utilized for cardiovascular risk panels)
- 81599 Unlisted multianalyte assay with algorithmic analysis (may be used for cardiovascular risk panels)
- 82040 Albumin serum plasma or whole blood
- 82043 Albumin, urine (e.g., microalbumin) quantitative
- 82172 Apolipoprotein, each
- 82306 Vitamin D; 25 hydroxy, includes fraction(s), if performed (see also medical policy 02.04.34)
- 82310 Calcium, total
- 82397 Chemiluminescent assay (Leptin)
- 82533 Cortisol, total
- 82542 Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug

analyte(s) not elsewhere specified, qualitative or quantitative, each specimen (Coenzyme 10 [CoQ10])

- 82565 Creatinine, blood
- 82607 Cyanocobalamin (Vitamin B-12)
- 82610 Cystatin C
- 82652 Vitamin D; 1,25 dihydroxy, includes fraction(s), if performed (see also medical policy 02.04.34)
- 82664 Electrophoretic technique, not otherwise classified
- 82728 Ferritin
- 82746 Folic acid, serum
- 82947 Glucose; quantitative, blood (except reagent strip)
- 83036 Hemoglobin; glycosylated (A1C)
- 83090 Homocysteine (see also medical policy 02.04.22)
- 83525 Insulin, total
- 83695 Lipoprotein (a) enzyme immunoassay
- 83698 Lipoprotein-associated phospholipase A2 (Lp-PLA2)
- 83700 Lipoprotein, blood; electrophoretic separation and quantitation
- 83701 high resolution fractionation and quantitation of lipoprotein subclasses when performed (e.g., electrophoresis, ultracentrifugation)
- 83704 quantitation of lipoprotein particle number(s) (e.g., by nuclear magnetic resonance spectroscopy) includes lipoprotein particle subclass(es) when performed
- 83722 Lipoprotein, direct measurement, small dense LDL cholesterol
- 83735 Magnesium
- 83876 Myeloperoxidase (MPO)
- 83880 Natriuretic peptide
- 84403 Testosterone, total
- 84439 Thyroxine; free (this test may be ordered as a FT4, free T4, FTI or FT4 index)
- 84443 Thyroid stimulating hormone (TSH)
- 84481 Triiodothyronine T3; free
- 84484 Troponin, quantitative
- 84520 Urea nitrogen, quantitative
- 85025 Blood count complete (CBC) automated (HGB, HCT, RBC, WBC and platelet count) and automated differential WBC count)
- 85384 Fibrinogen activity
- 85385 Fibrinogen antigen
- 0038U Vitamin D, 25 hydroxy D2 and D3, by LC-MS/MS, serum microsample, quantitative (see also medical policy 02.04.34)
- 0052U Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation (VAP Cholesterol Test)

- 0119U Cardiology, ceramides by liquid chromatography-tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events (MI-Heart Ceramides – Mayo Clinic)

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POLICY HISTORY		
Date	**Reason**	**Action**
April 2022	Annual Review	Policy Renewed
April 2021	Annual Review	Policy Renewed
April 2020	Annual Review	Policy Revised
April 2019	Annual Review	Policy Renewed
April 2018	Annual Review	Policy Revised
April 2017	Annual Review	Policy Revised
April 2016	Annual Review	Policy Revised
May 2015	Annual Review	Policy Revised
June 2014	Annual Review	Policy Revised
August 2013	Annual Review	Policy Revised
September 2012	Annual Review	Policy Renewed
September 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
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