Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Cardiovascular Risk Panels

Description/Background

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

Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate the risk of cardiovascular disease (CVD). There are numerous commercially available risk panels that include different combinations of lipids, noncardiac biomarkers, measures of inflammation, metabolic parameters, and/or genetic markers. Risk panel 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 DISEASE

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

As a result, accurate prediction of cardiovascular risk is a component of medical care that has the potential to focus on and direct preventive and diagnostic activities. Current methods of risk prediction in use in general clinical care are not highly accurate, and as a result, there is a potential unmet need for improved risk prediction instruments.

Risk Assessments

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

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

Many additional biomarkers, genetic factors, and radiologic measures have been associated with increased risk of CVD. Over 100 emerging risk factors have been proposed as useful for refining estimates of CVD risk.(3-5) Some general categories of these potential risk factors are as follows:

- **Lipid markers**. In addition to LDL and HDL, other lipid markers may have predictive ability, including the apolipoproteins, lipoprotein (a) (Lp[a]), lipid subfractions, and/or other measures.
- **Inflammatory markers**. Many measures of inflammation have been linked to the likelihood of CVD. High-sensitivity C-reactive protein (hs-CRP) is an example of an inflammatory marker; others include fibrinogen, interleukins, and tumor necrosis factor.
- **Metabolic syndrome biomarkers**. Measures associated with metabolic syndromes, such as specific dyslipidemic profiles or serum insulin levels, have been associated with an increased risk of CVD.
- **Genetic markers**. A number of variants associated with increased thrombosis risk, such as the 5,10-methylenetetrahydrofolate reductase (*MTHFR)* variant, or the prothrombin gene variants, have been associated with increased CVD risk. Also, numerous single nucleotide variants have been associated with CVD in large genome-wide studies.

Risk Panel Testing

CVD risk panels may contain measures from 1 or all of the previous categories and may include other measures not previously listed such as radiologic markers (carotid medial thickness, coronary artery calcium score). Some CVD risk panels are relatively limited, including a few markers in addition to standard lipids. Others include a wide variety of potential risk factors from a number of different categories, often including both genetic and nongenetic risk factors. Other panels are composed entirely of genetic markers.

Some examples of commercially available CVD risk panels are as follows:

- **Cardio inCode® Score (Gen inCode):**CARDIO inCode® Score analyses 12 Single Nucleotide Polymorphism (SNPs) genetic variants using qPCR.

- **CardioRisk+, Gene by Gene, Ltd, OpenDNA, Ltd**: comprehensive genetic test that uses AI to analyze over 6 million SNPs (single nucleotide polymorphisms) as well as an extensive number of clinical biomarkers associated with cardiovascular disease, hypertension, diabetes, and hypercholesterolemia.

- **CV Health Plus Genomics™ Panel (Genova Diagnostics):** apolipoprotein **(**apo) E; prothrombin; factor V Leiden; fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; Lp(a); lipoprotein-associated

phospholipase A_2 (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; Lp(a); Lp-PLA2; triglycerides; VLDL; VLDL size; vitamin D; hs-CRP.

- **CVD Inflammatory Profile (Cleveland HeartLab):** hs-CRP, urinary microalbumin, myeloperoxidase, Lp-PLA2, F_2 isoprostanes.

- **Applied Genetics Cardiac Panel:** genetic variants associated with coronary artery disease: cytochrome p450 variants associated with metabolism of clopidogrel, ticagrelor, warfarin, β-blockers, rivaroxaban, prasugrel (2C19, 2C9/*VKORC1*, 2D6, 3A4/3A5), factor V Leiden, prothrombin gene, *MTHFR* gene, *APOE* gene.

- **Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel:** factor V Leiden, factor V R2, prothrombin gene, factor XIII, fibrinogen-455, plasminogen activator inhibitor-1, platelet GP IIIA variant HPA-1 GPIIIs (PLA1/2), *MTHFR* gene, angiotensin-converting enzyme insertion/deletion, apo B, apo E.

- **SOMAmer®SomaLogic**: measures thousands of protein analytes from a single sample simultaneously which allows categorical risk-prediction and aids in stratification of individuals residual cardiovascular risks and aids physician decision-making on whether to add further cardio-protective therapies.

In addition to panels that are specifically focused on CVD risk, a number of commercially available panels include markers 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. The following is an example:

- **Advanced Health Panel (Thorne):** total cholesterol, HDL, LDL, triglycerides, HDL ratios, non-HDL cholesterol, LDL particle number, small LDL, medium LDL, LDL pattern, LDL peak size, large HDL, apo A1, apo B, Lp(a), cortisol, hs-CRP, homocysteine, glucose, hemoglobin A1c, insulin, homeostatic model assessment for insulin resistance, free T4, free T3, thyroid-stimulating hormone, reverse T3, dehydroepiandrosterone sulfate, estradiol, follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin, total testosterone, free testosterone, albumin, globulin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, total bilirubin, total serum protein, blood urea nitrogen, creatinine, blood urea nitrogen/creatinine ratio, estimated glomerular filtration rate form creatinine, estimated glomerular filtration rate from cystatin C, cystatin C, fibrinogen, platelet count, white cell count, absolute neutrophils, lymphocytes, absolute lymphocytes, monocytes, absolute monocytes, eosinophils, absolute eosinophils, basophils, absolute basophils, red blood cell count, hemoglobin, hematocrit, mean platelet volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, folate, vitamin B12, vitamin D, red blood cell magnesium, calcium, carbon dioxide, chloride, potassium, sodium, ferritin, iron total iron binding capacity, omega-3 index, omega-6 to omega-3 ratio, arachidonic acid, eicosapentaenoic acid, eicosapentaenoic acid/arachidonic acid ratio, docosahexaenoic acid, free fatty acids.(6)

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 (FDA) 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.

Medical Policy Statement

The peer reviewed medical literature has not demonstrated the clinical utility of cardiovascular risk panels (other than simple lipid panels) consisting of multiple individual biomarkers to assess cardiac disease risk. Therefore, this service is experimental/investigational.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

Policy Guidelines

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

- Total cholesterol
- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol
- Triglycerides

Certain calculated ratios (e.g., total/high-density lipoprotein cholesterol) may also be reported as part of a simple lipid panel.

Other types of lipid testing (i.e., apolipoproteins, lipid particle number or particle size, lipoprotein [a]) are not considered components of a simple lipid profile.

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

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

**Other codes (investigational, not medically necessary, etc.):*

81599	83722	84999	0019M	0401U	0466U

*Established codes may be considered investigational for the purpose of this policy

There is no specific CPT code for cardiovascular risk panels. If there are CPT codes for the component tests in the panel and there is no algorithmic analysis used, the individual CPT codes may be reported. Examples of possible components codes include:

81291	82465	82652	83090	83698	83718
83721	83880	84478	86141		

If the testing involves multiple analytes and an algorithmic analysis, 81599 would be reported.

Rationale

CARDIOVASCULAR DISEASE RISK TESTING PANELS

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

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with risk factors for CVD.

Interventions
The relevant intervention of interest is testing with CVD risk panels.

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

Outcomes
The beneficial outcomes of interest are decreased in morbidity and mortality from CVD.

The development of 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.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from the development cohort.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response(beneficial or adverse).

Review of Evidence

Association Between Single Risk Markers and CVD Risk

Systematic Reviews
There is a large evidence base on the association of individual risk markers and cardiovascular (CV) risk. Many observational studies have established that individual risk markers are independent predictors of cardiac risk.(3,5)

Antonopoulos et al (2022) conducted a meta-analysis to evaluate biomarkers of vascular inflammation for CV risk prognosis in stable patients without known CHD. (7) Various biomarkers of vascular inflammation (such as C-reactive protein, interleukin-6 and tumor necrosis factor-alpha) were evaluated in the 39 studies (N=175,778) that were included. The primary composite endpoint was the difference in c-index with the use of inflammatory biomarkers for major adverse cardiovascular events (MACE) and mortality. Vascular inflammation biomarkers provided added prognostic value for the composite endpoint and for MACEs only. However, limitations in the published literature included a lack of reporting on the net clinical benefit, cost-effectiveness of such biomarkers in clinical practice, and other metrics of improvement of risk stratification.

Van Holten et al (2013) conducted a systematic review of meta-analyses of prospective studies evaluating the association between serologic biomarkers and primary CV events (i.e., CV events and stroke in CVD-naive populations) and secondary CV events (i.e., CV events and stroke in populations with a history of CVD).(8) The final data synthesis included 85 studies published from 1988 to 2011. Sixty-five meta-analyses reported biomarkers' association with primary CV events and 43 reported associations with secondary CV events. Eighteen meta-analyses reported biomarkers' association with ischemic stroke in individuals with a history of CVD. Only 2 meta-analyses that reported associations with ischemic stroke in individuals with no history of CVD were identified, and results were not reported. CVD risks for markers with the strongest associations are summarized in Table 1.

Table 1. Serum Biomarkers and CVD Risk

Marker	RR, HR, or OR	95% Confidence Interval
Prediction of CV events in patients with no history of CVD		
C-reactive protein	2.43 (RR)	2.10 to 2.83

Fibrinogen	2.33 (HR)	1.91 to 2.84
Cholesterol	0.44 (HR)	0.42 to 0.48
Apo B	1.99 (RR)	1.65 to 2.39
Apo A: Apo B ratio	1.86 (RR)	1.55 to 2.22
HDL	1.83 (HR)	1.65 to 2.03
Vitamin D	1.83 (HR)	1.19 to 2.80
Prediction of CV events in patients with a history of CVD		
cTn I and T	9.39 (OR)	6.46 to 13.67
High-sensitivity C-reactive protein	5.65 (OR)	1.71 to 18.73
Creatinine	3.98 (HR)	3.02 to 5.24
Cystatin C	2.62 (RR)	2.05 to 3.37
Prediction of ischemic stroke in patients with a history of CVD		
Fibrinogen	1.75 (HR)	1.55 to 1.98
Uric acid	1.47 (RR)	1.19 to 1.76

Adapted from van Holten et al (2013)
Apo: apolipoprotein; cTn: cardiac troponin; CV: cardiovascular; CVD: cardiovascular disease; HDL: high-density lipoprotein; HR; hazard ratio; OR: odds ratio; RR: relative risk.

Prospective and Retrospective Studies

Since the publication of the van Holten et al (2013) review, multiple studies have reported on the associations between various risk factors and CVD outcomes. Representative examples of reported associations include: endothelin-1 in predicting mortality in patients with heart failure with reduced ejection fraction;(9) troponin and B-type natriuretic peptide in predicting CVD-related death;(10,11) growth differentiation factor and interleukin 6 (IL-6) with CVD- and non-CVD-related death;(10) and mid-regional pro-atrial natriuretic peptide and C-terminal pro-endothelin-1 with morbidity and mortality after cardiac surgery,(12) and triglyceride-glucose index with the incidence of acute coronary syndrome.(13)

Mohebi et al (2023) conducted a review of data from the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) cohort study to identify a panel of biomarkers to help stratify patient risk for CV events within 2 years of coronary angiography.(14) All patients in the study (n=446) had chronic kidney disease (stage 1 to 2, 84.8%; stage 3 to 5, 15.2%). Monte Carlo simulation was used to identify a prognostic panel of biomarkers, which consisted of NT-proBNP, kidney injury molecule-1, osteopontin, and tissue inhibitor of matrix metalloproteinase-1. The panel had a C-statistic for predicting CV events of 0.77 (95% confidence interval [CI], 0.72 to 0.82). Among patients with stage 1 to 2 chronic kidney disease, the hazard ratio (HR) for CV events was 2.82 (95% CI, 1.53 to 5.22) in patients with higher CV risk compared to lower CV risk. In patients with stage 3 to 5 chronic kidney disease, the HR was 8.32 (95% CI, 1.12 to 61.76) in patients with higher CV risk compared to lower CV risk.

Safo et al (2023) derived a protein biomarker risk score to predict CVD in patients with HIV.(15) The risk score was derived from 4 trials conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) and included the following 8 proteins: FAM3B, integrin α11, interleukin-6, hepatocyte growth factor, C-C motif chemokine 25, gastrotropin, platelet-activating factor acetylhydrolase, and secretoglobin family 3A member. After adjusting for CVD at baseline and HIV-related factors, the protein score was associated with an increased risk of CVD (odds ratio, 2.17; 95% CI, 1.58 to 2.99).

Wallentin et al (2021) analyzed data in a subset of patients with chronic CHD from the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial to assess the association between various CV and inflammatory biomarkers and CV death;

patients in the STABILITY trial had a median follow-up time of 3.7 years.(16) Biomarkers were compared between patients who experienced CV death (n=605) and those who did not experience CV death (n=2788). Another prospective observational study (the Ludwigshafen Risk and Cardiovascular Health [LURIC] study) was used for replication. This study followed a cohort of 3316 patients scheduled for coronary angiography over a period of 12 years to assess CV mortality. Both studies included patients with a median age of 65 years and 20% smokers; the STABILITY trial included 82% males, 70% with hypertension, and 39% with diabetes while the LURIC trial had 76% males, 78% with hypertension, and 30% with diabetes. Unadjusted and adjusted Cox regression analyses showed that N-terminal pro-brain natriuretic peptide (NT-proBNP; HR for 1 standard deviation [SD] increase of the logscale of the distribution of the biomarker in the replication cohort, 2.079 (95% CI, 1.799–2.402) and high-sensitivity troponin T (HR, 1.715; (95% CI, 1.491–1.973) had the highest prognostic values for CV death.

Wuopio et al (2018) analyzed 10-year data from the CLARICOR trial in Denmark to investigate the association between serum levels of cathepsin B and S and cardiovascular risk and mortality in patients with stable coronary heart disease.(17) The researchers used the placebo group (n=1998) as a discovery sample and the treatment group (n=1979) as a replication sample. A multivariable Cox regression model was used to adjust for risk factors and other variables. Analysis showed that cathepsin B was associated with increased risk of cardiovascular events and mortality ($p<0.001$ for both groups), but cathepsin S was not ($p>0.45$). Limitations included unknown generalizability to patients with acute symptoms, other ethnic groups, and those unlikely to volunteer for such trials. In another evaluation involving the placebo group of the CLARICOR trial (n=1998), Winkel et al (2020) evaluated whether 12 novel circulating biomarkers (serum N-terminal pro-B-type natriuretic peptide [NT-proBNP], high-sensitive assay cardiac troponin T, YKL40, osteoprotegerin, pregnancy-associated plasma protein A, cathepsin B, cathepsin S, endostatin, soluble tumor necrosis factors 1 and 2, calprotectin, and neutrophil gelatins-associated lipocalin) when added to "standard predictors" (e.g., age, smoking, plasma lipids) improved the 10-year prediction of CV events and mortality in patients with stable CHD.(18) Results of the analysis revealed that the overall contribution of these novel biomarkers to all-cause death and composite CV outcome predictions was minimal. Two of the 12 biomarkers (calprotectin and cathepsin S) were not associated with the outcomes, not even as single predictors. The addition of the 10 remaining biomarkers to the "standard predictors" only increased the correct all-cause death predictions from 83.4% to 84.7% and the composite outcome predictions from 68.4% to 69.7%.

Welsh et al (2017) analyzed data from the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) drug trial to assess the prognostic value of emerging biomarkers in CVD screening.(19) A panel of several biomarkers was measured at randomization in 1853 participants with complete data, and the relation between these biomarkers and a primary composite end point of heart-failure hospitalization or cardiovascular death over 28 months of follow-up (n=834) was evaluated using Cox proportional hazards regression. Analysis showed that N-terminal-pro-brain natriuretic peptide (HR, 3.96) and high-sensitivity troponin (HR=3.09) far outperformed other emerging biomarkers studied for predicting adverse cardiovascular outcomes. Limitations included the homogenous sample from the trial cohort and regional differences.

Harari et al (2017) conducted a prospective cohort study analyzing the association between non-HDL-C levels and CVD mortality in a long-term follow-up of 4832 men drawn from the

Cardiovascular Occupational Risk Factor Determination in Israel Study.(20) Patients were between the ages of 20 and 70 years (mean age, 42.1 years at baseline); all completed multiple questionnaires that evaluated medical history and possible risk factors for CVD, in addition to blood tests. Before adjusting for potential confounders, a positive association was found between several comparator cholesterol categories (simple lipids including total cholesterol, triglycerides, and HDL-C) and all-cause or CVD mortality; however, in multivariate analysis, many of these associations were no longer statistically significant. For 1 of the primary outcomes (the efficacy of non-HDL-C in predicting CVD mortality), after adjusting for the known risk factors, results were statistically significant, with an association between non-HDL-C levels greater than 190 mg/dL and risk of mortality from CVD (HR=1.80; 95% CI, 1.10 to 2.95; p=0.020). Another primary outcome was the prediction value of non-HDL for all-cause mortality; for this outcome, the association between all levels of non-HDL-C were statistically insignificant after adjusting for potential confounders (for 130-159 mg/dL, p=0.882; 160-189 mg/dL, p=0.611; ≥190 mg/dL, p=0.464); likewise, the association between simple lipids and all-cause mortality was not statistically significant after adjusting for confounders. The authors also acknowledged that the association between CVD mortality and higher non-HDL-C levels (≥190 mg/dL) was not statistically significant when adjusting for low-density lipoprotein cholesterol (HR=2.39; 95% CI, 0.92 to 6.13; p=0.073), but concluded that given the trends in p values, non-HDL-C levels appeared superior at predicting mortality, compared with simple lipid testing.

Kunutsor et al (2016) published both a primary analysis and meta-analysis of current studies evaluating the association between levels of paraoxonase-1 (PON-1) and CVD risk; for all analyses, the primary end-point was first-onset CVD.(21) Of 6902 patients drawn from the Prevention of Renal and Vascular End-Stage Disease study, the mean age was 48 years, and 3321 (48%) of the patients were men; for the meta-analysis, researchers used data from 6 studies (n=15,064). The authors noted that PON-1 activity showed a log-linear association with CVD risk but compared the independence of PON-1 with that of high-density lipoprotein cholesterol (HDL-C). In a model adjusted for known risk factors and confounding elements, PON-1 had a hazard ratio (HR) of 0.93 (95% confidence interval [CI], 0.86 to 0.99; p=0.037); comparatively, HDL-C showed a stronger association with risk of CVD, given the same adjustments (HR=0.84; 95% CI, 0.76 to 0.94; p=0.002). Also, the HR for PON-1 was no longer statistically significant when the model accounted for HDL-C (0.95; 95% CI, 0.88 to 1.02; p=0.153), suggesting that the link between PON-1 and HDL-C inhibits the independence of PON-1 as a risk marker. Secondary end points were CHD and stroke; for CHD, as with CV events, HRs for PON-1 were not statistically significant when fully adjusted for confounders (p=0.058) and HDL-C (p=0.471), compared with a strong association between HDL-C and CHD (HR, 0.67; 95% CI, 0.57 to 0.78; p<0.001). The meta-analysis was limited by considerable heterogeneity between studies but resulted in a pooled relative risk of 0.87 (95% CI, 0.80 to 0.96; p=0.005), reported as the CV event per 1 SD increase in PON-1 values. Acknowledging the link between PON-1 and HDL-C as risk markers, the authors concluded that PON-1 added “no significant improvement in CVD risk assessment beyond conventional CVD risk factors.”

Risk Markers and CVD Risk Reclassification

Other studies have demonstrated that risk markers can be used to reclassify patients into different risk categories. Helfand et al (2009) reported on a summary of 9 systematic reviews evaluating novel risk factors’ association with coronary heart disease (CHD).(3) Of the laboratory risk factors evaluated, C-reactive protein (CRP), homocysteine, and lipoprotein (a)

were independent predictors of major CHD events when added to the Framingham risk score (FRS). However, none of the available systematic reviews evaluated the effect of each novel risk factor on risk classification among patients classified as intermediate-risk by the FRS. In a 2012 study of 165,544 patients without baseline CVD enrolled in 37 prospective cohorts, the addition of individual novel lipid-related risk factors to conventional risk classification models resulted in net reclassification improvements of less than 1% with the addition of each marker.(22)

Association Between Multi-Marker Panels and CVD Risk

A more limited body of literature has evaluated the association between panels of markers and CVD risk and/or the reclassification of patients into different risk categories.

Keller et al (2017) conducted a case-control study of the prognostic ability of a panel of 5 micro-RNAs (miR-34a, miR-223, miR-378, miR-499, miR-133), using 2 cohorts with patients randomly selected from previous studies; the combined primary outcome was overall mortality and CV events.(23) In the derivation cohort, 21 of 178 patients experienced a CV event and/or death within 5 years; in the validation cohort, which excluded patients with a history of CVD, 64 of 129 patients died during a 12-year follow-up. While the individual micro-RNAs lacked a significant association with the outcome, the panel as a whole improved both prognostic and predictive value for overall mortality, particularly when adjusted for FRS variables (HR=2.89; 95% CI, 1.32 to 6.33; p=0.008). For the derivation cohort, the investigators reported an increase in the AUC curve from 0.77 to 0.85 with the addition of the miR panel in predicting mortality risk within 5 years (p=0.039); this improvement was confirmed by a net reclassification index (NRI) of 0.42 in the validation cohort (p=0.014). The authors reported that the C index was statistically unaffected by the miR panel, but that the miR panel was significantly associated with mortality in the validation cohort (HR=1.31; 95% CI, 1.03 to 1.66; p=0.03).

A prospective cohort study by de Lemos et al (2017) evaluated a panel of 5 biomarker tests to develop a composite score to predict CVD risk.(24) The 2 cohorts were drawn from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Dallas Heart Study (DHS): from MESA, 3112 (47%) patients were men; and from DHS, 969 (44%) of the patients were men, none of whom had prevalent CVD at baseline. Each test had its own prespecified level of abnormality: a 12-lead electrocardiogram measured the presence or absence of left ventricular hypertrophy; additional tests measured for coronary artery calcium levels greater than 10 units, N-terminal probrain natriuretic peptide (NT-proBNP) levels of 100 pg/mL or more, high sensitivity cardiac troponin (hs-cTNT) levels of 5 ng/L or more, and hs-CRP levels of 3 mg/L or more. Tests data were analyzed as categorical and continuous variables and included models with and without all 5 test results; in all models for MESA, there was an independent association between the tests and the primary end point (global CVD). There was no association between hs-CRP and the primary outcome in the DHS cohort, between hs-CRP and a secondary outcome (atherosclerotic cardiovascular disease) in the MESA cohort, or between hs-CRP and hs-cTNT and atherosclerotic cardiovascular disease in the DHS cohort. In MESA, the C statistic for the primary outcome increased from 0.73 when adjusted for variables alone to 0.786 when adjusted for individual test results (p<0.001), and the DHS cohort showed a similar significant improvement (0.832 to 0.850; p<0.01). The category-free NRI for both cohorts were as follows: MESA NRI, 0.473 (95% CI, 0.383 to 0.563); and DHS NRI, 0.261 (95% CI, 0.052 to 0.470). Based on the results from the 5 tests, the authors assigned each patient a risk score, which

they suggested could aid caregivers in identifying patients who need specific treatment or changes in preventive management.

Greiseneggar et al (2015) evaluated the association between a panel of biomarkers and mortality after a transient ischemic attack and minor ischemic stroke.(25) The study population included 929 patients who were enrolled from 2002-2007 and followed until 2013. Fifteen potential risk markers were prospectively measured (IL-6, CRP, neutrophil-gelatinase-associated lipocalin, soluble tumor necrosis factor α receptor-1 [sTNFR-1], thrombomodulin, fibrinogen, von Willebrand factor [vWF], P-selectin, protein Z, D-dimer, antiphosphorylcholin, N-terminal pro-B-type natriuretic peptide [NT-proBNP], heart-type fatty acid binding protein [HFABP], neuron-specific enolase, and brain-derived neurotrophic factor). None of the biomarkers were predictive of nonfatal ischemic stroke or myocardial infarction (MI). Six factors were individually associated with CVD death, of which the 4 with the strongest association (vWF, HFABP, NT-proBNP, soluble tumor necrosis factor α receptor-1) were entered into a predictive model. The independent contribution of the 4 biomarkers taken together added more prognostic information than the established clinical risk factors used in a conventional model (clinical risk factors: $p=0.002$; 4 biomarkers, $p<0.001$).

Cho et al (2015) reported on the impact of 6 biomarkers (high-sensitivity CRP [hs-CRP]; IL-6; receptor for advanced glycation end products; lipoprotein-associated phospholipase A_2; adiponectin; regulated on activation, normal T cell expressed and secreted) on CVD risk classification in a case-control study with 503 patients with coronary artery disease and 503 healthy controls.(26) The addition of the 6 novel biomarkers to the multivariable risk prediction model led to an improvement in the C statistic (0.953 vs 0.937, $p<0.001$). However, the performance of the model in a cohort not enriched with coronary artery disease patients is unknown.

Wilsgaard et al (2015) evaluated 51 protein biomarkers for association with a risk of incident MI with the goal of developing a clinically significant risk model that would add information to conventional risk models.(27) Patients were drawn from a population-based cohort study to form a case-control study, with 419 cases who experienced the first-ever MI within the 10-year follow-up and 398 controls randomly selected from participants who had no MI during the follow-up. Fifty-one markers were selected for evaluation based on previously reported associations and the availability of immunoassay techniques and passage of internal quality controls. Seventeen markers were predictive of MI after adjustment for traditional CVD risk factors. By adding risk markers back into the traditional risk factor-based model, the authors determined that a composite of apo B/apo AI, plasma kallikrein, lipoprotein (a), and matrix metalloproteinase 9 increased the model's area under the receiver operating curve by 0.027, with an NRI of 9%.

Guarrera et al (2015) evaluated DNA methylation profiles and LINE-1 hypomethylation in the prediction of MI in 2015, analyzing data from 609 cases and 554 controls drawn from the Italian European Prospective Investigation into Cancer and Nutrition study (EPICOR), and the Dutch EPIC study (EPIC-NL).(28) Rather than analyze single 5'-C-phosphate-G-3' sites (CpGs) for their association with CVD, the authors focused on differentially methylated regions, as well as LINE-1 methylation profiles, adjusting models to account for their addition to traditional risk factors. A cluster of 15, 5'- C-phosphate-G3' sites, was statistically significant in both cohorts; the region was in exon 1 of the zinc finger and BTB domain containing the protein 12 gene (ZBTB12) and showed hypomethylation comparable between EPICOR cases

and controls (effect size, -0.019; 95% CI, -0.03 to -0.01; p=1.94 x 10^{-7}, Q=0.005). Although the association was not statistically significant for women in the EPICOR cohort, the EPIC-NL cohort showed significant hypomethylation in the ZBTB12 region between cases and controls as a whole (effect size, -0.013; 95% CI, -0.02 to -0.005; p<0.001), as well as for male (effect size, -0.014; 95% CI, -0.03 to -0.001; p=0.034) and female subgroups (effect size, -0.012; 95% CI, -0.02 to 0.004; p=0.006). There was also significant association between LINE-1 hypomethylation in EPICOR cases vs controls (effect size, -0.511; 95% CI, -0.80 to -0.22; p <0.001, and this association held for the male subgroup (effect size, -0.520; 95% CI, -0.87 to -0.17; p=0.004) but not in the female subgroup (effect size, - -0.496; 95% CI, -1.12 to -0.13; p=0.12). Secondary endpoints involved comparing the risk prediction for MI in the cumulative DNA methylation profile of LINE-1 sequences with that of traditional risk factors alone; while the association between LINE-1 and MI was significant for men in the EPIC-NL cohort (overall response, 1.95; 95% CI, 1.02 to 3.71; p=0.043, reference group above the median), the association was not significant for women in this same cohort (overall response, 1.05; 95% CI, 0.65 to 1.67; p=0.850). When the model included both traditional risk factors and the DNA methylation profile, NRI and integrated discrimination improvement measures were statistically significant, compared with risk factors alone. In the EPIC-NL cohort, NRI and integrated discrimination improvement among men were 0.47 (95% CI, 0.19 to 0.76; p=0.001) and 0.04 (95% CI, 0.01 to 0.08; p=0.004), respectively; among women, they were 0.23 (95% CI, 0.02 to 0.43; p=0.034) and 0.03 (95% CI, 0.01 to 0.05; p=0.001), respectively.

Association Between Multiple-Marker Panels and Wellness

The preponderance of the literature on CVD risk panels have focused on risk of specific events related to CVD (e.g., stroke, MI) or on the development of CVD. With the development of panels that address “wellness” more broadly, studies were sought on the association between risk markers and measures of overall wellness or health. No empirical studies were identified. In 2015, Lara et al reported the recommendations of the U. K. Medical Research Council to develop recommendations for a panel of biomarkers for healthy aging.(29) A variety of markers, some laboratory-based, associated with the physical capability and physiologic, cognitive, endocrine, immune, and sensory functions were proposed.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

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.(3,22,30) 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,(31,32) 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.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of CV risk panel testing has not been established, a chain of evidence cannot be constructed to support the clinical utility of testing.

Section Summary: Cardiovascular Disease Risk Testing Panels
Many of the individual risk factors included in CVD risk panels are associated with an 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 of any individual risk factor beyond simple lipid measures, it is unlikely that the use of CVD risk panels improves outcomes. 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.

SUMMARY OF EVIDENCE
For individuals who have risk factors for CVD who receive CVD risk panels, the evidence includes multiple cohort and case-control studies and systematic reviews of these studies. Relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in CVD risk panels are associated with an 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 clinical utility of any individual risk factor beyond simple lipid measures, 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 health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Cardiology/American Heart Association

The American College of Cardiology and the American Heart Association (2013) issued joint guidelines for the assessment of cardiovascular risk.(33) These guidelines recommend that age- and sex-specific pooled cohort equations, which included total cholesterol and high-density lipoprotein HDL 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). The guidelines did not recommend panels of cardiac risk factors.

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 dyslipidaemias: lipid modification to reduce CV risk.(35) This guideline contains updated recommendations for lipid analyses for CV disease risk estimation. Beyond traditional lipid markers (i.e., total cholesterol, HDL, 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)]. Panel testing was not mentioned in the guidelines.

In 2021, the European Society of Cardiology published a guideline on CVD prevention, however, the guideline did not recommend panels of cardiac risk factors for the assessment of CVD risk.(36)

National Institute for Health and Care Excellence

In 2023, the NICE updated its guidance on risk assessment and reduction, including lipid modification of CVD.(37) The guidance recommended measuring a full lipid profile including total cholesterol, 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 a 40% reduction in non-HDL. No mention was made for panel testing.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

The U.S. Preventive Services Task Force (2018) updated its recommendation on the use of nontraditional risk factors in coronary heart disease risk assessment. No recommendations specific to the use of cardiovascular risk panels were identified.(38)

Government Regulations

National:

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Local:

Local Coverage Determination (LCD): MolDX: Biomarkers in Cardiovascular Risk Assessment (L36523), Original Effective Date: For services performed on or after 06/16/2016, Revision Effective Date: For services performed on or after 3/30/23

Coverage Indications, Limitations, and/or Medical Necessity
Under preventative services, Medicare Part B covers the basic lipid panel (total cholesterol, high density lipoprotein-cholesterol (HDL-C), triglycerides, and low-density lipoprotein-cholesterol (LDL-C) for cardiovascular (CV) disease screening, every 5 years when ordered by a doctor.

NCD 190.23 covers lipid panel testing for symptomatic patients for evaluating atherosclerotic CV disease, to monitor the progress of patients on anti-lipid dietary management and pharmacologic therapy for various lipid disorders.

This policy denies coverage for **all CV risk assessment panels,** except the basic lipid panel, for symptomatic (with signs and symptoms) patients with suspected or documented CV disease because panel testing is not specific to a given patient's lipid abnormality or disease. The policy indicates the medical indication(s) based on published scientific articles and consensus guidelines for individual lipid biomarkers that may be covered to characterize a given lipid abnormality or disease, to determine a treatment plan or to assist with intensification of therapy. Each individual lipid biomarkers must be specifically ordered and the reason for the test order documented in the patient's medical record. The policy denies coverage for all **non-lipid** biomarkers when used for CV risk assessment including but not limited to, biochemical, immunologic, hematologic, and genetic biomarkers for CV risk assessment regardless of whether ordered in a panel or individually.

The following biomarkers, when they are included in a CV risk assessment panel, are non-covered:
- Lipoprotein subclasses;
- LDL particles;
- Intermediate density lipoproteins;
- High density lipoprotein AI9LpAI and AI/AII;
- Lipoprotein(a);
- Apolipoprotein B (Apo B), apo A-I and apo E;
- Lipoprotein-associated phospholipase A2 (Lp-PLA2)
- BNP
- Cystatin C
- Thrombogenic/hematologic actors
- Interleukin-6 (IL-6), tissue necrosis factor- a (TNF- a) , plasminogen activator inhibitor-1 (PAI-1) and IL-6 promoter polymorphism
- Free fatty acids
- Visfatin, angiotensin-converting enzyme 1 (ACE2) and serum amyloid A
- Microalbumin
- Myeloperoxidase (MPO)
- Homocysteine and methylenetetrahydrofolate reductase (MTHFR) mutation testing
- Uric acid
- Vitamin D

- White blood cell count
- Long-chain omega-3 fatty acids in red blood cell membranes
- Gamma-glutamyltransferase (GGT)
- Genomic profiling including CardiaRisk angiotensin gene
- Leptin, ghrelin, adiponectin and adipokines including retinol binding protein 4 (RBP4) and resistin
- Inflammatory markers including VCAM-1, P-selectin (PSEL) and E-selectin (ESEL)
- Cardiovascular risk panels

Note #1: There is no Medicare benefit for screening CV risk assessment testing for asymptomatic (without signs or symptoms of disease) patients. Screening asymptomatic patients for cardiovascular risk is statutorily excluded by Medicare and will not be addressed in this policy.

Note #2: FDA approval/clearance means that a test/assay has analytical and clinical validity. The FDA does not review clinical utility (that the test/assay demonstrates improved patient outcomes). To meet Medicare's "reasonable and necessary" criteria for coverage, a test/assay must have proven clinical utility.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing for Cardiac Ion Channelopathies
- Genetic Testing for Dilated Cardiomyopathy
- Genetic Testing for Inherited Hypertrophic Cardiomyopathy
- Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk
- Myeloperoxidase (MPO) Immunoassay for Cardiac Disease Risk
- Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

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References

1. Niakouei A, Tehrani M, Fulton L. Health Disparities and Cardiovascular Disease. Healthcare (Basel).Mar 22 2020; 8(1). PMID 32235705
2. D'Agostino RB, Sr., Grundy S, Sullivan LM et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. Jul 11, 2001;286(2):180-7. PMID 11448281
3. Helfand M, Buckley DI, Freeman M et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Ann Intern Med*. Oct 6 2009;151(7):496-507. PMID 19805772
4. Brotman DJ, Walker E, Lauer MS et al. In search of fewer independent risk factors. *Arch Intern Med*. Jan 24 2005;165(2):138-45. PMID 15668358

5. Greenland P, Alpert JS, Beller GA et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* Dec 14 2010;56(25):e50-103. PMID 21144964
6. Thorne. Advanced Health Panel. https://www.thorne.com/products/dp/advanced-health-panel. Accessed October 16, 2023.
7. Antonopoulos AS, Angelopoulos A, Papanikolaou P, et al. Biomarkers of Vascular Inflammation for Cardiovascular Risk Prognostication: A Meta-Analysis. JACC Cardiovasc Imaging. Mar 2022; 15(3):460-471. PMID 34801448
8. van Holten TC, Waanders LF, de Groot PG, et al. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. *PLoS One*. May 2013;8(4):e62080. PMID 23630624
9. Gottlieb SS, Harris K, Todd J, et al. Prognostic significance of active and modified forms of endothelin 1 in patients with heart failure with reduced ejection fraction. *Clin Biochem.* Mar 2015;48(4-5):292-296. PMID 25541019.
10. Patterson CC, Blankenberg S, Ben-Shlomo Y, et al. Which biomarkers are predictive specifically for cardiovascular or for non-cardiovascular mortality in men? Evidence from the Caerphilly Prospective Study (CaPS). *Int J Cardiol*. Dec 15 2015;201:113-118. PMID 26298350
11. Malachias MVB, Jhund PS, Claggett BL, et al. NT-proBNP by Itself Predicts Death and Cardiovascular Events in High-Risk Patients With Type 2 Diabetes Mellitus. J Am Heart Assoc. Oct 20 2020; 9(19): e017462. PMID 32964800
12. Schoe A, Schippers EF, Ebmeyer S, et al. Predicting mortality and morbidity after elective cardiac surgery using vasoactive and inflammatory biomarkers with and without the EuroSCORE model. *Chest*. Nov 2014;146(5):1310-1318. PMID 24992322
13. Şaylık F, Akbulut T. Temporal relationship between serum calcium and triglyceride-glucose index and its impact on the incident of the acute coronary syndrome: a cross-lagged panel study. Acta Cardiol. Jul 2023; 78(5): 586-593. PMID 35969239
14. Mohebi R, van Kimmenade R, McCarthy CP, et al. Performance of a multi-biomarker panel for prediction of cardiovascular event in patients with chronic kidney disease. Int J Cardiol. Jan 15 2023; 371: 402-405. PMID 36202172
15. Safo SE, Haine L, Baker J, et al. Derivation of a Protein Risk Score for Cardiovascular Disease Among a Multiracial and Multiethnic HIV+ Cohort. J Am Heart Assoc. Jul 04 2023; 12(13): e027273. PMID 37345752
16. Wallentin L, Eriksson N, Olszowka M, et al. Plasma proteins associated with cardiovascular death in patients with chronic coronary heart disease: A retrospective study. PLoS Med. Jan 2021; 18(1): e1003513. PMID 33439866
17. Wuopio J, Hilden J, Bring C, et al. Cathepsin B and S as markers for cardiovascular risk and all-cause mortality in patients with stable coronary heart disease during 10 years: a CLARICOR trial sub-study. Atherosclerosis. Sep 15, 2018;278:97-102. PMID 30261474
18. Winkel P, Jakobsen JC, Hilden J, et al. Prognostic value of 12 novel cardiological biomarkers in stable coronary artery disease. A 10-year follow-up of the placebo group of the Copenhagen CLARICOR trial. BMJ Open. Aug 20, 2020; 10(8): e033720. PMID 32819979
19. Welsh P, Kou L, Yu C, et al. Prognostic importance of emerging cardiac, inflammatory, and renal biomarkers in chronic heart failure patients with reduced ejection fraction and anaemia: RED-HF study. Eur J Heart Fail. Feb 2018;20(2):268-277. PMID 28960777

20. Harari G, Green MS, Magid A, et al. Usefulness of non-high-density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men in 22-year follow-up. Am J Cardiol. Apr 15 2017;119(8):1193-1198. PMID 2826796
21. Kunutsor SK, Bakker SJ, James RW, et al. Serum paraoxonase-1 activity and risk of incident cardiovascular disease: The PREVEND study and meta-analysis of prospective population studies. *Atherosclerosis*. Feb 2016;245:143-154. PMID 26724525
22. Di Angelantonio E, Gao P et al. Lipid-related markers and cardiovascular disease prediction. *JAMA*. June 2012;307(23):2499-2506. PMID 22797450
23. Keller T, Boeckel JN, Gross S, et al. Improved risk stratification in prevention by use of a panel of selected circulating microRNAs. Sci Rep. Jul 03 2017;7(1):4511. PMID 28674420
24. de Lemos JA, Ayers CR, Levine B, et al. Multimodality strategy for cardiovascular risk assessment: performance in 2 population-based cohorts. Circulation. May 30 2017;135(22):2119-2132. PMID 28360032
25. Greisenegger S, Segal HC, Burgess AI, et al. Biomarkers and mortality after transient ischemic attack and minor ischemic stroke: population-based study. *Stroke*. Mar 2015;46(3):659-666. PMID 25649803
26. Cho S, Lee SH, Park S, et al. The additive value of multiple biomarkers in prediction of premature coronary artery disease. *Acta Cardiol*. Apr 2015;70(2):205-210. PMID 26148381
27. Wilsgaard T, Mathiesen EB, Patwardhan A, et al. Clinically significant novel biomarkers for prediction of first ever myocardial infarction: the Tromso Study. *Circ Cardiovasc Genet*. Apr 2015;8(2):363-371. PMID 25613532
28. Guarrera S, Fiorito G, Onland-Moret NC, et al. Gene-specific DNA methylation profiles and LINE-1 hypomethylation are associated with myocardial infarction risk. *Clin Epigenetics*. 2015;7:133. PMID 26705428
29. Lara J, Cooper R, Nissan J, et al. A proposed panel of biomarkers of healthy ageing. *BMC Med*. Sep 15 2015;13:222. PMID 26373927
30. Paynter NP, Chasman DI, Pare G et al. Association between a literature-based genetic risk score and cardiovascular events in women. *JAMA*. Feb 17 2010;303(7):631-637. PMID 20159871
31. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. Feb 14 2007;297(6):611-619. PMID 17299196
32. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med*. May 15 2008;358(20):2107-2116. PMID 18480203
33. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. June 24 2014;129(25 Suppl2):S49-73. PMID 24222018
34. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Special Report from the American Heart Association and American College of Cardiology. Circulation. Jun 18 2019; 139(25): e1162-e1177. PMID 30586766
35. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. Jan 01 2020; 41(1): 111-188. PMID 31504418

36. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. Sep 07 2021; 42(34): 3227-3337. PMID 34458905
37. National Institute for Health and Care Excellence (NICE). Cardiovascular disease: risk assessment and reduction, including lipid modification [CG181]. updated May 2023; https://www.nice.org.uk/guidance/cg181. Accessed March 28, 2024.
38. U.S. Preventive Services Task Force. Coronary Heart Disease: Screening Using Non-Traditional Risk Factors. 2009. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/coronary-heartdisease-screening-using-non-traditional-risk-factors. Accessed October 16, 2023
39. GeninCode. "Cardio inCode Score." https://genincode.com/cardio-incode-eu/. Accessed March 28, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 3/27/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/15	10/21/14	11/7/14	Joint policy established
1/1/16	10/13/15	10/27/15	Routine maintenance
1/1/17	10/11/16	10/11/16	Routine maintenance
1/1/18	10/19/17	10/19/17	Routine maintenance
1/1/19	10/16/18	10/16/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance Nomenclature removed from body of the policy
9/1/23	6/13/23		Routine maintenance (slp) Vendor managed: Avalon
9/1/24	6/11/24		• Routine maintenance (slp) • Vendor managed: Avalon • 0401U and 0019M added to policy (EI)

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CARDIOVASCULAR RISK PANELS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.