2.04.100	Cardiovascular Risk Panels		
Original Policy Date:	October 30, 2015	**Effective Date:**	February 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 18

Policy Statement

I. Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels, see Policy Guidelines section), are considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

A simple lipid panel is generally composed of the following lipid measures:
- Total cholesterol
- Low-density lipoprotein (LDL) cholesterol
- High-density lipoprotein (HDL) 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.

Coding
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**: MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
- **82465**: Cholesterol, serum or whole blood, total
- **82652**: Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed
- **83090**: Homocysteine
- **83698**: Lipoprotein-associated phospholipase A2 (Lp-PLA2)
- **83718**: Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)
- **83721**: Lipoprotein, direct measurement; LDL cholesterol
- **83880**: Natriuretic peptide
- **84478**: Triglycerides
- **86141**: C-reactive protein; high sensitivity (hsCRP)

If the testing involves multiple analytes and an algorithmic analysis, the unlisted multianalyte assay with algorithmic analysis (MAAA) code 81599 would be reported.

Below is a CPT PLA code:
- **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

The following CPT code is available for a direct single-step method for the quantification of small dense low-density lipoprotein cholesterol:
- **83722**: Lipoprotein, direct measurement; small dense LDL cholesterol

There is a CPT PLA code that reports the Mayo Clinic Laboratory MI-HEART Ceramides (Plasma):
- **0119U**: Cardiology, ceramides by liquid chromatography-tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events

Description

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 panels report the results of multiple individual tests, as distinguished from quantitative risk scores that combine the results of multiple markers into a single score.

Related Policies

- Ultrasonographic Measurement of Carotid Intimal-Medial Thickness as an Assessment of Subclinical Atherosclerosis

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 FDA has chosen not to require any regulatory review of this test.

Rationale

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

Risk Assessment

Components of CVD risk include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. Also, numerous laboratory tests have been associated with CVD risk, most prominently lipids such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL). These clinical and lipid factors are often combined into simple risk prediction instruments, such as the Framingham Risk Score.[2] The Framingham Risk Score provides an estimate of the 10-year risk for developing cardiac disease and is currently used in clinical care to determine the aggressiveness of risk factor intervention, such as the decision to treat hyperlipidemia with statins.

Many additional biomarkers, genetic factors, and radiologic measures have been associated with an increased risk of CVD. Over 100 emerging risk factors have been proposed as useful for refining estimates of CVD risk.[3,4,5] 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-methylene tetrahydrofolate reductase (*MTHFR*) variant or the prothrombin gene variants, have been associated with increased CVD risk. Also, numerous single nucleotide variants have been associated with CVD in large genome-wide studies.

Risk Panel Testing

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

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

- **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 A2 (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 the metabolism of clopidogrel, ticagrelor, warfarin, beta-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 glycoprotein (GP) IIIA variant human platelet antigen (HPA)-1 (PLA1/2), *MTHFR* gene, angiotensin-converting enzyme insertion/deletion, apo B, apo E.

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. An example of these panels is:

- **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,]

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities

[Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Cardiovascular Disease Risk Testing Panels
Clinical Context and Test Purpose
The purpose of cardiovascular disease (CVD) risk panel testing in individuals who have risk factors for CVD is to inform management and treatment decisions.

The following PICO was 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 decreases 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 Cardiovascular Disease Risk

Systematic Reviews
There is a large evidence base on the association between individual risk markers and CVD 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 cardiovascular (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 patients with a history of CVD. Only 2 meta-analyses that reported associations with ischemic stroke in patients 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 Cardiovascular 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)[8,]

Apo: apolipoprotein; cTn: cardiac troponin; CV: cardiovascular; CVD: cardiovascular disease; HDL: high-density lipoprotein; HR; hazard ratio; OR: ; 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 markers 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 with CVD- and non-CVD-related death[10,], 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 log scale of the distribution of the biomarker in the replication cohort, 2.079; 95% CI , 1.799 to 2.402) and high-sensitivity troponin T (HR, 1.715; 95% CI, 1.491 to 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 CV risk and mortality in patients with stable CHD.[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 an increased risk of CV events and mortality (p<.001 for both groups), but cathepsin S was not (p>.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 (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 endpoint of heart failure hospitalization or CV death over 28 months of follow-up (n=834) was evaluated using Cox proportional hazards regression. Analysis showed that NT-proBNP (HR, 3.96) and high-sensitivity

troponin T (HR, 3.09) far outperformed other emerging biomarkers studied for predicting adverse CV 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-high-density lipoprotein cholesterol (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 one 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=.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 to 159 mg/dL, p=.882; 160 to 189 mg/dL, p=.611; ≧190 mg/dL, p=.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=.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 endpoint was first-onset CVD.[21,] Of 6902 patients drawn from the Prevention of Renal and Vascular End-stage Disease (PREVEND) 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 HDL-C. In a model adjusted for known risk factors and confounding elements, PON-1 had an HR of 0.93 (95% CI, 0.86 to 0.99; p=.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=.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=.153), suggesting that the link between PON-1 and HDL-C inhibits the independence of PON-1 as a risk marker. Secondary endpoints were CHD and stroke. For CHD, as with CV events, HRs for PON-1 were not statistically significant when fully adjusted for confounders (p=.058) and HDL-C (p=.471), compared with a strong association between HDL-C and CHD (HR, 0.67; 95% CI, 0.57 to 0.78; p<.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=.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 Cardiovascular Disease 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 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 Multimarker Panels and Cardiovascular Disease 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=.008). For the derivation cohort, the investigators reported an increase in the area under the curve from 0.77 to 0.85 with the addition of the miR panel in predicting mortality risk within 5 years (p=.039). This improvement was confirmed by a net reclassification index (NRI) of 0.42 in the validation cohort (p=.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=.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, NT-proBNP levels of 100 pg/mL or more, high-sensitivity cardiac troponin levels of 5 ng/L or more, and high-sensitivity CRP (hs-CRP) levels of 3 mg/L or more. Test 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 endpoint (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 CVD) in the MESA cohort, or between hs-CRP and high-sensitivity cardiac troponin and atherosclerotic CVD 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<.001), and the DHS cohort showed a similar significant improvement (0.832 to 0.850; p<.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.

Greisenegger 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 to 2007 and followed until 2013. Fifteen potential risk markers were prospectively measured (interleukin 6, CRP, neutrophil-gelatinase-associated lipocalin, soluble tumor necrosis factor α receptor-1, thrombomodulin, fibrinogen, von Willebrand factor, P-selectin, protein Z, D-dimer, antiphosphorylcholin, NT-proBNP, heart-type fatty acid-binding protein, 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 (von Willebrand factor, heart-type fatty acid-binding protein, NT-proBNP, and 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=.002; 4 biomarkers , p<.001).

Cho et al (2015) reported on the impact of 6 biomarkers (hs-CRP; interleukin 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 of 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<.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 a 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 Long Interspersed Nuclear Element 1 (LINE-1) hypomethylation in the prediction of MI, 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 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-G-3' 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<.001), as well as for male (effect size, -0.014; 95% CI, -0.03 to -0.001; p=.034) and female subgroups (effect size, -0.012; 95% CI, -0.02 to -0.004; p=.006). There was also a significant association between LINE-1 hypomethylation in EPICOR cases versus controls (effect size, -0.511; 95% CI, -0.80 to -0.22; p<.001), and this association held for the male subgroup (effect size, -0.520; 95% CI, -0.87 to -0.17; p=.004) but not in the female subgroup (effect size, -0.496; 95% CI, -1.12 to -0.13; p=.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=.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=.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=.001) and 0.04 (95% CI, 0.01 to 0.08; p=.004), respectively; among women, they were 0.23 (95% CI, 0.02 to 0.43; p=.034) and 0.03 (95% CI, 0.01 to 0.05; p=.001), respectively.

Association Between Multimarker Panels and Wellness

The preponderance of the literature on CVD risk panels have focused on the 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. Lara et al (2015) 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, 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.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US

representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology/American Heart Association

In 2013, the American College of Cardiology and the American Heart Association issued joint guidelines for the assessment of cardiovascular disease (CVD) risk.[33,]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 CVD 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.

In 2019, the American College of Cardiology/American Heart Association issued a special report on the use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic CVD.[34,] Although the report did not recommend specific novel cardiac risk factors or panels of cardiac risk factors, it discusses features of current US-based cardiovascular (CV) risk assessment tools including the Reynolds Risk Score, which includes hs-CRP level as one of its variables, mentions risk-enhancing factors for a clinician-patient risk discussion including elevated hs-CRP, lipoprotein(a), and apolipoprotein B levels, and the use of CAC measurement to reclassify CVD risk.

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, 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 IIa recommendation; Level C evidence].

In 2021, the European Society of Cardiology published a guideline on CVD prevention ; however, the guideline did not recommend specific novel cardiac risk factors or panels of cardiac risk factors for the assessment of CVD risk.[36,] The guideline states that "main causal and modifiable ASCVD [atherosclerotic cardiovascular disease] risk factors are blood apolipoprotein-B-containing lipoproteins, high BP [blood pressure], cigarette smoking, and DM [diabetes mellitus]". The guideline also states that the ABI may be considered as a risk modifier in CVD risk assessment but the "routine collection of other potential modifiers, such as genetic risk scores, circulating or urinary biomarkers, or

vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination), is not recommended."

U.S. Preventive Services Task Force Recommendations
No recommendations specific to the use of CVD risk panels were identified. In 2018, the U.S. Preventive Services Task Force updated its recommendation on the use of nontraditional risk factors in CVD risk assessment:
"The USPSTF concludes that there are insufficient adequately powered clinical trials evaluating the incremental effect of the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hs-CRP) level, or coronary artery calcium (CAC) score in risk assessment and initiation of preventive therapy. Furthermore, the clinical meaning of improvements in measures of calibration, discrimination, and reclassification risk prediction studies is uncertain."[37,]

Medicare National Coverage
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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT03599531	A Pilot Study to Evaluate the Utility of the SomaLogic CVD Secondary Risk Panel as a Tool to Stratify Cardiovascular Risk	244	Oct 2020

NCT: national clinical trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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

Type	Code	Description
	0119U	Cardiology, ceramides by liquid chromatography-tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events
	0377U	Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables) *(Code effective 4/1/2023)*
	0401U	Cardiology (coronary heart disease [CAD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event *(Code effective 10/1/2023)*
	81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
	82465	Cholesterol, serum or whole blood, total
	82652	Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed
	83090	Homocysteine
	83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
	83718	Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)
	83721	Lipoprotein, direct measurement; LDL cholesterol
	83722	Lipoprotein, direct measurement; small dense LDL cholesterol
	83880	Natriuretic peptide
	84478	Triglycerides
	86141	C-reactive protein; high sensitivity (hsCRP)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/30/2015	BCBSA Medical Policy adoption
03/01/2016	Policy revision without position change
05/01/2017	Policy revision without position change
02/01/2018	Policy revision without position change
02/01/2019	Policy revision without position change. Coding update.
11/01/2019	Coding update
02/01/2020	Annual review. No change to policy statement. Literature review updated.
02/01/2021	Annual review. No change to policy statement. Literature review updated.
02/01/2022	Annual review. No change to policy statement. Literature review updated.
02/01/2023	Annual review. No change to policy statement. Literature review updated.
06/01/2023	Coding update
08/01/2023	Coding update
11/01/2023	Coding update
02/01/2024	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Cardiovascular Risk Panels 2.04.100 Policy Statement: I. Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels, see Policy Guidelines section), are considered **investigational**.	Cardiovascular Risk Panels 2.04.100 Policy Statement: I. Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels, see Policy Guidelines section), are considered **investigational**.