

## Cardiovascular Risk Panels

<b>Policy Number:</b> MM.02.032	<b>Current Effective Date:</b> November 18, 2022
<b>Lines of Business:</b> PPO; HMO; Quest Integration	<b>Original Effective Date:</b> September 01, 2017
<b>Place of Service:</b> Outpatient	<b>Precertification:</b> Not Required

### I. 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.

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. The 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 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 outcomes.

### II. Policy Criteria

Cardiovascular risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels), are not covered because they are not known to be effective in improving health outcomes.

### III. Administrative Guidelines

- A. The provider cannot bill or collect charges for these services unless a written acknowledgement of financial responsibility, specific to the service, is obtained from the Member prior to the time services are rendered. Modifier code GA should be appended to the CPT when billing for these services.
- B. Applicable codes that do not meet payment determination, include but are not limited to:

CPT Code	Description
81291	MTHFR (5,10-methylenetetrahydrofolate reductase)(e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
86141	C-reactive protein; high sensitivity (hsCRP)

83700	Lipoprotein, blood; electrophoretic separation and quantitation
83701	high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (e.g., electrophoresis, ultracentrifugation)
83704	quantitation of lipoprotein particle numbers and lipoprotein particle subclasses (e.g., nuclear magnetic resonance spectroscopy)
83695	Lipoprotein (a)
83876	Myeloperoxidase
82172	Apolipoprotein, each (except when billed for hepatitis C)
0119U	Cardiology, ceramides by liquid chromatography–tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events

#### IV. Scientific Background

##### Cardiovascular Disease

CVD remains the single largest cause of morbidity and mortality in the developed world. 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. The Framingham Risk Score provides an estimate of the ten-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. 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 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 one 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, F2 isoprostanes.
- **Applied Genetics Cardiac Panel:** genetic variants associated with the coronary artery disease: cytochrome p450 variants associated with the metabolism of clopidogrel, ticagrelor, warfarin, b-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 (PLA1/2), MTHFR gene, angiotensin-converting enzyme insertion/deletion, apo B, apo E.
- **Cardiac-Related Test Panels (Singulex):** Several panels of markers related to cardiac dysfunction, vascular inflammation and dysfunction, dyslipidemia, and cardiometabolic status are offered by Singulex. Some are offered in conjunction with a CVD testing and wellness management service. The test panels use an immunoassay method referred to as “ultra-sensitive Single Molecule Counting [SMC] technology.
  - Cardiac Dysfunction panel: SMC™ cTnI (high-sensitivity troponin), N-terminal pro-B-type natriuretic peptide.
  - Vascular Inflammation and Dysfunction panel: SMC™ IL-6, SMC™ IL-17A, SMC™ TNF $\alpha$ , SMC™ Endothelin, Lp-PLA2, hs-CRP, homocysteine, vitamin B12, folate.
  - Dyslipidemia panel: total cholesterol, LDL-C (direct), apo B, small dense LDL, HDL cholesterol, apo AI, HDL2b, triglycerides, Lp(a).
  - Cardiometabolic panel: parathyroid, vitamin D, calcium, magnesium, leptin, adiponectin, ferritin, cortisol, cystatin C, hemoglobin A1c, glucose, insulin, thyroid-stimulating hormone, T3 and free T4, uric acid, liver panel, renal panel, thyroid peroxidase antibody, thyroglobulin antibody.

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. Examples of these panels include:

- **Cardiometabolic Panel (Singulex):** described above.
- **WellnessFX Premium (WellnessFX):** total cholesterol, HDL, LDL, triglycerides, apo AI, apo B, Lp(a), Lp-PLA2, omega-3 fatty acids, free fatty acids, lipid particle numbers, lipid particle sizes, blood urea nitrogen/creatinine, aspartate aminotransferase and alanine aminotransferase, total bilirubin, albumin, total protein, dehydroepiandrosterone, free testosterone, total testosterone,

estradiol, sex hormone binding globulin, cortisol, insulin-like growth factor 1, insulin, glucose, hemoglobin A1c, total T4, T3 uptake, free T4 index, thyroid-stimulating hormone, total T3, free T3, reverse T3, free T4, hs-CRP, fibrinogen, homocysteine, complete blood count with differential, calcium, electrolytes, bicarbonate, ferritin, total iron-binding capacity, vitamin B12, red blood cell magnesium, 25-hydroxy vitamin D, progesterone, follicle-stimulating hormone, luteinizing hormone.

### **Regulatory Status**

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

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

### **Rationale**

This evidence review was created in November 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 14, 2019.

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.

## **Cardiovascular Disease Risk Testing Panels**

### **Clinical Context and Test Purpose**

The purpose of CVD risk panel testing in patients who have risk factors for CVD is to inform management and treatment decisions.

The question addressed in this evidence review is: Does the use of CVD risk panels in patients who have a risk for CVD improve health outcomes?

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

### **Patients**

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

**Interventions**

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

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

**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 five to ten 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.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

**Association Between Single Risk Markers and CVD 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.<sup>2,4</sup> 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 (ie, CV events and stroke in CVD-naive populations) and secondary CV events (ie, CV events and stroke in populations with a history of CVD).<sup>7</sup> 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 two 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 CVD Risk**

Marker	RR, HR, or OR	95% Confidence Interval
<b>Prediction of CV events in patients with no history of CV disease</b>		
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
<b>Prediction of CV events in patients with positive history of CVD</b>		
cTn I and T	9.39 (OR)	6.46 to 13.67
High sensitivity C-reactive protein	5.65 (OR)	1.17 to 18.73
Creatinine	3.98 (HR)	3.02 to 5.24
Cystatin C	2.62 (RR)	2.05 to 3.37
<b>Prediction of ischemic stroke in patients with positive history of CVD</b>		
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 who had heart failure with reduced ejection fraction; troponin and B-type natriuretic peptide in predicting CVD-related death; growth differentiation factor and interleukin 6 with CVD- and non-CVD-related death; and mid-regional pro-atrial natriuretic peptide and C-terminal pro-endothelin-1 with morbidity and mortality after cardiac surgery.

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 events and mortality in patients with stable CHD. The researchers used the drug trial's 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 ( $p < 0.001$  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.

Welsh et al (2017) analyzed data from the Reduction of Events by Darbepoetin Alfa in Heart Failure drug trial to assess the prognostic value of emerging biomarkers in CVD screening. A panel of several biomarkers were 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 N-terminal probrain natriuretic peptide (NT-proBNP) (hazard ratio [HR], 3.96) and high-sensitivity troponin T (HR=3.09) far outperformed other emerging biomarkers studied at 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. 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% confidence interval [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 not statistically insignificant after adjusting for potential confounders (for 130-159 mg/dL, p=0.882; 160-189 mg/dL, p=0.611;  $\geq 190$  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 ( $\geq 190$  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 endpoint was first-onset CVD. 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 (total n=15064 patients). 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=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 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=0.058) and HDL-C (p=0.471), compared with a strong association between HDL-C and CHD (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 standard deviation 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 CHD. 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 165544 patients without baseline CVD enrolled in 37 prospective cohorts, the addition of individual novel lipid-related risk factors to conventional risk-classification models including total cholesterol and HDL-C, net reclassification improvements were less than 1% with the addition of each of these markers to risk scores containing conventional risk factors.

### **Association Between Multimarker 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. 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 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 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=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. 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 U, 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. Tests data were analyzed as categorical and as continuous variables, and included models with and without all five 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<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 results from the five 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. Further discussion of this risk score is beyond the scope of this evidence review.

Greisenegger et al (2015) evaluated the association between a panel of biomarkers and mortality after the transient ischemic attack and minor ischemic stroke. The study population included 929 patients who were enrolled from 2002-2007 and followed until 2013. Fifteen potential risk markers were prospectively measured (interleukin 6, CRP, neutrophil-gelatinase-associated lipocalin, soluble tumor necrosis factor  $\alpha$  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, brain-derived neurotrophic factor). None of the biomarkers was predictive of nonfatal ischemic stroke or myocardial infarction (MI). Six factors were individually associated with CVD death, of which the four with the strongest association (von Willebrand factor, heart-type fatty acid-binding protein, NT-proBNP, soluble tumor necrosis factor  $\alpha$  receptor-1) were entered into a predictive model. The independent contribution of the four biomarkers taken together added more prognostic information than the established clinical risk factors used in a conventional model (clinical risk factors:  $p=0.002$ ; four biomarkers:  $p<0.001$ ).

Cho et al (2015) reported on the impact of 6 biomarkers (hs-CRP; interleukin 6; receptor for advanced glycation end products; lipoprotein-associated phospholipase A2; 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. 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 risk of incident MI with the goal of developing a clinically significant risk model that would add information to conventional risk models. 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 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). Rather than analyze single 5 $\zeta$ -C-phosphate-G-3 $\zeta$  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 $\zeta$ -C-phosphate-G-3 $\zeta$  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;  $p=1.94 \times 10^{-7}$ ,  $Q=0.005$ ). 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 Multimarker Panels and Wellness**

The preponderance of the literature on CVD risk panels have focused on the risk of specific events related to CVD (eg, 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. 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 avoid unnecessary 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. Because of this uncertain impact on management, the clinical utility for any of the individual risk markers is either low or uncertain.

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

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

Furthermore, there are no standardized methods for combining multiple individual risk factors with each other, or with established risk prediction instruments such as the FRS. Therefore, there is a potential for both overestimation and underestimation of the true cardiac risk. This may lead to management decisions based on an inaccurate risk assessment.

### **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 cardiovascular risk panel testing has not been established, a chain of evidence cannot be constructed to support the clinical utility of testing.

### **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. The 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 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 outcomes.

## **V. Supplemental Information**

### **Practice Guidelines and Position Statements**

The American College of Cardiology and the American Heart Association (2013) issued joint guidelines on the assessment of cardiovascular disease risk. These guidelines recommend that age- and sex-specific pooled cohort equations, which include total cholesterol and high-density lipoprotein to predict the 10-year risk of a first hard atherosclerotic cardiovascular disease event, be used in non-Hispanic blacks and non-Hispanic whites between 40 and 79 years of age (American Heart Association/American College of Cardiology class of recommendation I, American Heart Association/American College of Cardiology level of evidence B). Regarding newer risk markers after quantitative risk assessment, the guidelines stated the following: “If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of  $\geq 1$  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.

### U.S. Preventive Services Task Force Recommendations

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

“The (USPSTF) concludes that the evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors to screen asymptomatic men and women with no history of CHD to prevent CHD events. Grade: I

“The nontraditional risk factors included in this recommendation are high-sensitivity C-reactive protein (hs-CRP), ankle-brachial index (ABI), leukocyte count, fasting blood glucose level, periodontal disease, carotid intima-media thickness (carotid IMT), coronary artery calcification (CAC) score on electron-beam computed tomography (EBCT), homocysteine level, and lipoprotein(a) level.”

This USPSTF recommendation is currently being updated.

### 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 ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Ongoing and Unpublished Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT03599531	A Pilot Study to Evaluate the Utility of the SomaLogic CVD Secondary Risk Panel as a Tool to Stratify Cardiovascular Risk	200	Dec 2018
<b>Unpublished</b>			
NCT00969865 <sup>a</sup>	Individualized Comprehensive Atherosclerosis Risk-reduction Evaluation Program (iCARE)	170	Dec 2016 (completed)

## VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

## VII. References

1. 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):180-187. PMID 11448281
2. 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
3. Brotman DJ, Walker E, Lauer MS, et al. In search of fewer independent risk factors. *Arch Intern Med*. Jan 24 2005;165(2):138-145. PMID 15668358
4. 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
5. Singulex. The Sgx Clarity System. 2015; <https://www.singulex.com/sgx-clarity-system/>. Accessed October 14, 2019.
6. WellnessFX. Premium: The Deluxe Deep Dive. n.d.; <https://www.wellnessfx.com/premium>. Accessed October 14, 2019.
7. 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
8. 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
9. 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
10. 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
11. 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*, 2018 Sep 28;278:97-102. PMID 30261474
12. 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.*, 2017 Sep 30;20(2). PMID 28960777

13. 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 28267961
14. 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
15. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, et al. Lipid-related markers and cardiovascular disease prediction. *JAMA*. Jun 20 2012;307(23):2499-2506. PMID 22797450
16. 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
17. 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
18. 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
19. 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
20. 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
21. 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
22. 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
23. 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
24. 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
25. 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
26. Goff DC, Jr., 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*. Jun 24 2014;129(25 Suppl 2):S49-73. PMID 24222018
27. U.S. Preventive Services Task Force. Coronary Heart Disease: Screening Using Non-Traditional Risk Factors. 2009; <https://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-summary--html/cardiovascular-disease-screening-using-nontraditional-risk-assessment>. Accessed October 14, 2019.
28. BCBSA Medical Policy Reference Manual. Cardiovascular Risk Panels #2.04.100. Last review January 2020.

#### VIII. Policy History

Action Date	Action
April 12, 2017	Policy reviewed by Medical Director Stefanie Park, M.D.

April 18, 2017	Policy approved by Medical Directors
April 28, 2017	Policy approved by UMC
September 15, 2017	Policy reviewed by Medical Director Stefanie Park, M.D.
September 19, 2017	Policy approved by Medical Directors
September 22, 2017	Policy approved by UMC
January 16, 2018	Policy reviewed by Medical Director Stefanie Park, M.D.
February 20, 2018	Policy approved by Medical Directors
February 23, 2018	Policy approved by UMC
February 28, 2019	Policy reviewed by Medical Director Rupal Gohil, M.D.
March 19, 2019	Policy approved by Medical Directors
March 22, 2019	Policy approved by UMC
February 27, 2020	Policy reviewed by Medical Director Rupal Gohil, M.D.
March 03, 2020	Policy approved by Medical Directors
March 27, 2020	Policy approved by UMC
July 01, 2020	60 Day Notice
November 30, 2021	Policy reviewed by Medical Director Rupal Gohil, M.D.
December 7, 2021	Policy approved by Medical Directors
December 17, 2021	Policy approved by UMC
November 8, 2022	Policy reviewed by Medical Director Rupal Gohil, M.D.
November 15, 2022	Policy approved by Medical Directors
November 18, 2022	Policy approved by UMC