



Louisiana

Cardiovascular Risk Panels

Policy # 00398

Original Effective Date: 02/19/2014

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Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers cardiovascular (CV) risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels), to be **investigational**.* (See Note)

Note:

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

- *Low-density lipoprotein (LDL) cholesterol*
- *High-density lipoprotein (HDL) cholesterol*
- *Triglycerides*
- *Total cholesterol*

Certain calculated ratios, such as the total/high-density lipoprotein (HDL) 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), etc., are not considered to be components of a simple lipid profile.

Background/Overview

CARDIOVASCULAR DISEASE

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 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 LDL and 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 10-year risk for developing cardiac disease and is currently used in clinical care to

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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 syndrome, such as specific dyslipidemic profiles or serum insulin levels, have been associated with 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:

- **Cardiac Risk Panel (Health Diagnostics):** *MTHFR* gene analysis, common variants; vitamin D, 1,25 dihydroxy; B-type natriuretic peptide; lipoprotein-associated phospholipase A₂ (Lp-PLA₂); myeloperoxidase; apolipoprotein (apo); immune complex assay; lipoprotein, blood; electrophoretic separation and quantitation; very long chain fatty acids; total cholesterol; HDL; LDL; triglycerides; hs-CRP; Lp(a); insulin, total; fibrinogen; multiple SNVs associated with coronary artery disease.
- **CV Health Plus Genomics™† Panel (Genova Diagnostics):** apo E; prothrombin; factor V Leiden; fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; Lp(a); Lp-PLA₂; *MTHFR* gene; triglycerides; very-low-density lipoprotein (VLDL); VLDL size; vitamin D; hs-CRP.
- **CV Health Plus™† Panel (Genova Diagnostics):** fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; lipid panel; 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.

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- **Applied Genetics Cardiac Panel:** genetic variants associated with coronary artery disease: cytochrome p450 variants associated with metabolism of clopidogrel, ticagrelor, warfarin, β -blockers, rivaroxaban, prasugrel (2C19, 2C9/VKORC1, 2D6, 3A4/3A5), factor V Leiden, prothrombin gene, *MTHFR* gene, *APOE* gene.
- **Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel:** factor V Leiden, factor V R2, prothrombin gene, factor XIII, fibrinogen-455, plasminogen activator inhibitor-1 (PAI-1), platelet GP IIIA variant HPA-1 (PLA1/2), *MTHFR* gene, angiotensin-converting enzyme insertion/deletion (ACE I/D), 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™ \ddagger cTnl (high-sensitivity troponin), N-terminal pro-B-type natriuretic peptide.
 - Vascular Inflammation and Dysfunction panel: SMC™ \ddagger IL-6, SMC™ \ddagger IL-17A, SMC™ \ddagger TNF α , SMC™ \ddagger 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, HDL_{2b}, triglycerides, Lp(a).
 - Cardiometabolic panel: parathyroid, vitamin D, calcium, magnesium, leptin, adiponectin, ferritin, cortisol, cystatin C, hemoglobin A_{1c}, 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 A_{1c}, 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.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Multiple assay methods for cardiac risk marker components, such as lipid panels and other biochemical assays, have clearance for marketing through the U.S. FDA 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

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.

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

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

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Helfand et al. have suggested a similar framework for evaluating the utility of risk factors that includes the concept of reclassifying patients into clinically relevant risk factors. These suggested criteria are as follows:

- Risk factor should be easily and reliably measured.
- Risk factor should be an independent predictor of major CV events in patients with an intermediate risk of CV disease and no history of CV disease.
- Risk factor should reclassify a substantial portion of intermediate risk patients as high-risk.
- Reclassified individuals should be managed differently than they otherwise would have been.
- If other risk factors provide similar prognostic information, then convenience, availability, cost and safety should be considered in choosing among them.

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 use of CVD risk panels in patients who have a risk for CVD improve health outcomes?

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

Patients

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 comparator of interest is the 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.

Timing

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 ten years.

Setting

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

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Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires 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

Association Between Single Risk Markers and CVD Risk

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. In 2013, van Holten et al 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). 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 CVD Risk

Marker	RR, HR, or OR	95% Confidence Interval
Prediction of CV events in patients with no history of CVD		
C-reactive protein	2.43 (RR)	2.10 to 2.83
Fibrinogen	2.33 (HR)	1.91 to 2.84
Cholesterol	0.44 (HR)	0.42 to 0.48
Apo B	1.99 (RR)	1.65 to 2.39
Apo A:Apo B ratio	1.86 (RR)	1.55 to 2.22
HDL	1.83 (HR)	1.65 to 2.03
Vitamin D	1.83 (HR)	1.19 to 2.80
Prediction of CV events in patients with a history of CVD		
cTn I and T	9.39 (OR)	6.46 to 13.67
High-sensitivity C-reactive protein	5.65 (OR)	1.71 to 18.73
Creatinine	3.98 (HR)	3.02 to 5.24
Cystatin C	2.62 (RR)	2.05 to 3.37
Prediction of ischemic stroke in patients with a history of CVD		
Fibrinogen	1.75 (HR)	1.55 to 1.98
Uric acid	1.47 (RR)	1.19 to 1.76

Adapted from van Holten et al (2013).⁷

Apo: apolipoprotein; cTn: cardiac troponin; CV: cardiovascular; CVD: cardiovascular disease; HDL: high-density lipoprotein; HR; hazard ratio; OR: odds ratio; RR: relative risk.

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Since the publication of the van Holten 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 (IL-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.

In 2016, Kunutsor et al published both a primary analysis and meta-analysis of current studies evaluating the association between levels of paraoxonase-1 (PON-1) and CVD risk; for all analyses, the primary end point was first-onset CVD. Of 6902 patients drawn from the 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 (total N=15,064 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 high-density lipoprotein cholesterol (HDL-C). In a model adjusted for known risk factors and confounding elements, PON-1 had a hazard ratio (HR) of 0.93 (95% confidence interval [CI], 0.86 to 0.99; $p=0.037$); comparatively, HDL-C showed a stronger association with risk of CVD, given the same adjustments (HR=0.84; 95% CI, 0.76 to 0.94; $p=0.002$). Also, the HR for PON-1 was no longer statistically significant when the model accounted for HDL-C (0.95; 95% CI, 0.88 to 1.02; $p=0.153$), suggesting that the link between PON-1 and HDL-C inhibits the independence of PON-1 as a risk marker. Secondary end points were CHD and stroke; for CHD, as with CV events, HRs for PON-1 were not statistically significant when fully adjusted for confounders ($p=0.058$) and HDL-C ($p=0.471$), compared with a strong association between HDL-C and CHD (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.”

A 2017 prospective cohort study by Harari et al analyzed the association between non-HDL-C levels and CVD mortality in a long-term follow-up of 4832 men drawn from the Cardiovascular Occupational Risk Factor Determination in Israel Study (CORDIS). 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; $p=0.020$). 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

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confounders (for 130-159 mg/dL, $p=0.882$; 160-189 mg/dL, $p=0.611$; ≥ 190 mg/dL, $p=0.464$); likewise, the association between simple lipids and all-cause mortality was not statistically significant after adjusting for confounders. The authors also acknowledged that the association between CVD mortality and higher non-HDL-C levels (≥ 190 mg/dL) was not statistically significant when adjusting for low-density lipoprotein cholesterol (HR=2.39; 95% CI, 0.92 to 6.13; $p=0.073$), but concluded that given the trends in p values, non-HDL-C levels appeared superior at predicting mortality, compared with simple lipid testing.

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 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 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.

Greisenegger et al (2015) evaluated the association between a panel of biomarkers and mortality after 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 (IL-6, CRP, neutrophil-gelatinase-associated lipocalin, soluble tumor necrosis factor α receptor-1 [sTNFR-1], thrombomodulin, fibrinogen, von Willebrand factor [vWF], P-selectin, protein Z, D-dimer, antiphosphorylcholin, N-terminal pro-B-type natriuretic peptide [NT-proBNP], heart-type fatty acid binding protein [HFABP], neuron-specific enolase, 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 (vWF, HFABP, NT-proBNP, sTNFR-1) were entered into a predictive model. The independent contribution of the 4 biomarkers taken together added more prognostic information than the established clinical risk factors used in a conventional model (clinical risk factors: $p=0.002$; 4 biomarkers: $p<0.001$).

Cho et al (2015) reported on the impact of 6 biomarkers (high-sensitivity CRP [hs-CRP]; IL-6; receptor for advanced glycation end products; lipoprotein-associated phospholipase A_2 ; adiponectin; regulated on activation, normal T cell expressed and secreted) on CVD risk classification in a case-control study 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, $p<0.001$).

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However, the performance of the model in a cohort not enriched with coronary artery disease patients is unknown.

In 2017, Keller et al 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 AUC curve from 0.77 to 0.85 with the addition of the miR panel in predicting mortality risk within 5 years (p=0.039); this improvement was confirmed by a net reclassification index (NRI) of 0.42 in the validation cohort (p=0.014). The authors reported that the C index was statistically unaffected by the miR panel, but that the miR panel was significantly associated with mortality in the validation cohort (HR=1.31; 95% CI, 1.03 to 1.66; p=0.03).

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 evaluated DNA methylation profiles and LINE-1 hypomethylation in the prediction of MI in 2015, analyzing data from 609 cases and 554 controls drawn from the Italian European Prospective Investigation into Cancer and Nutrition study (EPICOR), and the Dutch EPIC study (EPIC-NL). Rather than analyze single 5'-C-phosphate-G-3' sites (CpGs) for their association with CVD, the authors focused on differentially methylated regions, as well as LINE-1 methylation profiles, adjusting models to account for their addition to traditional risk factors.

A cluster of 15 CpGs, was statistically significant in both cohorts; the region was in exon 1 of the zinc finger and BTB domain containing the protein 12 gene (*ZBTB12*), and showed hypomethylation comparable between EPICOR cases and controls (effect size, -0.019; 95% CI, -0.03 to -0.01; p=1.94 x 10⁻⁷, Q=0.005). Although the association was not statistically significant for women in the EPICOR cohort, the EPIC-NL cohort showed significant hypomethylation in the *ZBTB12* region between cases and controls as a whole (effect size, -0.013; 95% CI, -0.02 to -0.005; p<0.001), as well as for male (effect size, -0.014; 95% CI, -0.03

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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.

A 2017 prospective cohort study by de Lemos et al 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, N-terminal probrain natriuretic peptide (NT-proBNP) levels of 100 pg/mL or more, high-sensitivity cardiac troponin (hs-cTNT) levels of 5 ng/L or more, and hs-CRP levels of 3 mg/L or more. Tests data were analyzed as categorical and as continuous variables, and included models with and without all 5 test results; in all models for MESA, there was an independent association between the tests and the primary end point (global CVD). There was no association between hs-CRP and the primary outcome in the DHS cohort, between hs-CRP and a secondary outcome (atherosclerotic cardiovascular disease) in the MESA cohort, or between hs-CRP and hs-cTNT and atherosclerotic cardiovascular disease in the DHS cohort. In MESA, the C statistic for the primary outcome increased from 0.73 when adjusted for variables alone to 0.786 when adjusted for individual test results ($p < 0.001$), and the DHS cohort showed a similar significant improvement (0.832 to 0.850; $p < 0.01$). The category-free NRI for both cohorts were as follows: MESA NRI, 0.473 (95% CI, 0.383 to 0.563); and DHS NRI, 0.261 (95% CI, 0.052 to 0.470). Based on 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. Further discussion of this risk score is beyond the scope of this evidence review.

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. In 2015, Lara et al reported the

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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

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

Moreover, the available evidence on individual risk markers is only of limited value in evaluating CVD risk panels. It is difficult to extrapolate the results of single risk factors to panels, given the variable composition of panels. Ideally, panels should be evaluated individually based on their impact on clinical decision making. No published studies were identified that evaluated the use of commercially available CVD risk panels as risk prediction instruments in clinical care. Some studies have attempted to incorporate novel risk markers into an overall quantitative risk score, but these risk scores are not the same as CVD risk panels, which report the results of individual risk factors.

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

SUMMARY OF EVIDENCE

For individuals who have risk factors for CVD who receive CVD risk panels, the evidence includes multiple cohort and case-control studies and systematic reviews of these studies. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in 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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Cardiovascular Risk Panels", 2.04.100, 12:2017.

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- 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* 2001; 286(2):180-7.
- 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* 2009; 151(7):496-507.
- Brotman DJ, Walker E, Lauer MS et al. In search of fewer independent risk factors. *Arch Intern Med* 2005; 165(2):138-45.
- 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* 2010; 56(25):e50-103.
- Singulex. Clinical Lab Testing Services: Enabling proactive cardiovascular health management. 2015; <http://www.singulex.com/cardiovascular-health-management>. Accessed October 14, 2015.
- WellnessFX. Premium: The Deluxe Deep Dive. 2015; <http://www.wellnessfx.com/premium>. Accessed October 14, 2015.
- 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*. 2013;8(4):e62080. PMID 23630624
- 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
- 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
- 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
- Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P et al. Lipid-related markers and cardiovascular disease prediction. *JAMA* 2012; 307(23):2499-506.
- 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
- 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
- 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
- Lara J, Cooper R, Nissan J, et al. A proposed panel of biomarkers of healthy ageing. *BMC Med*. 2015;13:222. PMID 26373927
- Paynter NP, Chasman DI, Pare G et al. Association between a literature-based genetic risk score and cardiovascular events in women. *JAMA* 2010; 303(7):631-7.
- 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* 2007; 297(6):611-9.
- 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* 2008; 358(20):2107-16.
- 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
- 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
- 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
- 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
- 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

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02/06/2014 Medical Policy Committee review
 02/19/2014 Medical Policy Implementation Committee approval. New policy.
 02/05/2015 Medical Policy Committee review
 02/18/2015 Medical Policy Implementation Committee approval. No coverage changes.
 08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
 02/04/2016 Medical Policy Committee review
 02/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
 02/02/2017 Medical Policy Committee review
 02/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 02/01/2018 Medical Policy Committee review
 02/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 07/01/2018 Coding update
 Next Scheduled Review Date: 02/2019

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HCPCS	No codes
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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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