Cardiovascular Risk Panels

I. Description

Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate risk of cardiovascular (CV) disease. 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 1 score.

The evidence for the use of CV risk panels in individuals who have risk factors for CV disease 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 CV risk panels are associated with increased risk of CV disease. 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 CV 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. 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.
A simple lipid panel is generally composed of the following lipid measures:
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides

Certain calculated ratios, such as the total/HDL cholesterol may also be reported as part of a simple lipid panel.

III. Limitation

A. Other types of lipid testing, ie, apolipoproteins, lipid particle number or particle size, lipoprotein (a), etc., are not considered to be components of a simple lipid profile.
B. This policy does not address the use of panels of biomarkers in the diagnosis of acute myocardial infarction.

IV. 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:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81291</td>
<td>MTHFR (5,10-methylenetetrahydrofolate reductase)(eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)</td>
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<tr>
<td>82465</td>
<td>Cholesterol, serum or whole blood, total</td>
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<tr>
<td>82652</td>
<td>Vitamin D; 1,25 dihydroxy, includes fraction(s), if performed</td>
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<tr>
<td>83090</td>
<td>Homocysteine</td>
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<tr>
<td>83698</td>
<td>Lipoprotein-associated phospholipase A2 (Lp-PLA2)</td>
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<tr>
<td>83718</td>
<td>Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)</td>
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<tr>
<td>83721</td>
<td>Lipoprotein, direct measurement; LDL cholesterol</td>
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<tr>
<td>83880</td>
<td>Natriuretic peptide</td>
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<tr>
<td>84478</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>86141</td>
<td>C-reactive protein; high sensitivity (hsCRP)</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>80061</td>
<td>Lipid panel</td>
</tr>
</tbody>
</table>

V. Background

Cardiovascular (CV) disease remains the single largest cause of morbidity and mortality in the developed world. As a result, accurate prediction of CV 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.

Components of CV risk include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. In addition, numerous laboratory tests have been associated with CV 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 (FRS). The FRS provides an estimate of the 10-year risk for developing cardiac disease and is currently used in clinical care to determine the aggressiveness of risk factor intervention, such as the decision to treat hyperlipidemia with statins.

Many additional biomarkers, genetic factors and radiologic measures have been associated with increased risk of CV disease. Over 100 emerging risk factors have been proposed as useful for refining estimates of cardiovascular 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 CV disease. 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 CV disease.
- **Genetic markers.** A number of mutations associated with increased thrombosis risk, such as the MTHFR mutation or the prothrombin gene mutations, have been associated with increased CV risk. In addition, numerous single nucleotide polymorphisms (SNPs) have been associated with CV disease in large genome-wide studies.

CV risk panels may contain measures from one or all of the previous categories and may include additional measures not previously listed such as radiologic markers (carotid CMT, calcium score). Some cardiovascular 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 CV risk panels are as follows:

- **Health Diagnostics Cardiac Risk Panel:** MTHFR gene analysis, common variants; vitamin D, 1, 25 dihydroxy; B-type natriuretic peptide; lipoprotein-associated phospholipase A2 (Lp-
PLA2); myeloperoxidase; apolipoprotein; 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; apolipoprotein analysis; multiple SNPs associated with coronary artery disease (CAD).

- **Genova Diagnostics CV Health Plus Genomics™ Panel**: 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.

- **Genova Diagnostics CV Health Plus™ Panel**: 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.

- **Cleveland HeartLab CVD Inflammatory Profile**: hs-CRP, urinary microalbunmin, myeloperoxidase, Lp-PLA2, F2 isoprostanes.


- **Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel**: factor V Leiden, factor V R2, prothrombin gene, factor XIII, fibrinogen-455, PAI-1, GPIIIs (HPA-1), MTHFR, ACE I/D, apo B, apo E.

- **Singulex® Cardiac-Related Test Panels**: Several panels of markers related to cardiac dysfunction, vascular inflammation and dysfunction, dyslipidemia, and cardiometabolic status are offered by Singulex (Alameda, CA). Some of these panels are offered in conjunction with a CV disease testing and wellness management service. The test panels use an immunoassay method referred to as “Proprietary high-precision Single Molecule Counting [SMC] technology.”
  - Cardiac Dysfunction panel: SMC™ cTnl (high-sensitivity troponin), N-terminal pro-B-type natriuretic peptide
  - Vascular Inflammation and Dysfunction panel: SMC™ IL-6, SMC™ IL-17A, SMC™ TNFα, 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 (TSH), T3 and free T4, uric acid, liver panel, renal panel, thyroid peroxidase antibody, thyroglobulin antibody.

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

- **Singulex Cardiometabolic Panel**: described above.
- **WellnessFX (San Francisco, CA) Premium6**: 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, TSH, 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 through 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 (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. Food and Drug Administration has chosen not to require any regulatory review of this test.

**VI. Rationale**

This evidence review was created in November 2013, and has been updated periodically with literature reviews through searches of the MEDLINE database, most recently through October 14, 2015.

There is a large amount of literature on the association of individual risk factors with cardiovascular (CV) disease. Most 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 with 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 with standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

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:
Cardiovascular Risk Panels

- 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.

Literature Review

Literature was sought that addressed the criteria for demonstrating clinical utility outlined above.

Clinical Validity

Association of Single Risk Markers With CV Risk

There is a large evidence base on the association of individual risk markers with CV 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 disease events and stroke in CV disease-naive populations) and secondary CV events (ie, CV disease events and stroke in populations with a history of CV disease). 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 CV disease. Only 2 meta-analyses that reported associations with ischemic stroke in patients with no history of CV disease were identified, and results were not reported. CV disease risks for markers with the strongest associations are summarized in Table 1.

| Table 1: Serum Biomarkers and Cardiovascular Risk in van Holten et al (2013) |
|-----------------------------|-----------------|-----------------|
| Marker                      | RR, HR, or OR   | 95% Confidence Interval Prediction of CV |
| **Prediction of CV events in patients with no history of CV disease** |
| CRP                         | 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 positive history of CV disease** |
| cTn I and T                 | 9.39 (OR)       | 6.46 to 13.67   |
| High sensitivity CRP        | 5.65 (OR)       |                 |
| Creatinine                  | 3.98 (HR)       |                 |
| Cystatin C                  | 2.62 (RR)       |                 |
Prediction of ischemic stroke in patients with positive history of CV disease

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<th>HR (95% CI)</th>
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<tr>
<td>Fibronogen</td>
<td>1.75 (1.55 to 1.98)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>1.47 (1.19 to 1.76)</td>
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</tbody>
</table>

Apo: apolipoprotein; CRP: C-reactive protein; cTn: cardiac troponin; CV: cardiovascular; HDL: high-density lipoprotein; HR: hazard ratio; OR: odds ratio; RR: relative risk.

Summary of Evidence

The evidence for the use of cardiovascular (CV) risk panels in individuals who have risk factors for CV disease 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 CV risk panels are associated with increased risk of CV disease. 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 CV 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.

Supplemental Information

Practice Guidelines and Position Statements

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued guidelines on the assessment of CV 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 CV disease event be used in non-Hispanic blacks and non-Hispanic whites age between 40 and 79 years (AHA/ACC class of recommendation I, AHA/ACC level of evidence B). Regarding newer risk markers after quantitative risk assessment, the guidelines state 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 do 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 2009, the U.S. Preventive Services Task Force made the following recommendation about using nontraditional risk factors in coronary heart disease risk assessment:
The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of CHD to prevent CHD events (select "Clinical Considerations" for suggestions for practice when evidence is insufficient). Grade: I

The nontraditional risk factors included in this recommendation are hsCRP, ABI, leukocyte count, fasting blood glucose level, periodontal disease, carotid intima-media thickness, coronary artery calcification score on electron beam computed tomography, homocysteine level, and lipoprotein (a) level.

**Medicare National Coverage**
There is no national coverage determination (NCD).

**VII. 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), 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.
VIII. References


