Protocol

Cardiovascular Risk Panels

(204100)

Medical Benefit		**Effective Date**: 04/01/15	**Next Review Date**: 01/19
Preauthorization	No	**Review Dates**: 01/15, 01/16, 01/17, 01/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With risk factors for cardiovascular disease	Interventions of interest are: • Cardiovascular risk panels	Comparators of interest are: • Management with clinical risk factors with or without simple lipid testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Change in disease status • Morbid events

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 one score.

Summary of Evidence

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.

Policy

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

Policy Guidelines

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.

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.

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

Background

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).[1] 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.[2-4] 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 A_2 (Lp-PLA_2); 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-PLA_2; *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-PLA_2; triglycerides; VLDL; VLDL size; vitamin D; hs-CRP.
- Cleveland HeartLab *CVD Inflammatory Profile*: hs-CRP, urinary microalbumin, myeloperoxidase, Lp-PLA_2, F_2 isoprostanes.
- Applied Genetics *Cardiac Panel*: genetic mutations associated with CAD: cytochrome p450 mutations 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, 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."[5]
    - 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™ TNFα, SMC™ Endothelin, Lp-PLA_2, hs-CRP, homocysteine, vitamin B_{12}, 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 (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 inflam-

mation, thyroid disorders and other hormonal deficiencies, and other disorders. Examples of these panels include:

- Singulex Cardiometabolic Panel: described above.
- WellnessFX (San Francisco, CA) Premium[6]: total cholesterol, HDL, LDL, triglycerides, Apo AI, Apo B, LP(a), Lp-PLA_2, 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, 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 B_{12}, 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 FDA has chosen not to require any regulatory review of this test.

Related Protocols

Gene Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease

Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

---

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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. Clinical Lab Testing Services: Enabling proactive cardiovascular health management. 2015; http://www.singulex.com/cardiovascular-health-management. Accessed October 14, 2015.
6. WellnessFX. Premium: The Deluxe Deep Dive. 2015; http://www.wellnessfx.com/premium. Accessed October 14, 2015.
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. 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. 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
12. 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
13. 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
14. 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
15. Lara J, Cooper R, Nissan J, et al. A proposed panel of biomarkers of healthy ageing. BMC Med. 2015; 13:222. PMID 26373927
16. 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
17. 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
18. 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
19. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. November 12, 2013.