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Medical Benefit		Effective Date: 04/01/15	Next Review Date: 01/21
Preauthorization	No	Review Dates: 01/15, 01/16, 01/17, 01/18, 01/19, 01/20	

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: <ul style="list-style-type: none"> • With risk factors for cardiovascular disease 	Interventions of interest are: <ul style="list-style-type: none"> • Cardiovascular risk panels 	Comparators of interest are: <ul style="list-style-type: none"> • Management of clinical risk factors with or without simple lipid testing 	Relevant outcomes include: <ul style="list-style-type: none"> • 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 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.

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 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.

POLICY

Cardiovascular disease 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
- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol
- Triglycerides

Certain calculated ratios, (e.g., total/high-density lipoprotein cholesterol) may also be reported as part of a simple lipid panel.

Other types of lipid testing (i.e., apolipoproteins, lipid particle number or particle size, lipoprotein (a)), are not considered components of a simple lipid profile.

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

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 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.¹ 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.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 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:

- 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 coronary artery disease: cytochrome p450 variants associated with 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 (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.”⁵
 - 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™ TNF α , 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.⁶

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.

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 and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services 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.

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