BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Cardiovascular Risk Panels

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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:
Total cholesterol

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

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 risk panels refer to different combinations of cardiac markers that are intended to evaluate risk of 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.

Cardiovascular 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 LDL and 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-

Cardiovascular Risk Panels

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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 CV 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), 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 (CRP) is one 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.

Cardiovascular risk panels may contain measures from one or all of the above categories, and may include additional measures not listed above such as radiologic markers (carotid CMT, calcium score). Some CV 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 (BNP); Lp-PLA2; myeloperoxidase; apolipoprotein; immune complex assay; lipoprotein, blood; electrophoretic separation and quantitation; very long chain fatty acids; total cholesterol; HDL; LDL; triglycerides; (high-sensitivity CRP, hsCRP); lipoprotein (a); insulin, total; fibrinogen; apolipoprotein analysis; multiple SNPs associated with coronary artery disease (CAD).

Boston Heart *Advanced Risk Markers Panel*: small dense LDL, lipoprotein (a), apolipoprotein B, hsCRP, lipoprotein-associated phospholipase A2, homocysteine.

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; lipoprotein (a); LP-PLA2; *MTHFR* gene; triglycerides, very low-density lipoprotein (VLDL); VLDL size; vitamin D; hs-CRP.

Metametrix *Cardiovascular Health Profile*: total cholesterol, HDL, LDL, triglycerides, lipoprotein (a), ferritin, fibrinogen, hsCRP, coenzyme Q, vitamin E, lipid peroxides, homocysteine, red blood cell (RBC) magnesium, insulin, testosterone, sex hormone-binding globulin, free androgen index.

Cardiovascular Risk Panels

Policy # 00398
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Cleveland HeartLab *CVD Inflammatory Profile*: hs-CRP, urinary microalbumin, myeloperoxidase, Lp-PLA2, F2-isoprostanes.

Applied Genetics *Cardiac Panel*: genetic mutations associated with: cytochrome p450 (2C19, 2C9/VKORC1, 2D6, 3A4/3A5), factor V leiden, prothrombin gene, methylenetetrahydrofolate reductase *(MTHFR)* gene, apo-E 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.

FDA or Other Governmental Regulatory Approval

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

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.

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.

Literature Review

No published studies were identified that evaluated the use of commercially available CV 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 CV risk panels, which report the results of individual risk factors.

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. Other studies have demonstrated that risk markers can be used to reclassify patients into different risk categories. However, there is no convincing evidence that addition of any individual risk marker, or combination or risk markers, leads to clinically meaningful changes in management that improve outcomes. In the available studies, the improvement in risk prediction has generally been of a small magnitude, and/or has 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. In all cases where individual risk factors have been evaluated, the individual risk factors did not meet the criteria for medical necessity.

The available evidence on individual risk markers is only of limited value in evaluating CV 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 as to their impact on clinical decision making.

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 that are based on an inaccurate risk assessment. As a result of these deficiencies, it is not possible to make a reliable assessment of the impact of using CV risk panels on health outcomes.

Summary

Numerous CV risk panels are commercially available. These panels report results for multiple individual CV risk markers and have wide variability in the risk factors included in the panel. While the individual risk factors have in most cases been associated with increased risk of CV disease, it is not clear how the results of individual risk factors impact management changes, so it is also not certain 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. As a result, the use of cardiac risk panels for predicting risk of CV disease is considered investigational.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Cardiovascular Risk Panels”, 2.04.100, 11:2013.
2. 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.
3. 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.
4. Brotman DJ, Walker E, Lauer MS et al. In search of fewer independent risk factors. Arch Intern Med 2005; 165(2):138-45.
5. 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.

Cardiovascular Risk Panels

Policy # 00398
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6. 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.
7. 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.
8. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P et al. Lipid-related markers and cardiovascular disease prediction. JAMA 2012; 307(23):2499-506.
9. 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.

Coding

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81599
HCPCS	No Codes
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	No codes

Policy History

Original Effective Date: 02/19/2014
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02/06/2014 Medical Policy Committee review
02/19/2014 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 02/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

Cardiovascular Risk Panels

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A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
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:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. reference to federal regulations.

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