BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Cardiovascular Risk Panels

Policy #: 538
Category: Laboratory

Latest Review Date: December 2019
Policy Grade: B

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on and after November 17, 2013:

Blue Advantage will treat **cardiovascular disease risk panels**, consisting of multiple individual biomarkers intended to assess cardiac risk (other than **simple lipid panels**-see below), as a **non-covered benefit and as investigational**.

A **simple lipid panel** is generally composed of the following lipid measures: triglycerides, HDL, LDL and total cholesterol. Certain calculated ratios, such as the total/HDL cholesterol may also be reported as a 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 panel.

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

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate risk of cardiovascular disease (CVD). There are numerous commercially available risk panels that include different combinations of lipids, non-cardiac 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.

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 is a component of medical care that has the potential to focus on 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 include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. In addition, 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

(FRS). 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. 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 CRP is one example of an inflammatory markers, other include fibrinogen, interleukins, and tumor necrosis factor.
- Metabolic syndrome biomarkers. Measures associated with metabolic syndromes, such as specific dyslipidemic profiles or serum insulin levels, have been associated with an increased risk of CVD.
- Genetic markers. A number of variants that associated with increased thrombosis risk, such as the MHTFR variant or the prothrombin gene variants, have been associated with increased CVD risk. In addition, numerous single-nucleotide variants (SNV's) 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 non-genetic 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 CAD: cytochrome p450 variants associated with the 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, GPIIIs (HPA-1), MTHFR, angiotensin-converting enzyme insertion/deletion, 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 (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 "ultra-sensitive 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 CVD 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:

- 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, 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.

KEY POINTS:

The most recent literature update was performed through October 14, 2019.

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.

Practice Guidelines and Position Statements

In 2013, the American College of Cardiology and the American Heart Association issued joint guidelines for the assessment of cardiovascular disease risk. These guidelines recommended that age- and sex-specific pooled cohort equations, which included total cholesterol and high-density lipoprotein to predict the ten-year risk of a first hard atherosclerotic cardiovascular disease event, be used in non-Hispanic blacks and non-Hispanic whites between 40 and 79 years of age (American Heart Association/American College of Cardiology class of recommendation I, American Heart Association/American College of Cardiology level of evidence B). Regarding newer risk markers after quantitative risk assessment, the guidelines stated 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 did 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 2018, the USPSTF updated its recommendation on the use of nontraditional risk factors in coronary heart disease risk assessment:

"The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, or coronary artery calcium (CAC) score to traditional risk assessment for cardiovascular disease (CVD) in asymptomatic adults to prevent CVD events."

KEY WORDS:
Cardiovascular risk panel, cardiovascular disease, CAD, Health Diagnostics Cardiac Risk Panel, Genova Diagnostics CV Health Plus Genomics™ Panel, Genova Diagnostics CV Health Plus™ Panel, Cleveland HeartLab CVD Inflammatory Profile, Applied Genetics Cardiac Panel, Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel, Singulex® Cardiac-Related Test Panels, Singulex Cardiometabolic Panel, WellnessFX Premium, MTHFR, MI-Heart, Ceramides

APPROVED BY GOVERNING BODIES:
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.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CODING:
CPT Codes:
There are no specific codes for cardiovascular risk testing by panels.

If the specific analyte/gene mutation/biomarker is listed in CPT codes **81161-84830*** and **86000-86593**, the specific CPT code would be reported.

If the specific analyte/gene mutation/biomarker is not listed in the more specific CPT codes, unlisted codes **81599, 81479** or **84999** would be reported.

*Code 83992 is out of numerical sequence. See CPT codes 80320 – 80374 for this code.
For Secretory type II phospholipase:

0423T	Secretory type II phospholipase A2(sPLA2-IIA)

For MI-heart:

0119U	Cardiology, ceramides by liquid

	chromatography-tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular event **(Effective 10/1/19)**

0052U	Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation **(Effective 07/01/18)**

REFERENCES:

1. Brotman DJ, Walker E, Lauer MS et al. In search of fewer independent risk factors. Archives of internal medicine 2005; 165(2):138-45.
2. 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.
3. 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: the journal of the American Medical Association 2001; 286(2):180-7.
4. 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.
5. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P et al. Lipid-related markers and cardiovascular disease prediction. JAMA: the journal of the American Medical Association 2012; 307(23):2499- 506.
6. 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 2013.
7. Goff, Jr 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 [published online before print] accessed online at circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437741.48606.98.
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.
9. 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. Journal of the American College of Cardiology 2010; 56(25):e50-103.

10. 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.
11. 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.
12. 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.
13. 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. Annals of internal medicine 2009; 151(7):496-507.
14. Keller T, Boeckel JN, Gross S, et al. Improved risk stratification in prevention by use of a panel of selected circulating microRNAs. Sci Rep. Jul 03 2017; 7(1):4511.
15. 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.
16. Lara J, Cooper R, Nissan J, et al. A proposed panel of biomarkers of healthy ageing. BMC Med. 2015; 13:222.
17. 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.
18. Paynter NP, Chasman DI, Pare G et al. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA: the journal of the American Medical Association 2010; 303(7):631-7.
19. 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: the journal of the American Medical Association 2007; 297(6):611-9.
20. 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.
21. Singulex. Clinical Lab Testing Services: Enabling proactive cardiovascular health management. 2015; //www.singulex.com/cardiovascular-health-management.
22. Singulex. The Sgx Clarity System. 2015; www.singulex.com/sgx-clarity-system/. Accessed November 30, 2017.
23. U.S. Preventive Services Task Force. Coronary Heart Disease: Screening Using Non-Traditional Risk Factors. 2018; www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cardiovascular-disease-screening-using-nontraditional-risk-assessment. Accessed November 26, 2018.
24. 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.

25. WellnessFX. Premium: The Deluxe Deep Dive. 2015; //www.wellnessfx.com/premium. Accessed November 30, 2017.
26. Welsh P, Kou L, Yu C, et al. Prognostic importance of emerging cardiac, inflammatory, and renal biomarkers in chronic heart failure patients with reduced ejection fraction and anaemia: RED-HF study. Eur J Heart Fail. Feb 2018; 20(2):268-277.
27. 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.
28. Wuopio J, Hilden J, Bring C, et al. Cathepsin B and S as markers for cardiovascular risk and all-cause mortality in patients with stable coronary heart disease during 10 years: a CLARICOR trial sub-study. Atherosclerosis. Sep 15 2018; 278:97-102.
29. Zethelius B, Berglund L, Sundstrom J et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. The New England journal of medicine 2008; 358(20):2107-16.

POLICY HISTORY:

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