

# LCD - MoIDX: Biomarkers in Cardiovascular Risk Assessment (L36362)

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<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	02101 - MAC A	J - F	Alaska
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	02102 - MAC B	J - F	Alaska
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	02201 - MAC A	J - F	Idaho
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## LCD Information

### Document Information

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MoIDX: Biomarkers in Cardiovascular Risk Assessment

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**CMS National Coverage Policy**

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that “are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.”

42 eCFR §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS Internet Online Manual Pub. 100-02 (Medicare Benefit Policy Manual), Chapter 15, Section 80, “Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests”.

**Coverage Guidance**

**Coverage Indications, Limitations, and/or Medical Necessity**

**Indications and Limitations**

Under preventative services, Medicare Part B covers the basic lipid panel (total cholesterol, high density lipoprotein-cholesterol (HDL-C), triglycerides, and low density lipoprotein-cholesterol (LDL-C)) for cardiovascular (CV) disease screening, every 5 years when ordered by a doctor.

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NCD 190.23 covers **lipid panel** testing for symptomatic patients for evaluating atherosclerotic CV disease, to monitor the progress of patients on anti-lipid dietary management and pharmacologic therapy for various lipid disorders. Per NCD 190.23, "Routine screening and prophylactic testing for lipid disorders are not covered by Medicare. While lipid screening may be medically appropriate, Medicare by statute does not pay for it. Lipid testing in asymptomatic individuals is considered to be screening regardless of the presence of other risk factors such as family history, tobacco use, etc."

This policy denies coverage for **all CV risk assessment panels**, except the basic lipid panel, for symptomatic (with signs and symptoms) patients with suspected or documented CV disease because panel testing is not specific to a given patient's lipid abnormality or disease. The policy indicates the medical indication(s) based on published scientific articles and consensus guidelines for individual lipid biomarkers that may be covered to characterize a given lipid abnormality or disease, to determine a treatment plan or to assist with intensification of therapy. Each individual lipid biomarkers must be specifically ordered and the reason for the test order documented in the patient's medical record. The policy denies coverage for all **non-lipid** biomarkers when used for CV risk assessment including but not limited to, biochemical, immunologic, and hematologic, and genetic biomarkers for CV risk assessment regardless of whether ordered in a panel or individually.

The following biomarkers, when they are included in a CV risk assessment panel, are non-covered:

- Lipoprotein subclasses;
- LDL particles;
- Intermediate density lipoproteins;
- High density lipoprotein AI9LpAI and AI/AII;
- Lipoprotein(a);
- Apolipoprotein B (Apo B), apo A-I and apo E;
- Lipoprotein-associated phospholipase A2 (Lp-PLA2)
- BNP
- Cystatin C
- Thrombogenic/hematologic actors
- Interleukin-6 (IL-6), tissue necrosis factor-  $\alpha$  (TNF-  $\alpha$ ), plasminogen activator inhibitor-1 (PAI-1) and IL-6 promoter polymorphism
- Free fatty acids
- Visfatin, angiotensin-converting enzyme 1 (ACE2) and serum amyloid A
- Microalbumin
- Myeloperoxidase (MPO)
- Homocysteine and methylenetetrahydrofolate reductase (MTHFR) mutation testing
- Uric acid
- Vitamin D
- White blood cell count
- Long-chain omega-3 fatty acids in red blood cell membranes
- Gamma-glutamyltransferase (GGT)
- Genomic profiling including CardiaRisk angiotensin gene
- Leptin, ghrelin, adiponectin and adipokines including retinol binding protein 4 (RBP4) and resistin
- Inflammatory markers including VCAM-1, P-selectin (PSEL) and E-selectin (ESEL)
- Cardiovascular risk panels

Note #1: There is no Medicare benefit for screening CV risk assessment testing for asymptomatic (without signs or symptoms of disease) patients. Screening asymptomatic patients for cardiovascular risk is statutorily excluded by Medicare and will not be addressed in this policy.

Note #2: FDA approval/clearance means that a test/assay has analytical and clinical validity. The FDA does not review clinical utility (that the test/assay demonstrates improved patient outcomes). To meet Medicare's "reasonable and necessary" criteria for coverage, a test/assay must have proven clinical utility.

### **Traditional vs Non-traditional CV Risk Assessment**

During the last two decades the interest in CV biomarkers as early screening tools has risen dramatically, largely fueled by the recognition that traditional CV risk factors (diabetes, smoking, hypertension and hyperlipidemia) do not fully explain individual variation in CV risk, and by advances in genetic and molecular research. Risk assessment for determining the 10-year risk for developing CHD is traditionally carried out using the Framingham risk score (<http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf>) or other classification that incorporates a lipid profile in the calculation.

Despite the Framingham risk-scoring tool, clinicians have sought non-traditional lipid and other biomarker measurements to predict CV events. The most promising biomarkers are the ones that closely correlate with the pathophysiological process of the disease. In general, there is evidence that some of these biomarkers may alter risk categorization (higher or lower) compared to traditional risk prediction, but it has not been established that changes in categorization provides clinically actionable information beyond that of traditional lipid measures. In addition, no study has provided high-quality evidence that measurement of non-traditional lipid and other biomarkers leads to changes in management that improve health outcomes.

To provide clinically useful knowledge, a biomarker should meet the following criteria:

- Adds clinical knowledge that improves patient outcomes (criteria for Medicare "reasonable and necessary");
- Provides risk information that is independent of established predictors;
- Is easy to measure and interpret in the clinical setting; and
- Is accurate, reproducible and standardized.

### **High-sensitivity C-reactive protein (hs-CRP)**

CRP is a protein produced in the liver during episodes of acute inflammation or infection. The hs-CRP test measures CRP that is in the normal range for healthy people, and is used to distinguish people with low normal levels from those with high normal levels. In recent years, prospective epidemiologic studies have demonstrated that inflammation is essential for CV disease pathogenesis and that high normal levels of hs-CRP correlate with an increased risk of CV events such as myocardial infarction (MI), stroke, sudden cardiac death and peripheral vascular disease (PVD) even when lipid levels are within acceptable ranges. The American Heart Association (AHA) and the US Centers for Disease Control and Prevention (CDC) recommend averaging two hs-CRP levels obtained two weeks apart. Based on hs-CRP test results, they recognize: low (3.0 mg/L) risk groups.

In 2009, the US Preventive Services Task Force (USPSTF) report on the use of non-traditional risk factors

noted there is insufficient evidence to recommend the use of non-traditional risk factors to screen asymptomatic individuals with no history of CHD to prevent CHD events. The non-traditional risk factors in their recommendation included: hs-CRP, ankle-brachial index (ABI), leukocyte count, fasting blood glucose level, periodontal disease, carotid intima-media thickness, coronary artery calcification (CAC) score on electron beam computerized tomography (EBCT), homocysteine level, and lipoprotein(a) level. The USPSTF stated there is insufficient evidence to determine the percentage of intermediate-risk individuals who would be reclassified by screening with non-traditional risk factors, other than hs-CRP or ABI. For individuals reclassified as high-risk by hs-CRP or ABI, data are not available to determine whether they benefit from additional treatment. They note the potential harms resulting from re-classification including the use of medications without proven benefit and psychological effects. The USPSTF stated that clinicians should continue to use the Framingham model to assess CHD risk and guide risk-based preventive therapy.

While data from the Physicians' Health Study and Framingham Heart Study have shown that hs-CRP measurements may result in reclassification of an individual's risk compared to standard risk prediction models, meta-analysis including data from the second Northwick Park Heart Study (NPHS II) and the Edinburgh Artery Study concluded that the ability of hs-CRP to reclassify risk correctly was modest and inconsistent.

The Jupiter trial, a randomized, double-blind, placebo-controlled trial of the use of rosuvastatin vs placebo in the primary prevention of CVD in patients without diabetes with LDL-C <130mg/dL and CRP =2 mg/dL was associated with a significant reduction in the primary endpoint of CV events. These findings suggest that hs-CRP measurement in highly preselected patients may have important clinical implications. However, the Jupiter study was not a trial of hs-CRP because individuals with unknown or low hs-CRP concentrations were not studied. Despite evidence that elevated hs-CRP levels are associated with increased risk of CHD, it has not been determined whether hs-CRP is causally related to CHD.

In 2010, The American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) published guidance as to when and in whom to measure blood levels of hs-CRP. The guidance states that hs-CRP levels may assist in the selection of patients for statin therapy according to the following criteria (Class IIa; Level of evidence (LOE): B):

- Men >50 years of age, or women >60 years of age or older,
- LDL-C
- Patients not on lipid-lowering, hormone replacement, or immunosuppressant therapy,
- Patients without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins

For example, a patient may appear to have a low or low-moderate elevated risk of CV events based on traditional risk factor scoring with cholesterol levels, weight, level of exercise, smoking history, diabetes and hypertension. However, an elevated hs-CRP level would indicate that the cardiac risk may be substantially greater than traditional risk factors suggest, and that treatment might be considered. For patients who are already known to have high risk, according to current recommendations, hs-CRP levels will not add any substantially new information, since the patient should already be receiving all available therapy including statins to reduce the risk.

The ACCF/AHA recommended measurement of hs-CRP for CV risk assessment in asymptomatic

intermediate-risk men 50 years of age or younger, or women 60 years of age or younger (Class IIb; LOE B). Since screening (asymptomatic patient) is statutorily excluded from coverage, hs-CRP testing for these individuals is not a Medicare benefit. They found no benefit for hs-CRP testing in asymptomatic high-risk adults or men and women below the ages stated above. (Class III; LOE B).

The Canadian Cardiovascular Society guidelines recommend hs-CRP testing in men older than 50 and women older than 60 years of age who are at intermediate risk (10-19%) according to their Framingham risk score and who do not otherwise qualify for lipid-lowering therapy. They also state that subjects who meet Jupiter criteria can be considered for treatment based on the results of that study.

In the National Academy of Clinical Biochemistry's practice guidelines on emerging CV risk factors, only hs-CRP met the stated criteria as a biomarker for risk assessment in primary prevention. They recommended:

- If the 10-year predicted risk, after standard global risk assessment, is <5%, hs-CRP should not be measured.
- If the 10-year risk is 5-10%, it is expected that 10% might be reclassified to a higher risk group with the test.
- If the risk is intermediate (10-20%), and uncertainty remains as to the use of preventive therapies such as statins or aspirin, then hs-CRP measurement might be useful for further stratification into a higher or lower risk category.

The NACB also recommended that:

- Therapies based on hs-CRP should be based on a clinician's clinical judgment because benefits of such treatment are uncertain;
- There is insufficient data that therapeutic monitoring using hs-CRP over time is useful to evaluate effects of treatment in primary prevention;
- The utility of hs-CRP levels to motivate patients to improve lifestyle behaviors has not been demonstrated;
- Evidence is inadequate to support concurrent measurement of other inflammatory markers in addition to hs-CRP for coronary risk assessment.

In 2012, the American Association of Clinical Endocrinologist gave a 2b recommendation for the use of hs-CRP to stratify borderline CV risk in patients with a standard risk assessment, or those with an LDL-C. The AHA's statement on non-traditional risk factors and biomarkers in CV disease in youth notes "There is currently no clinical role for measuring CRP routinely in children when assessing or considering therapy for CVD risk factors." The AHA also state that it is not clear whether high hs-CRP levels during childhood and adolescence lead to an increased risk of CVD in adult life. While lifestyle changes have been shown to decrease hs-CRP in children, and statins reduce CRP in adults, the AHA indicates there is minimal information available on the effect of statins on hs-CRP in children and whether lowering hs-CRP in children mitigates preclinical disease or CVD in adulthood. Similarly, the National Heart, Blood and Lung Institute (NHBLI) guideline on CV risk in children and adolescents found insufficient evidence to recommend hs-CRP testing in these patient groups.

In summary, this contractor expects testing to be limited to the following criteria:

1. Patient has intermediate CV risk (10-20% risk of CVD per 10 years using the Framingham point score); **and**
2. Patient has LDL-C between 100-130 mg/dL; **and**

3. Patient has two or more CHD major risk factors, including

- Age (Men > 50 years; Women >60 years)
- Current cigarette smoking
- Family history of premature CHD (CHD in male first degree relative <55; CHD in female first degree relative)
- Hypertension (Systolic > 140 mm Hg, or on anti-hypertensive medication)
- Low HDL-C

The use of hs-CRP testing to evaluate the effects of treatment or to motivate patients to improve lifestyle behaviors are not considered medically reasonable and necessary, and therefore not covered by Medicare.

### **Lipoprotein subclasses**

Lipoprotein subclass determination based on density, electric charge and other physical chemistry aspect of particles such as nuclear magnetic resonance allow more specific characterization of the major subclasses (VLDL, LDL, IDL and HDL). Studies showed that small, dense LDL particles were highly associated with the occurrence of CVD and diabetes.

### **LDL Particles (LDL-P) (aka LDL or Lipoprotein Particles or Particle Number, LDL or Lipid Subfractionation, Lipid Phenotyping, Nuclear Magnetic Resonance or NMR Profile)**

Small dense LDL with elevated triglyceride levels and low HDL-cholesterol levels constitute the "atherogenic lipoprotein phenotype" form of dyslipidemia that is a feature of type II diabetes and the metabolic syndrome. Measurement of LDL particle density has been proposed as a technique to further risk stratification in patients with elevated LDL levels or for patients with normal LDL levels who have other high risk factors for CAD, or to predict response to a particular therapy.

Although great progress has been made in the development of refined lipoprotein assessment and such measurements have helped in understanding the atherosclerotic process, it is not known whether measurements beyond traditional lipids can identify CV risk subgroups and how treatment would differ based on subgroup classification. Furthermore, it is not known whether this additional information helps the health care provider to identify with greater precision and accuracy the person who will develop clinical or subclinical CVD.

The NACB does not recommend testing as there is insufficient data that measurement of lipoprotein subclasses can identify CV risk subgroups, how treatment would differ based on subgroup classification and whether, over time, measurement is useful to evaluate the effects of treatments. In addition, the 2010 ACCF/AHA guidelines for assessment of lipoprotein, other lipoprotein parameters and modified lipids state that "measurement of lipid parameters, including lipoproteins, apolipoproteins, particle size, and density, beyond standard fasting lipid profile is not recommended for cardiovascular disease risk assessment in asymptomatic adults."

Unlike lipoprotein size or subclass measures, which seek to improve CV risk assessment beyond conventional lipid testing, LDL particle number tests (NMR LDL-P) and apoB) are simply an alternate measure of LDL quantity. Current data supports the ability of LDL particle number to provide clinically actionable information beyond traditional lipid measures to adjudicate individual response to treatment and guide adjustment in therapy. In addition, recent data demonstrate that patients with established CHD,

stroke, TIA, peripheral arterial or diabetes achieving NMR LDL-P < 1000 nmol/L during the course of their normal medical care experienced a significant 22-25% reduction in risk of CV events (myocardial infarction, revascularization, angina and stroke) versus patients managed to LDL-C < 100 mg/dL at 12, 24, and 36 months follow-up.

LDL particle number (NMR LDL-P), rather than LDL size or subclass, has been shown to be significantly associated with CV risk independent of traditional lipid and established risk factors. The American Association of Clinical Endocrinologists (AACE), the National Lipid Association (NLA), the American Diabetes Association (ADA) in conjunction with the American College of Cardiology (ACC), and the American Association of Clinical Chemistry (AACC) have developed consensus position statement on lipoprotein particle management in individuals at risk for CVD. Due to the prevalence of discordantly elevated LDL-P despite achieving low LDL-C and non-HDL-C values, each endorses use of LDL particle number to evaluate LDL response and aid decision making regarding potential adjustment of therapy. The 2013 AACE Comprehensive Diabetes Management Algorithm, as well as the 2015 joint AACE/American College of Endocrinology Clinical Practice Guidelines for Comprehensive Diabetes Mellitus Care, advocate specific LDL particle number goals for statin treated diabetic patients at high CV risk.

### **Intermediate Density Lipoproteins (Remnant Proteins)**

Intermediate density lipoproteins (IDLs) have a density that falls between LDLs and VLDLs, and may be referred to as remnant lipoproteins because they vary in size and contain varying proportion of triglycerides and cholesterol. Although there is abundant evidence the remnant lipoproteins are atherogenic, and a risk factor for CAD, there is no evidence how testing improves patient outcomes.

### **High Density Lipoprotein (HDL) Subclass (Lipoprotein AI 9LpAI) and Lipoprotein AI/AII (LpAI/AII) and/or HDL3 and HDL2**

HDL cholesterol (HDL-C) is the risk indicator most often used in associated with CHD risk. HDL subfractions have been used for risk prediction. However data is lacking how the subfractions aid in the diagnosis and management of CHD. Neither the NCEP nor ACCF/AHA guidelines recommend the routine measurement of HDL subspecies in CHD risk assessment.

### **Lipoprotein(a) (Lp(a))**

Lp(a) is a modified form of LDL in which a large glycoprotein, apolipoprotein(a) is bound to apolipoprotein B. It promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques, and, because it is structurally similar to plasminogen, Lp(a) may contribute to clot formation. However, the complete role of lipoprotein(a) is not fully understood.

There is no standardized scale for measuring Lp(a) because there is no level that is considered "normal". Because Lp(a) levels are controlled predominantly by genes, cholesterol-lowering drugs have little effect on lowering Lp(a) levels. Elevated Lp(a) is considered an independent risk factor for cardiovascular events, including myocardial infarction, stroke, CVD, vein graft restenosis, and retinal arterial occlusion and may be used to identify individuals who might benefit from more aggressive treatment of other risk factors. However, regardless of the association between Lp(a) and CV disease, there is no data to suggest that more aggressive risk factor modification improves patient health outcomes.

The NACB specifies that Lp(a) screening is not warranted for primary prevention and assessment of



cardiovascular risk. They comment that Lp(a) measurement may be done at the physician's discretion if the risk is intermediate (10%–20%) and uncertainty remains as to the use of preventive therapies such as statins or aspirin (Recommendation – IIb; LOE – C). They further note there is insufficient evidence to support therapeutic monitoring of Lp(a) concentrations for evaluating the effects of treatment.

Similarly, the 2010 ACCF/AHA guidelines conclude that apolipoproteins is not recommended for CV disease risk assessment in asymptomatic adults. UpToDate notes that Lp(a) is a modest, independent risk factor for CVD, especially MI, but notes there are no clinical trials that have adequately tested the hypothesis that Lp(a) reduction reduces the incidence of first or recurrent CVD events.

Lp(a) testing may be indicated in select patients, particularly intermediate risk patient, to assist physicians with the use of preventive therapies. Routine testing is not covered by Medicare.

### **Apolipoprotein B (Apo B), Apolipoprotein A-I (Apo AI), and Apolipoprotein E (Apo E)**

Apo B is a constituent of LDL particles, and serves as an indirect measurement of the number of LDL particles. Consequently, elevated levels of Apo B suggest increased levels of small dense LDL particles that are thought to be atherogenic.

Apo AI is the major protein constituent of HDL-C. However, its measurement has not been established as a clinically useful test in determining clinical therapy for patients with CAD or dyslipidemia at the current time.

While Apo B and Apo A-I are thought to be the main structural proteins of atherogenic and anti-atherogenic lipoproteins and particles, testing for these compounds has not been validated as a tool for risk assessment. As such, the 2010 ACCF/AHA guidelines indicate that apolipoproteins testing is not recommended for CV risk assessment in asymptomatic adults. However, AACE recommends apoB testing to assess residual risk in patients for CAD (even when LDL-C levels are controlled) in patient when the triglyceride concentration is >150 mg/dL or the HDL-C concentration is

Medicare expects testing to be limited to assessment of residual risk in patients with CAD with triglyceride concentrations of >150 mg/dL or HDL-C of

Apo E, the major constituent of VLDL and chylomicrons, acts as the primary binding protein for LDL receptors in the liver and is thought to play a role in lipid metabolism. Although some individuals hypothesize that Apo E genotypes may be useful in the selection of drug therapy, the value of Apo E testing in the diagnosis and management of CHD is insufficient and needs further evaluation.

The National Cholesterol Education Program (NCEP) expert panel concluded that Apo AI is carried in HDL and it is usually low when HDL is reduced. A low Apo AI thus is associated with increased risk of CHD, but not independently of low HDL. Whether it has independent predictive power beyond HDL-C is uncertain and its measurement is not recommended for routine risk assessment in Adult Treatment Panel (ATP III) Guidelines.

### **Testing for Lipoproteins**

#### **Apolipoproteins**

Apolipoproteins are measured in routine clinical laboratories with the use of immunonephelometric or immunoturbidimetric assays. ApoB reflects the number of potentially atherogenic lipoprotein particles because each particle of VLDL, IDL, LDL and lipoprotein(a) particle carries on its surface 1 Apo B100

protein. Most of plasma Apo B is found in LDL particles. HDL particles do not carry Apo B. Instead they carry Apo AI, which does not correspond directly to the concentration of HDL particles in a 1-to-1 fashion.

### **LDL Gradient Gel Electrophoresis (GGE) (used by Berkeley Heart Lab, Berkeley, CA)**

GGE is the most commonly used lab technique to measure LDL particle density. It has been promoted as an important criteria of CHD risk, and as a guide to drug and diet therapy in patients with CAD. While the measurement of LDL subclass patterns may be useful in elucidating possible atherogenic dyslipidemia in patients without abnormal total cholesterol, HDL, LDL and triglycerides, there is inadequate evidence that LDL sub-classification by GGE improves outcomes in patients with CV disease.

### **Density Gradient Ultracentrifugation (DGU) (used by Atherotec Inc, Birmingham, AL)**

The Vertical Auto Profile (VAP) test measures the relative distribution of cholesterol within various lipoprotein subfractions, quantifying the cholesterol content in the VLDL, IDL, LDL, lipoprotein(a) and HDL subclasses. It includes components (e.g., total cholesterol, direct measured LDL-C, HDL-C and triglycerides), LDL density (i.e. pattern A versus pattern B), IDL, HDL sub types, VLDL density and Lp(a), and non-lipid CV risk assessment biomarkers including hs-CRP, homocysteine, Lp-PLA2, apo-E genotype, vitamin D, cystatin and NT-proBNP.

### **Nuclear Magnetic Resonance Spectroscopy**

In this method (NMR LipoProfile® is FDA cleared and available from LipoScience Inc, Raleigh, NC) particle concentrations of lipoprotein subfractions of different size are obtained from the measured amplitudes of their lipid methyl group NMR signals. Lipoprotein particle sizes are then derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal.

Note: FDA clearance does not mean the test has clinical utility.

### **Ion-Mobility Analysis**

This method (available from Quest Diagnostics Inc, Madison, NJ) measures both the size and concentration of lipoprotein particle subclasses on the basis of gas-phase differential electric mobility.

### **Summary of Lipoprotein Testing**

At the current time, none of the above tests for lipoproteins have better predictive strength than total/HDL-C ratio and there has been no clear benefit for measuring particle number in most studies to date. Additional research is needed to establish the utility of following changes in lipoproteins as a therapeutic target and determine if any subgroups of patients benefit.

### **Lipoprotein-Associated Phospholipase A2 (Lp-PLA2)**

Lp-PLA2 is also known as platelet activating factor acetylhydrolase. This enzyme hydrolyzes phospholipids and is primarily associated with LDLs. It has been suggested that this enzyme has a proinflammatory role in the development of atherosclerosis. Studies show that Lp-PLA2 is an independent predictor of CV risk but fail to demonstrate improved health outcomes. To improve outcomes, studies must demonstrate how risk

factors improve risk classification and change in physician practice to improve patient outcomes.

The NCEP ATP III panel concluded that routine measurement of inflammatory markers (including Lp-PLA2) for the purpose of modifying LDL-cholesterol goals in primary prevention is not warranted. In the 2010 ACCF/AHA guidelines for assessment of CV risk, the experts concluded “lipoprotein-associated phospholipase (Lp-PLA2) might be reasonable for cardiovascular risk assessment in intermediate risk asymptomatic adults”. However, at the current time, it is not known whether Lp-PLA2 concentrations are clinically effective for motivating patients, guiding treatment, or improving outcomes.

### **B-type Natriuretic Peptide (BNP)**

BNP and NT-proBNP, hormones produced by cardiocytes in response to hemodynamic stress, have emerged as preferred biomarkers for assessing heart-related stress. There is evidence that these hormones provide prognostic information of mortality and first CV events beyond traditional risk factors. However, there is currently no evidence that treatment or intervention based on the increased risk implied by these biomarkers improves patient outcomes.

These hormones do play a role in the acute setting for use in diagnosing decompensated heart failure. For coverage guidance regarding the use of B type natriuretic peptide as a diagnostic tool in the acute setting please refer to Noridian LCD L34038.

### **Cystatin C**

Cystatin C, encoded by the CST3 gene, is a small serine protease inhibitor protein secreted by all functional cells in the body. It is used as a biomarker for renal function, and in CV risk assessment although there is no evidence that this marker improves outcomes when used in clinical care. The NACB guidelines on Biomarkers of Renal Function and Cardiovascular Disease Risk do not recommend testing. The NCEP advocates clinical studies to characterize the utility of these markers in the global assessment of CV disease risk.

### **Thrombogenic/Hematologic Factors**

Hematologic factors including coagulation factors and platelets play a role in acute coronary syndrome although the precise mechanism is not known. That platelets are involved in this process is supported by strong evidence that aspirin and other antiplatelet therapies reduce the risk of myocardial infarction.

Fibrinogen has also been associated with CHD risk. A high fibrinogen level is associated with increased risk for coronary events, independent of cholesterol levels, while a low fibrinogen indicates a reduced risk even with high cholesterol levels. Other hemostatic factors associated with increased coronary risk include, but are not limited to, activated factor VII (aFVII), tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (wWF), Factor V Leiden (FVL), Factor II (F2), Protein C (PC) and antithrombin III.

In 2009, the NACB guidelines reported there was sufficient data that fibrinogen is an independent marker of CVD risk. In addition, measurement of fibrinogen was not recommended because they expressed analytical concerns regarding insufficient assay standardization and uncertainty in identifying treatment strategies. Additionally, the NCEP expert panel concluded “ATPIII does not recommend measurement of prothrombotic factors as part of routine assessment of CHD risk”. They indicated that the strength of the association

between thrombogenic/hematologic factors and CHD risk has not been defined and recommended clinical trials that target specific prothrombotic factors.

D-dimer is associated with an increased risk of venous and arterial thrombotic events, irrespective of baseline vascular disease, even after adjusting for confounders such as age, smoking and diabetes. In CVD, an increased fibrin turnover represents not only a prothrombotic state, but also is a marker for the severity of atherosclerosis. Although D-dimer is a simple test that is widely available, it remains unclear whether D-dimer plays a causal role in the pathophysiology of CV adverse events, or whether D-dimer is simply a marker of the extent of disease.

### **Interleukin-6 (IL-6), Tissue Necrosis Factor- $\alpha$ (TNF- $\alpha$ ), Plasminogen Activator Inhibitor-1 (PAI-1), and IL-6 Promoter Polymorphism**

Adipose tissue is a prominent source of PAI-1. Recent data indicates there is continuous production of large amounts of active PAI-1 in platelets that may contribute to clot stabilization. PAI-1 is the primary physiological inhibitor of plasminogen activation. Increased PAI-1 expression acts as a CV risk factor and plasma levels of PAI-1 strongly correlate with body mass index (BMI). Similar associations have been reported between PAI-1 activity and plasma insulin and triglyceride levels in patients with CAD and diabetes. However, there is no data that PAI-1 testing changes physician management to improve patient outcomes.

IL-6, an inflammatory cytokine, is involved in metabolic regulation of CRP. IL-6 plays an important role in the process of rupture or erosion of atherosclerotic plaques, and its serum levels are elevated during these events. At the current time, there is no consensus on IL-6 assay methods or reference values, and no data that demonstrates IL-6 testing changes physician management to improve patient outcomes.

Early in atherosclerotic plaque formation, leukocytes adhere to and are entrapped in the endothelial wall, a process mediated by inflammatory adhesion molecules such as P-selectin and ICAM-1 that are modulated by TNF- $\alpha$ . However, to date, these biomarkers have not provided additional predictive power above that of traditional lipid markers.

Because a polymorphism in the promoter region of IL-6 (174 bp upstream from the start site) appears to influence the transcription of the IL-6 gene and plasma levels of IL-6, this functional polymorphism was considered a candidate gene in the development of CV disease. However, multiple studies have produced inconsistent findings. In a large population-based study, no significant relationship between IL-6 promoter polymorphism and risk of CHD was identified. The authors concluded that IL-6-174 promoter polymorphism is not a suitable genetic marker for increased risk of CHD in person aged 55 years or older.

### **Free Fatty Acids (FFA, Saturated and Unsaturated)**

The role of plasma FFA in thrombogenesis in humans is poorly established and no strong direct evidence is available. Increasing plasma FFA concentration is known to induce endothelial activation, increase plasma MPO level and promote a prothrombotic state in non-diabetic healthy subjects. Studies are ongoing to demonstrate the role of FFA in the pathogenesis of atherosclerosis. However, at the current time, there is sparse data on its role in early atherosclerosis and no evidence how testing improves patient outcomes.

### **Visfatin, Angiotensin-Converting Enzyme 2 (ACE2) and Serum Amyloid A**

Visfatin is an active player promoting vascular inflammation and associated with atherosclerosis-related

disease. It is involved in cytokine and chemokine secretion, macrophage survival, leukocyte recruitment by endothelial cells, vascular smooth muscle inflammation and plaque destabilization. Although visfatin has emerged as a promising pharmacological target in the context of CV complications, there is no evidence how testing improves patient outcomes.

The renin-angiotensin system (RAS) plays a major role in the pathophysiology of CVD. The enzyme angiotensin-converting enzyme (ACE) converts angiotensin I into the vasoconstrictor, angiotensin II, the main effector of the renin-angiotensin system. It has been suggested that circulating ACE2 may be a marker of CVD with low levels of ACE2 in healthy individuals and increased levels in those with CV risk factors or disease. However, larger clinical studies are needed to clarify the role of ACE2 as a biomarker of CVD, determine the prognostic significance of circulating ACE2 activity and assess whether the measurement of ACE2 will improve CVD risk prediction.

Serum amyloid A (SAA) is a sensitive marker of inflammation and its elevation has been implicated in obesity and in CVD. It is a highly conserved acute-phase protein, stimulated by proinflammatory cytokines such as IL-6, TNF, interferon-gamma and transforming growth factor-beta (TGF- $\beta$ ). SAA is also a kind of apolipoprotein that is involved in cholesterol metabolism. However, there is sparse data on its role in early atherosclerosis and no evidence how testing improves patient outcomes.

### **Microalbumin**

Microalbuminuria is both a renal risk factor and a CV risk factor in patients with diabetes, and particularly a risk marker of CV mortality in the general population. Microalbuminuria also appears to be a sensitive marker for detecting new onset of hypertension and diabetes. However, for albuminuria to be a target for therapy, one needs to prove that lowering of albuminuria per se is cardioprotective. Albuminuria-lowering effect of antihypertensive agents, particularly those that interfere with RAS, and the use of statins and glucoseaminoglycans have been proved in randomized, controlled trial to be cardioprotective. However, few have been directed at albuminuria lowering per se to evaluate the effect on CV outcome. The question remains as to whether microalbuminuria is the consequence or the cause of organ damage, particularly whether high levels of albuminuria in young children reflect normal physiological variations in endothelial function associated with CV and renal risk in later age. While albumin excretion levels may represent a primary marker for success of intervention strategies aimed at repairing vascular function, there is no data how testing improves patient outcomes at the current time.

### **Myeloperoxidase (MPO)**

Elevated levels of myeloperoxidase, secreted during acute inflammation, are thought by some to be associated with coronary disease and predictive of acute coronary syndrome in patients with chest pain. Many studies have implicated MPO in the pathogenesis of atherosclerosis, showing that it is enriched within atheromatous plaques. Inflammatory cells recruited into the vascular wall release MPO-derived reactive oxygen species that can promote endothelial dysfunction by reducing the bioavailability of nitric oxide, generate atherogenic oxidized-LDL, and modify HDL, impairing its function in cholesterol efflux. However, at the current time there is insufficient data to demonstrate that plasma MPO can predict CHD independent of other CVD risk factors and there is no data that demonstrates how plasma MPO levels affect management of individuals at risk for or patients with CHD.

PPAR- $\beta/\delta$  is a key regulator of fatty acid metabolism, promoting its storage in adipose tissue and reducing circulating levels of free fatty acids. Activation of PPAR- $\beta/\delta$  has favorable effects on surrogate measures of

adipocyte function, insulin sensitivity, lipoprotein metabolism, and vascular structure and function. However clinical trials of thiazolidinedione PPAR- $\beta/\delta$  activators have not provided conclusive evidence that they reduce CV morbidity and mortality.

At the current time, there is no clinical data that demonstrates the clinical utility of testing for lipid peroxidation, isoprostanes, malondialdehyde, nitrotyrosine, S-glutathionylation, oxidized LDL, or oxidized phospholipids. Additionally, genetic testing for genes that regulate cellular and systemic oxidative stress, including but not limited to, nuclear factor-2 (Nrf-2), peroxisome proliferator-activated receptor gamma-co-activator 1alpha (PCG-1a), and the thioredoxin family or proteins have no clinical data that demonstrates utility.

### **Homocysteine and Methylenetetrahydrofolate Reductase (MTHFR) Mutation Testing**

Homocysteine is an amino acid found in the blood. Observational evidence generally supports the association of homocysteine levels with CV risk, particularly observational data that patients with hereditary homocystinuria, an inborn error of metabolism associated with high plasma levels of homocysteine, have markedly increased risk of CV disease. Folic acid and the B vitamins are involved in the metabolism of homocysteine. Several studies found the higher levels of B vitamins are associated with lower homocysteine levels, while other evidence shows that low levels of folic acid are linked to a higher risk of CHD and stroke. However, large randomized controlled trials do not support a protective effect of folic acid supplementation (rectifying homocysteine levels) in cardiovascular disease.

MTHFR is a key enzyme in folate metabolism. Two variants of the MTHFR polymorphisms result in reduced enzyme activity, impaired methylation and increased risk of CVD, stroke, and hypertension. MTHFR mutation testing has been advocated to evaluate the cause of elevated homocysteine levels.

However, in 2009, the US Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to assess the benefits and harms of using non-traditional risk factors to screen asymptomatic adults with no history of CHD to prevent CHD events. Homocysteine was one of the non-traditional factors considered in the recommendation. In 2010, later updated in March 2014, the AHA stated that a causal link between homocysteine levels and atherosclerosis has not been established, and noted that high homocysteine levels is not a major risk factor for CV disease. The 2012 American Association of Clinical Endocrinologists (AACE) guidelines for management of dyslipidemia and prevention of atherosclerosis stated that testing for homocysteine, uric acid, PAI-1 or other inflammatory markers is not recommended.

### **Uric acid**

A recent systemic review and meta-analysis suggests that elevated uric acid levels may modestly increase the risk of stroke and mortality. However, future studies are needed to determine whether lowering uric acid levels has any beneficial effects on stroke risk. Data is inadequate to show that uric acid testing changes physician management to improve patient outcomes.

### **Vitamin D**

Low levels of vitamin D are an independent risk factor for CV death in populations without pre-existing CV disease. However, systematic reviews on interventional vitamin D supplementation and CV disease risk reported that vitamin D supplementation had no effect on cardiovascular disease risk, indicating a lack of a causal relationship.

An additional concern regarding vitamin D testing is the considerable variation between results obtained with the various methods (competitive immunoassays, direct detection by high performance liquid chromatography or liquid chromatography combined with tandem mass spectrometry), as well as between laboratories. Immunoassay technologies are less sensitive and specific for vitamin D than liquid chromatography with or without mass spectrometry.

## **WBC**

A large body of data from prospective studies has established an association of leukocyte count with increased risk for CVD events. Leukocytes are thought to play a role in the development and/or progression of atherosclerotic plaques and their rupture due to their proteolytic capacity and oxidative properties. WBC count is correlated with other coronary disease risk factors, including cigarette smoking, BMI, cholesterol level, HDL-C (inversely), triglycerides, diabetes and blood glucose level, physical activity (inversely) and blood pressure. However, the NACB does not recommend WBC testing because clinical utility in reclassifying risk level and identifying treatment strategies is not known.

## **Long-chain Omega-3 Fatty Acids in Red Blood Cell (RBC) Membranes**

It has been proposed that the fatty acid composition of RBCs are an index of long-term intake of eicosapentaenoic (EPA) plus docosahexaenoic (DPA) acids. The omega-3 fatty acids are considered a new modifiable and clinically relevant risk factor for death from CHD. Most studies to date have focused on the association between fish consumption and risk of CHD. In the Rotterdam Study, analysis of EPA plus DHA and fish intake was assessed in relation of incident heart failure (HF). With nearly 5300 study individuals, the authors concluded that their findings did not support a major role for fish intake in the prevention of HF. Not only is there no association between fish intake and EPA+DHA levels regarding prevention of HF, there is no scientific evidence regarding how measurements of RBC omega-3 fatty acids composition would affect management of individuals at risk for or patients with CHD. A recent article (Maraj, 2014) notes that the available data do not support testing for omega-3 polyunsaturated fatty acids (EPA + DHA) among healthy subjects and patients with specific cardiac diseases.

## **Gamma-glutamyltransferase (GGT)**

GGT, a marker of excessive alcohol consumption or liver disturbance, is an enzyme catalyzing the first step in extracellular degradation of the anti-oxidant glutathione and is thought to play a role in the atherosclerotic process. Coverage for GGT is limited to the indications and limitations specified in CMS NCD 190.32. Whether serum levels of GGT can aid in the detection of individuals at high risk for incident CV events is under investigation. Despite its potential role in stratifying patient risk, there is no evidence testing improves patient outcomes.

## **Gene Mutations (any methodology) and Genomic Profiling**

Proponents of molecular CV profile testing argue that improvement in CVD risk classification leading to management changes that improve outcomes warrants coverage of these tests. However, the Evaluation of Genomic Applications in Practice and Prevention Working Group (EWG) found insufficient evidence to recommend testing for 9p21 genetic variant or 57 other variants in 28 genes to assess risk for CVD in the general population, specifically heart disease and stroke.

The following genes were included in the EWG's assessment: ACE, AGT, AGTR1, APOB, APOC3, APOE, CBS, CETP, CYBA, CYP11B2, F2, F5, GNB3, GPX1, IL1B, LPL, ITGB3, MTHFR, MTR, MTRR, NOS3, PAI-1, PON1, SELE, SOD2, SOD3, TNF, and 9p21. The EWG found that the magnitude of net health benefit from the use of any of these tests alone or in combination is negligible.

CardiaRisk™ (Myriad, Salt Lake UT) markets a genetic test to identify a mutation in the AGT genes. This test supposedly identifies specific hypertensive patients at increased risk of CV disease and identifies patients likely to respond to antihypertensive drug therapy. However, at the present time there is no literature that points to clinical utility for this test.

### **Leptin, Ghrelin, Adiponectin, and Adipokines including Retinol Binding Protein 4 (RBP4) and Resistin**

Leptin, a satiety factor secreted by adipocytes that is instrumental in appetite regulation and metabolism, is elevated in heart disease. In a recent study, leptin levels and proinflammatory high-density lipoprotein (piHDL) when combined into a risk score (PREDICTS) confers 28-fold increased odds of the presence of any current, progressive, or acquired carotid plaque and significantly associated with higher rates of intima-media thickness. However, there is no data that demonstrates how measurement of leptin levels affects management of individuals at risk for or patients with CHD.

Ghrelin is a hormone produced in the stomach and pancreas that plays a role in hunger and weight gain. In a recent study, ghrelin when incorporated in the CV risk model improved the prediction of CVD events in hypertensive patients with reclassification of roughly 21%. However, there is no evidence how testing improves patient outcomes.

Adiponectin is an adipose-specific hormone that has anti-inflammatory properties, and is protective against obesity. Particularly in children, measurement of total adiponectin or high-molecular-weight adiponectin (HMW adiponectin) as a biomarker for insulin sensitivity and/or as a risk factor for CVD is gaining support. However, the additive value of adiponectin levels remains unclear and how it changes patient outcomes is not known. It is not recommended clinically in children or adults.

RBP4 is gaining recognition as an adipokine that may play an important role in obesity and insulin resistance. The relationship between RBP4 and other traditional and non-traditional risk factors for CVD, such as inflammatory factors and/or oxidative stress, have not been confirmed in larger populations, and causality has not been established.

Resistin is an adipokine expressed highly in visceral compared with subcutaneous adipose tissue. In the Study of Inherited Risk of Coronary Atherosclerosis, resistin levels were positively correlated with higher coronary calcium scores and correlated with higher levels of soluble TNF- $\alpha$ , receptor-2, Lp(a), and IL-6. The resistin gene (RETN) polymorphism (bp -420 and +299) leads to increased concentrations of the resistin peptide in circulation, which is associated with cardiomyopathy and CAD. One study suggests that in addition to primary risk factors (total cholesterol, LDL, triglycerides and low concentrations of HDL), resistin cytokine may be a risk factor for CVD. However, there is no clinical role for measuring resistin as no data demonstrates how measurement of resistin levels affects management of individuals at risk for or patients with CHD.

### **Inflammatory Markers – VCAM-1, ICAM-1, P-selectin (PSEL) and E-selectin (ESEL)**

Clinical studies have shown that elevated serum concentrations of cell adhesion molecules such as inter-



cellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), E-selectin (ESEL) and P-selectin (PSEL) may contribute to CVD through their inflammatory effects on the vascular endothelium and be independent risk factors for atherosclerosis and cardiovascular disease (CVD). However, at the current time, testing for these inflammatory markers has not been confirmed in larger populations, causality has not been established and testing has not resulted in improved patient outcomes.

### **Summary of Evidence**

N/A

### **Analysis of Evidence (Rationale for Determination)**

N/A

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## **General Information**

### **Associated Information**

#### **Documentation Requirements**

The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. (See "Coverage Indications, Limitations, and/or Medical Necessity") This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available to the MAC upon request.

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N/A

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## Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
04/22/2021	R8	<p>Under <b>CMS National Coverage Policy</b> Changed Code of Federal Regulations (CFR) to eCFR.</p> <p>Moved text from <b>Sources of Information</b> to <b>Bibliography</b> and changes were made to citations to reflect AMA citation guidelines. Accession dates were updated.</p>	<ul style="list-style-type: none"> <li>Other</li> </ul>
10/01/2019	R7	<p>10/01/2019: This LCD is being revised in order to adhere to CMS requirements per Chapter 13, Section 13.5.1 of the Program Integrity Manual. There has been no change in coverage with this LCD revision. Regulations regarding billing and coding were removed from the <b>CMS National Coverage Policy</b> section of this LCD and placed in the related Billing and Coding: Biomarkers in Cardiovascular Risk Assessment article</p>	<ul style="list-style-type: none"> <li>Provider Education/Guidance</li> </ul>
10/01/2019	R6	<p>As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD.</p> <p>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all of the fields included on the LCD are applicable as noted in this policy.</p>	<ul style="list-style-type: none"> <li>Revisions Due To Code Removal</li> </ul>
10/01/2019	R5	<p>The following revisions are made due to the 2019 Annual ICD-10 Code Update: the description changed for ICD-10 codes I70.238 and I70.248, ICD-10 code I48.2 was deleted, and ICD-10 codes I48.11, I48.19, I48.20, I48.21 were added.</p> <p>At this time 21st Century Cures Act will apply to new and</p>	<ul style="list-style-type: none"> <li>Revisions Due To ICD-10-CM Code Changes</li> </ul>

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
		<p>revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all of the fields included on the LCD are applicable as noted in this policy.</p>	
01/31/2019	R4	<p>3/1/2019: At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</p> <p>Removed ICD-10 Code: Z13.220 from Group 1 to be consistent with the national policy. This update is effective 1/31/19.</p>	<ul style="list-style-type: none"> <li>• Revisions Due To ICD-10-CM Code Changes</li> </ul>
10/01/2018	R3	<p>09/17/2018 - At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</p> <p>The following ICD-10 codes were deleted from the ICD-10 Codes that Support Medical Necessity field: E78.4 was deleted from Group 1.</p> <p>The following ICD-10 codes were added to the ICD-10 Codes that Support Medical Necessity field: E78.41, E78.49, I63.81, I63.89, I67.858, I63.00, I63.011, I63.012, I63.013, I63.019, I63.02, I63.031, I63.032, I63.033, I63.039, I63.09, I63.10, I63.111, I63.112, I63.113, I63.119, I63.12, I63.131, I63.132, I63.133, I63.139, I63.19, I63.20, I63.211, I63.212, I63.213, I63.219, I63.22, I63.231, I63.232, I63.233, I63.239, I63.29, I63.30, I63.311, I63.312, I63.313, I63.319, I63.321, I63.322, I63.323, I63.329, I63.331, I63.332, I63.333, I63.339, I63.341, I63.342, I63.343, I63.349, I63.39, I63.40, I63.411, I63.412, I63.413, I63.419, I63.421, I63.422, I63.423, I63.429, I63.431, I63.432, I63.433, I63.439, I63.441, I63.442, I63.443, I63.449, I63.49, I63.50, I63.511, I63.512, I63.513, I63.519, I63.521, I63.522, I63.523, I63.529, I63.531, I63.532, I63.533, I63.539, I63.541, I63.542, I63.543, I63.549, I63.59, I63.9.</p> <p>Corrected the links in Bibliography: #1 and #45.</p>	<ul style="list-style-type: none"> <li>• Creation of Uniform LCDs With Other MAC Jurisdiction</li> <li>• Revisions Due To ICD-10-CM Code Changes</li> </ul>

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
01/01/2017	R2	2017 CPT Code update: 83704 descriptor was changed in Group 1.	<ul style="list-style-type: none"> <li>Revisions Due To CPT/HCPCS Code Changes</li> </ul>
10/01/2016	R1	The following ICD-10 codes are added/deleted effective 10/1/16: Added code: E78.00 and E78.01. Deleted code: E78.0	<ul style="list-style-type: none"> <li>Revisions Due To ICD-10-CM Code Changes</li> </ul>

## Associated Documents

### Attachments

N/A

### Related Local Coverage Documents

### Articles

[A55095 - Billing and Coding: MoIDX: ApoE Genotype](#)

[A54976 - Billing and Coding: MoIDX: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy \(ARVD/C\) Testing](#)

[A57055 - Billing and Coding: MoIDX: Biomarkers in Cardiovascular Risk Assessment](#)

[A54979 - Response to Comments: MoIDX: Biomarkers in Cardiovascular Risk Assessment](#)

### LCDs

[DL36360 - \(MCD Archive Site\)](#)

[DL36362 - \(MCD Archive Site\)](#)

### Related National Coverage Documents

N/A

### Public Versions

UPDATED ON	EFFECTIVE DATES	STATUS
01/13/2022	04/22/2021 - N/A	Currently in Effect (This Version)
02/26/2020	10/01/2019 - 04/21/2021	Superseded
09/17/2019	10/01/2019 - N/A	Superseded

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## Keywords

N/A