Corporate Medical Policy

Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082

File Name:	genetic_testing_for_lipoprotein_a_variant(s)_as_a_decision_aid_for_aspirin_treatment_and_or_cvd_risk_assessment
Origination:	01/2019
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Description of Procedure or Service

Description

Lipoprotein(a) (Lp(a)) is a type of low-density lipoprotein (LDL) that consists of a cholesterol bearing LDL – like particle (apolipoprotein B-100) bound to the plasminogen-like glycoprotein apolipoprotein(a) (apo(a)) (Lu et al., 2015; Schmidt et al., 2016) and has been associated with increased risk for cardiovascular disease (CVD) (Tsimikas et al., 2018). Genetic variants of the Lp(a) gene, *LPA*, (rs3798220 and rs10455872) have been significantly associated with Lp(a) levels (Lu et al., 2015) and could serve as indicators of CVD risk (Lee et al., 2017). The genetic variant rs3798220 was found to have a higher risk for thrombosis and therefore may derive more benefit from the anti-thrombotic properties of aspirin (Chasman et al., 2009). As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment (Shiffman et al., 2012).

This policy only addresses the detection of specific genetic variants of Lp(a) as a decision aid for aspirin therapy or CVD risk.

For information on serum measurement of Lp(a) levels see medical policy titled Cardiovascular Disease Risk Assessment AHS – G2050.

For information on testing for salicylate resistance see medical policy titled Measurement of Thromboxane Metabolites for ASA Resistance AHS – G2107.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Genetic testing for lipoprotein A variant as a decision aid for aspirin treatment and/or CVD risk assessment is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082

When Genetic Testing for Lipoprotein A Variant as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment is covered

Not applicable.

When Genetic Testing for Lipoprotein A Variant as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment is not covered

Genetic testing for *LPA* variant(s) (e.g., LPA-Aspirin Check® and Cardio IQ® LPA Aspirin Genotype) is considered investigational.

Policy Guidelines

Background

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality; with over 11.5% of American adults (27.6 million) diagnosed with heart disease, it claims more lives each year than cancer and chronic lower respiratory disease combined (Benjamin et al., 2018). While progression of CVD is multifactorial, pathophysiological, and epidemiological, genetic studies have provided substantial evidence that Lp(a) is a causal risk factor contributing to CVD (Rosenson et al., 2022). Lp(a) is also elevated in heterozygous familial hypercholesterolemia, further increasing atherosclerotic CVD risk in that disease setting (Rosenson et al., 2022). The physiological role of Lp(a) is to bind and transport proinflammatory oxidized phospholipids in plasma, but its key relation to CVD has been the involvement in atherothrombosis, from the formation of an atherosclerotic plaque through inducing expression of inflammatory mediators and increasing foam formation, to thrombosis following plaque rupture (Fras, 2020). Independent of any other risk factors, Lp(a) was positively associated with increased risk of myocardial infarctions (MI) as well (Paré et al., 2019).

Since first described by Berg (1963) as a genetic trait increased in patients with coronary heart disease (Berg et al., 1974), Lp(a) has been characterized as a type of LDL consisting of apolipoprotein B-100 covalently bound to apolipoprotein(a) (Steyrer et al., 1994). Lipoprotein(a) levels are 75% to 95% heritable and predominately determined by single-nucleotide variants at the LPA gene and copy number variants (CNVs) in the kringle IV type 2 domain (Trinder et al., 2021). The plasma level and size of Lp(a) are regulated through strict genetic control by the apo(a) gene (*LPA*) on chromosome 6q26-27 with some influence from the *APOE* locus (Erhart et al., 2018; Lu et al., 2015; Moriarty et al., 2017). The *LPA* gene is highly polymorphic based on the number of kringle (five cysteine-rich domains) IV (KIV) repeats, therefore encoding >40 apo(a) isoforms (Marcovina et al., 1996) of varying molecular weights (Rosenson et al., 2022).

As it is genetically controlled, the concentration of Lp(a) is generally stable, correlates inversely with molecular size (smaller size correlating with higher serum levels), and is minimally influenced by age, weight, and diet (Enkhmaa et al., 2016; Tregouet et al., 2009). Genetic variants of apo(a) have been found to have predictive value in coronary heart disease (CHD) (Anderson et al., 2013; Cairns et al., 2017; Helgadottir et al., 2012; Lee et al., 2017; Zekavat et al., 2018; Zewinger et al., 2017). Beyond CHD, genetically lowered Lp(a) is also associated with a lower risk of peripheral vascular disease, stroke, heart failure, and aortic stenosis (Emdin et al., 2016).

The prevalence and association of these genetic variants with apo(a) size and Lp(a) levels are highly variable and ethnicity-specific. Out of 118 single nucleotide polymorphisms (SNPs) identified, rs3798220 is most prevalent in Hispanics (42.38%), rs10455872 in Whites (14.27%), and rs9457951 in Blacks (32.92%). In Hispanics, the rs3798220 variant was associated with large

isoforms and lower Lp(a) levels, but in Whites, this variant was associated with very small isoforms and higher Lp(a) levels (Lee et al., 2017). In a separate study that analyzed the relationship between Lp(a) concentration and risk of MI, Paré et al. (2019) found that the clinical use of Lp(a) concentrations for interventions to reduce MI risk would be useful among diverse populations, especially South Asians and Latin Americans, but not Africans or Arabs since there was an insignificant association between high Lp(a) concentration and MI risk in these populations (Paré et al., 2019).

Although its biology and pathophysiology are still incompletely understood (Tsimikas et al., 2018), Lp(a) is recognized as both atherogenic (Grainger et al., 1993; Hajjar et al., 1989; Helgadottir et al., 2012) and thrombogenic (Caplice et al., 2001; Marcovina & Koschinsky, 2003), possibly due to its structural homology with plasminogen (Hancock et al., 2003; McLean et al., 1987). It is thought that Lp(a) could compete with plasminogen for fibrin binding, ultimately resulting in impaired fibrinolysis (Hervio et al., 1995).

A specific SNP in the *LPA* gene (rs3798220) results in an isoleucine-to-methionine substitution within the inactive protease domain, triggering a smaller number of kringle IV repeats, elevated Lp(a) levels, and a greater risk for CVD (Clarke et al., 2009; Helgadottir et al., 2012; Luke et al., 2007). This amino acid substitution (I4399M) has been studied for its effects on coagulation, fibrinolysis, and overall fibrin cloth structure (Scipione et al., 2017).

Carriers of either the rs3798220 or rs10455872 variant were found to have no difference in plasminogen concentration or clot lysis time (Wang et al., 2016). The I4399M variant was found to accelerate the coagulation of plasma clots *in vitro*, therefore suggesting that those with this variant may benefit from the anti-thrombotic properties of aspirin (Scipione et al., 2017). Further, a difference in phenotypic expression between different ethnic groups has been found. Among non-Caucasians, carriers of the rs3798220 variant had increased clot permeability and shorter lysis time, whereas among Caucasians, the trend was for decreased permeability and longer lysis time (Rowland et al., 2014). A correlation was identified between the I4399M variant and both elevated plasma Lp(a) levels and an increased risk of CHD; carriers of this variant in population studies also showed an increased benefit of aspirin therapy (Scipione et al., 2017).

Clinical Utility and Validity

The additional information obtained from the testing for Lp(a) genotype may aid physicians in better estimating the benefit/risk of aspirin therapy and therefore aid in deciding whether to prescribe aspirin for individual patients. *LPA* genotyping in the context of the aspirin use guidelines for primary prevention of CVD was found to be potentially cost-effective (Shiffman et al., 2012). However, traditional plasma-based hemostasis-thrombosis laboratory testing may be more effective at managing venous thrombotic disease than a single DNA variant with a small effect size and no established mechanism linking aspirin with Lp(a) (Nagalla & Bray, 2016).

An analysis of the Women's Health Study comprised of a randomized trial of low-dose aspirin found that rs3798220 was associated with elevated Lp(a) and doubled CVD risk that could be attenuated by aspirin; carriers appeared to benefit more from aspirin than non-carriers (Chasman et al., 2009).

Ozkan et al. (2019) have recently shown that Lp(a) gene polymorphisms play a role in the development of calcific aortic stenosis or calcific aortic valve disease (CAVD). Blood samples were taken from 75 patients previously diagnosed with CAVD and 77 healthy controls, and results showed that "A significant association among smoking, elevated LDL level and creatinine, low albumin levels, Lp(a) level, rs10455872, and rs3798220 polymorphisms may be considered genetic risk factors for the development of calcific aortic stenosis" (Ozkan et al., 2019). However, even with a strong statistically significant relationship between the Lp(a) gene

polymorphisms (rs10455872 and rs3798220) and CAVD, this study contained a relatively small sample size, suggesting that more research needs to be completed to validate these results. This research has been corroborated by Pechlivanis et al. (2020) who demonstrated that the rs10455872 SNP has a statistically significant association with coronary artery calcification, a predictor of coronary artery disease (Pechlivanis et al., 2020).

A large-scale study with 44,703 participants of European descent was completed, and a relationship was identified between two Lp(a) variants (rs10455872 and rs3798220) and aortic stenosis (AS) development (Chen et al., 2018). While a relationship between both of these Lp(a) variants has already been established in regard to circulating Lp(a) plasma levels and a high Lp(a) risk score, these data seem to confirm the association between these Lp(a) variants and valvular or cardiac disease events. Final results from this study showed that the participants with these two high-risk alleles had a twice or greater chance of developing AS; however, it must be noted that participants with AS were on average older than the controls, meaning that some controls could still develop AS (Chen et al., 2018).

Mu-Han-Ha-Li et al. (2018) conducted a study with 1,863 Chinese patients with very high CVD risk (as identified on coronary angiography) to analyze the connection between Lp(a) levels and the risks of CVD and diabetes. Researchers concluded that a high number of *LPA* KIV type 2 repeats, and therefore lower serum Lp(a) levels, is associated with an increased risk of type 2 diabetes in a Chinese population with high CVD risk. This data suggests that a large Lp(a) isoform size, and thus low Lp(a) concentration, can have a causal effect on type 2 diabetes (Mu-Han-Ha-Li et al., 2018). With this novel association, it becomes essential for genetic testing of *LPA* gene variants to not only follow up on CVD risk to assess benefit from aspirin therapy, but for the possible latter development of comorbidities like type 2 diabetes.

Additional researchers have identified a potential relationship between Lp(a) SNPs and a high inflammatory response that may result in an increased CVD risk in pregnant women. Tuten et al. (2019) analyzed data from 200 pregnant Turkish women, evaluating 14 different Lp(a) SNPs. Results found that two of the Lp(a) SNPs, rs9355296 and rs3798220, were identified as risk factors for preeclampsia, and that rs9355296 carriers reported higher vascular inflammatory rates (Tuten et al., 2019). These results suggest that specific Lp(a) variants may possibly be used as biomarkers for future cardiovascular events and inflammation.

Moreover, Wang and Zhang (2019) showed that high Lp(a) levels are associated with adverse clinicopathological features in prostate cancer patients. Patients with a prostate specific antigen (PSA) level $\geq$ 100 ng/ml had significantly higher Lp(a) levels; this was believed to be a result of compensatory mechanisms to chronic inflammation caused by tumor aggressiveness and invasion. The researchers also found that the percentage of metastases increased with elevation in Lp(a) level, while body mass index (BMI) decreased with the Lp(a) elevation. The increased metastasis in the setting of high Lp(a) levels was believed to be due to facilitated formations of fibrin networks (apo(a), a part of Lp(a), has structural homologues to kringle IV in plasminogen, which normally induces fibrinolysis) and thrombus formation that allowed for cancer cell adhesion (Wang & Zhang, 2019). Genetic testing for Lp(a) may not only benefit CVD risk assessment with aspirin therapy considerations, but also may have implications for cancer development and treatment.

Pechlivanis et al. (2020) studied the association of LPA gene variants (rs10455872 and rs3798220) and IL1F9 (rs13415097) with coronary artery calcification (CAC). LPA levels from 3799 patients were analyzed using linear regression models to explore the association between the variants and CAC. The LPA SNP rs10455872 showed a statistically significant association with CAC. The results of this study show that "rs10455872, mediated by Lp(a) levels, might play a role in promoting the development of atherosclerosis leading to cardiovascular disease events" (Pechlivanis et al., 2020).

In a prospective study, Yoon et al. (2021) studied the association of LPA with recurrent ischemic events after percutaneous coronary intervention (PCI). Baseline LPA levels from 12,064 patients who underwent PCI were studied. 3,747 (31.1%) patients had high LPA (>30 mg/dL) and 8,317 (68.9%) patients had low LPA (≤30 mg/dL). After a seven-year follow-up, 2.0 per 100 person-years in the high-LPA group experienced CV death, spontaneous myocardial infarction, and ischemic stroke compared to 1.6 per 100 person-years in the low-LPA group. Overall, the authors conclude that "Elevated levels of Lp(a) were significantly associated with the recurrent ischemic events in patients who underwent PCI" which provides a rationale to test LPA lowering therapy for secondary prevention in patients undergoing PCI (Yoon et al., 2021).

Murdock et al. (2021) developed a panel test for genes associated with CVD that included an evaluation of *LPA* polymorphisms. The authors studied 709 patients from cardiology clinics. In total, “32% of patients had a genetic finding with clinical management implications.” *LPA* polymorphisms were found in 20% of patients, which lead to “diet, lifestyle, and other changes.” The authors concluded that the results “support the use of genetic information in routine cardiovascular health management” (Murdock et al., 2021).Familial hypercholesterolemia (FH) and elevated plasma Lp(a) are both inherited conditions associated with ASCVD. Chakraborty et al. (2022) studied the detection of elevated Lp(a) during cascade testing of relatives of people diagnosed with FH. The authors used an immunoassay to test for FH and Lp(a) in 162 people. The prevalence of FH and elevated Lp(a) was 60.5% in adults (n=136) and 41.1% in children (n=26). The proportion of relatives with elevated Lp(a) was higher when they had relatives with Lp(a) ≥100 mg/dL than relatives with Lp(a) between 50 and 99 mg/dL. The authors concluded that duel testing of families for FH and high Lp(a) from appropriate relatives can detect new cases of FH, and elevated Lp(a) with or without FH. Lastly, the authors note that “the findings accord with the co-dominant and independent heritability of FH and Lp(a)” (Chakraborty et al., 2022).

Guidelines and Recommendations

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)

The AACE/ACE published guidelines for the management of Dyslipidemia and Prevention of Cardiovascular Disease (Jellinger et al., 2017) which state:

“Testing for lipoprotein(a) is therefore not generally recommended, although it may provide useful information to ascribe risk in Caucasians with ASCVD, those with an unexplained family history of early ASCVD, or those with unknown family history such as adopted individuals.”

In 2020, the AACE and ACE released a consensus statement for the management of Dyslipidemia and Prevention of Cardiovascular Disease and provided recommendations for the assessment and management of elevated Lipoprotein (a). Within this statement, they recommend measuring Lp(a) in patients with a family history of premature ASCVD and/or increased Lp(a) and all patients with premature or recurrent ASCVD despite LDL-C lowering (Handelsman et al., 2020).

Genetic screening for lipoprotein(a) variants is not mentioned.

National Heart, Lung, and Blood Institute (NHLBI)

The NHLBI published Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis (Tsimikas et al., 2018) which endorsed the

European Society of Cardiology/European Atherosclerosis Society, Canadian Cardiovascular Society, and National Lipid Association Guidelines while making additional specific recommendations to facilitate basic, mechanistic, preclinical, and clinical research on Lp(a).

Genetic screening for lipoprotein(a) variants is not mentioned. (Tsimikas et al., 2018).

American College of Cardiology (ACC)/American Heart Association (AHH)

The ACC and AHA issued joint guidelines (Goff et al., 2014) on the assessment of cardiovascular risk based on a systematic review conducted by an expert panel appointed by the National Heart, Lung, and Blood Institute. The panel noted that LPA was considered as a risk predictor, but its contribution to risk assessment "awaits further consideration at a later time."

The ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents (Lloyd-Jones et al., 2016) refer to elevated lipoprotein(a) as an comorbidity that increased ASCVD risk. Genetic screening for Lp(a) variants is not mentioned.

In 2019, the ACC and AHA released guidelines on the primary prevention of CVD. The guidelines list "Risk-Enhancing Factors for Clinician–Patient Risk Discussion" which include Lp(a) as a "lipid/biomarker associated with increased atherosclerotic cardiovascular disease risk." The guidelines note, "elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a)" (Arnett et al., 2019).

In 2022, the AHA released a scientific statement about Lp(a) that supports the ACC/AHH joint guidelines. The statement also includes recommendations on how and when Lp(a) testing should be performed. "At present, the evidence in favor of screening for Lp(a) is the strongest for those with a family or personal history of ASCVD, with consideration of cascade screening in appropriate individuals" (Reyes-Soffer et al., 2022).

The National Lipid Association (NLA)

The NLA considers Lp(a) to be an important clinical biomarker and risk factor for atherosclerotic cardiovascular disease. It is stated that a main obstacle towards the clinical use of Lp(a) is that measurements and various other targeted levels have not yet been standardized in the industry; for example, several of the available assays are reporting results in differing units, such as in mass instead of concentration (Wilson et al., 2019). Based on current data, Wilson et al. (2019) has stated that Lp(a) testing in clinical practice is reasonable for select individuals with the qualifications listed below:

- Adults older than 20 years with a family history of premature atherosclerotic cardiovascular disease (ASCVD)
- "Individuals with premature ASCVD (55y of age in men; 65y of age in women), particularly in the absence of traditional risk factors

- Individuals with primary severe hypercholesterolemia (LDL-C ≥ 190 mg/dL) or suspected FH
- Individuals at very-high-risk of ASCVD to better define those who are more likely to benefit from PCSK9 inhibitor therapy"

Wilson et al. (2019) also stated that Lp(a) testing may be reasonable in patients with:

- "Intermediate (7.5%–19.9%) 10-y ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention
- Borderline (5%–7.4%) 10-y ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention
- Less-than-anticipated LDL-C lowering, despite good adherence to LDL-C lowering therapy
- A family history of elevated Lp(a)
- Calcific valvular aortic stenosis
- Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy"

The NLA has previously published recommendations for the Patient-Centered Management of Dyslipidemia (Jacobson et al., 2015) which lists Lipoprotein (a) >50mg/dL as an additional risk indicator that physicians could consider, partially in patients with moderate risk.

In 2022 scientific statement, the NLA writes:

- "Lp(a) testing is reasonable to refine risk assessment for ASCVD events in adults with:
  - First-degree relatives with premature ASCVD (<55 y of age in men; <65 y of age in women).
  - A personal history of premature ASCVD.
  - Primary severe hypercholesterolemia (LDL-C ≥190 mg/dL) or suspected FH.
- Lp(a) testing may be reasonable in adults:
  - To aid in the clinician-patient discussion about whether to prescribe a statin in those aged 40-75 y with borderline (5%-7.4%) 10-y ASCVD risk.
  - To identify a possible cause for a less-than-anticipated LDL-C lowering to evidence-based LDL-C-lowering therapy.
  - To use in cascade screening of family members with severe hypercholesterolemia.
  - To identify those at risk for progressive [valvular aortic stenosis]" (Wilson et al., 2022)

Genetic screening for Lp(a) variants is not mentioned in the NLA's official guidelines (NLA, 2022).

The European Society for Cardiology (ESC) and European Atherosclerosis Society (EAS)

The ESC and EAS published Guidelines for the Management of Dyslipidemias (Catapano et al., 2016) which recommend: "Plasma Lp(a) is not recommended for risk screening in the general population; however, Lp(a) measurement should be systematically considered in people with high CVD risk or a strong family history of premature atherothrombotic disease. The risk is regarded

as significant when Lp(a) is above the 80th percentile (50 mg/dL). Including Lp(a) in risk evaluation has been shown to give a correct reclassification and should be considered in patients on the borderline between high and moderate risk."

Genetic screening for Lp(a) variants is not mentioned (Catapano et al., 2016).

American Society for Clinical Pathology (ASCP)/Choosing Wisely

The American Society for Clinical Pathology (ASCP, 2016), as part of the Choosing Wisely Campaign, recommended that "a standard lipid profile includes total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These lipids are carried within lipoprotein particles that are heterogeneous in size, density, charge, core lipid composition, specific apolipoproteins, and function. A variety of lipoprotein assays have been developed that subfractionate lipoprotein particles according to some of these properties, such as size, density, or charge. However, selection of these lipoprotein assays for improving assessment of risk of cardiovascular disease and guiding lipid-lowering therapies should be on an individualized basis for intermediate to high-risk patients only. They are not indicated for population based cardiovascular risk screening."

Genetic screening for Lp(a) variants is not mentioned.

HEART UK Medical, Scientific, and Research Committee

HEART UK published guidelines for Lp(a) measurement in specific adult populations. HEART UK recommends that Lp(a) is measured in adults as follows: "1) those with a personal or family history of premature atherosclerotic CVD; 2) those with first-degree relatives who have Lp(a) levels >200 nmol/l; 3) patients with familial hypercholesterolemia; 4) patients with calcific aortic valve stenosis and 5) those with borderline (but <15%) 10-year risk of a cardiovascular event" (Cegla et al., 2019).

On genetic testing for Lp(a) levels, the guideline also noted, "Genetic testing for SNPs associated with serum Lp(a) levels is not currently advocated for in routine clinical practice" (Cegla et al., 2019).

U.S. Preventive Services Task Force (USPSTF)

The USPSTF 2022 guidelines on aspirin use to prevent cardiovascular disease do not mention Lp(a) or genetic screening for Lp(a) (Guirguis-Blake et al., 2016; USPSTF, 2022).

Nouvelle Société Francophone d'Athérosclérose (NSFA)

The NSFA in France released a consensus statement about Lp(a). "We recommend that lipoprotein(a) be measured once in subjects at high cardiovascular risk with premature coronary heart disease, in familial hypercholesterolaemia, in those with a family history of coronary heart disease and in those with recurrent coronary heart disease despite lipid-lowering treatment" (Durlach et al., 2021)

Applicable State and Federal Regulations

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

The LPA-Aspirin Check® detects the presence of the rs3798220 allele and is considered a laboratory developed test (LDT); this test is developed, validated, and performed by individual laboratories.

The Cardio IQ® LPA Aspirin Genotype test is able to detect individuals who are at risk of high plasma Lp(a) levels, which may suggest an increased risk of cardiovascular events; this assay may also assist in determining if the patient's cardiovascular disease risk may be lowered by low-dose aspirin therapy (Quest Diagnostics, 2019). This test has not been cleared or approved by the FDA.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81479

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Anderson, J. L., Knight, S., May, H. T., Horne, B. D., Bair, T. L., Huntinghouse, J. A., Rollo, J. S., Muhlestein, J. B., & Carlquist, J. F. (2013). Validation and quantification of genetic determinants of lipoprotein-a levels and predictive value for angiographic coronary artery disease. *Am J Cardiol*, *112*(6), 799-804. https://doi.org/10.1016/j.amjcard.2013.05.009

Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., Himmelfarb, C. D., Khera, A., Lloyd-Jones, D., McEvoy, J. W., Michos, E. D., Miedema, M. D., Muñoz, D., Smith, S. C., Jr., Virani, S. S., Williams, K. A., Sr., Yeboah, J., & Ziaeian, B. (2019). 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, *140*(11), e596-e646. https://doi.org/10.1161/cir.0000000000000678

ASCP. (2016). *Screening for cardiovascular disease | Choosing Wisely*. http://www.choosingwisely.org/clinician-lists/american-society-clinical-pathology-expanded-lipid-panels-to-screen-for-cardiovascular-disease/

Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., Cheng, S., Chiuve, S. E., Cushman, M., Delling, F. N., Deo, R., de Ferranti, S. D., Ferguson, J. F., Fornage, M., Gillespie, C., Isasi, C. R., Jimenez, M. C., Jordan, L. C., Judd, S. E., Lackland, D., . . . Stroke Statistics, S. (2018). Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation*, *137*(12), e67-e492. https://doi.org/10.1161/CIR.0000000000000558

Berg, K. (1963). A New Serum Type System in Man--the Lp System. *Acta Pathol Microbiol Scand*, *59*, 369-382. https://www.ncbi.nlm.nih.gov/pubmed/14064818

Berg, K., Dahlen, G., & Frick, M. H. (1974). Lp(a) lipoprotein and pre-beta1-lipoprotein in patients with coronary heart disease. *Clin Genet*, *6*(3), 230-235. https://www.ncbi.nlm.nih.gov/pubmed/4372011

Cairns, B. J., Coffey, S., Travis, R. C., Prendergast, B., Green, J., Engert, J. C., Lathrop, M., Thanassoulis, G., & Clarke, R. (2017). A Replicated, Genome-Wide Significant Association of Aortic Stenosis With a Genetic Variant for Lipoprotein(a): Meta-Analysis of Published and Novel Data. *Circulation*, *135*(12), 1181-1183. https://doi.org/10.1161/CIRCULATIONAHA.116.026103

Caplice, N. M., Panetta, C., Peterson, T. E., Kleppe, L. S., Mueske, C. S., Kostner, G. M., Broze, G. J., Jr., & Simari, R. D. (2001). Lipoprotein (a) binds and inactivates tissue factor pathway inhibitor: a novel link between lipoproteins and thrombosis. *Blood*, *98*(10), 2980-2987. https://www.ncbi.nlm.nih.gov/pubmed/11698280

Catapano, A. L., Graham, I., De Backer, G., Wiklund, O., Chapman, M. J., Drexel, H., Hoes, A. W., Jennings, C. S., Landmesser, U., Pedersen, T. R., Reiner, Z., Riccardi, G., Taskinen, M. R., Tokgozoglu, L., Verschuren, W. M. M., Vlachopoulos, C., Wood, D. A., Zamorano, J. L., Cooney, M. T., & Group, E. S. C. S. D. (2016). 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J*, *37*(39), 2999-3058. https://doi.org/10.1093/eurheartj/ehw272

Cegla, J., Neely, R. D. G., France, M., Ferns, G., Byrne, C. D., Halcox, J., Datta, D., Capps, N., Shoulders, C., Qureshi, N., Rees, A., Main, L., Cramb, R., Viljoen, A., Payne, J., & Soran, H. (2019). HEART UK consensus statement on Lipoprotein(a): A call to action. *Atherosclerosis*, *291*, 62-70. https://doi.org/10.1016/j.atherosclerosis.2019.10.011

Chakraborty, A., Pang, J., Chan, D. C., Ellis, K. L., Hooper, A. J., Bell, D. A., Burnett, J. R., Moses, E. K., & Watts, G. F. (2022). Cascade testing for elevated lipoprotein(a) in relatives of probands with familial hypercholesterolaemia and elevated lipoprotein(a). *Atherosclerosis*, *349*, 219-226. https://doi.org/10.1016/j.atherosclerosis.2021.11.004

Chasman, D. I., Shiffman, D., Zee, R. Y., Louie, J. Z., Luke, M. M., Rowland, C. M., Catanese, J. J., Buring, J. E., Devlin, J. J., & Ridker, P. M. (2009). Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy. *Atherosclerosis*, *203*(2), 371-376. https://doi.org/10.1016/j.atherosclerosis.2008.07.019

Chen, H. Y., Dufresne, L., Burr, H., Ambikkumar, A., Yasui, N., Luk, K., Ranatunga, D. K., Whitmer, R. A., Lathrop, M., Engert, J. C., & Thanassoulis, G. (2018). Association of LPA Variants With Aortic Stenosis: A Large-Scale Study Using Diagnostic and Procedural Codes From Electronic Health Records. *JAMA Cardiol*, *3*(1), 18-23. https://doi.org/10.1001/jamacardio.2017.4266

Clarke, R., Peden, J. F., Hopewell, J. C., Kyriakou, T., Goel, A., Heath, S. C., Parish, S., Barlera, S., Franzosi, M. G., Rust, S., Bennett, D., Silveira, A., Malarstig, A., Green, F. R., Lathrop, M.,

Gigante, B., Leander, K., de Faire, U., Seedorf, U., . . . Consortium, P. (2009). Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*, *361*(26), 2518-2528. https://doi.org/10.1056/NEJMoa0902604

Durlach, V., Bonnefont-Rousselot, D., Boccara, F., Varret, M., Di-Filippo Charcosset, M., Cariou, B., Valero, R., Charriere, S., Farnier, M., Morange, P. E., Meilhac, O., Lambert, G., Moulin, P., Gillery, P., Beliard-Lasserre, S., Bruckert, E., Carrié, A., Ferrières, J., Collet, X., . . . Anglés-Cano, E. (2021). Lipoprotein(a): Pathophysiology, measurement, indication and treatment in cardiovascular disease. A consensus statement from the Nouvelle Société Francophone d'Athérosclérose (NSFA). *Arch Cardiovasc Dis*, *114*(12), 828-847. https://doi.org/10.1016/j.acvd.2021.10.009

Emdin, C. A., Khera, A. V., Natarajan, P., Klarin, D., Won, H. H., Peloso, G. M., Stitziel, N. O., Nomura, A., Zekavat, S. M., Bick, A. G., Gupta, N., Asselta, R., Duga, S., Merlini, P. A., Correa, A., Kessler, T., Wilson, J. G., Bown, M. J., Hall, A. S., . . . Consortium, C. A. E. (2016). Phenotypic Characterization of Genetically Lowered Human Lipoprotein(a) Levels. *J Am Coll Cardiol*, *68*(25), 2761-2772. https://doi.org/10.1016/j.jacc.2016.10.033

Enkhmaa, B., Anuurad, E., & Berglund, L. (2016). Lipoprotein (a): impact by ethnicity and environmental and medical conditions. *J Lipid Res*, *57*(7), 1111-1125. https://doi.org/10.1194/jlr.R051904

Erhart, G., Lamina, C., Lehtimaki, T., Marques-Vidal, P., Kahonen, M., Vollenweider, P., Raitakari, O. T., Waeber, G., Thorand, B., Strauch, K., Gieger, C., Meitinger, T., Peters, A., Kronenberg, F., & Coassin, S. (2018). Genetic Factors Explain a Major Fraction of the 50% Lower Lipoprotein(a) Concentrations in Finns. *Arterioscler Thromb Vasc Biol*, *38*(5), 1230-1241. https://doi.org/10.1161/ATVBAHA.118.310865

Fras, Z. (2020). Increased cardiovascular risk associated with hyperlipoproteinemia (a) and the challenges of current and future therapeutic possibilities. *Anatol J Cardiol*, *23*(2), 60-69. https://doi.org/10.14744/AnatolJCardiol.2019.56068

Goff, D. C., Jr., Lloyd-Jones, D. M., Bennett, G., Coady, S., D'Agostino, R. B., Sr., Gibbons, R., Greenland, P., Lackland, D. T., Levy, D., O'Donnell, C. J., Robinson, J. G., Schwartz, J. S., Shero, S. T., Smith, S. C., Jr., Sorlie, P., Stone, N. J., & Wilson, P. W. (2014). 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. *J Am Coll Cardiol*, *63*(25 Pt B), 2935-2959. https://doi.org/10.1016/j.jacc.2013.11.005

Grainger, D. J., Kirschenlohr, H. L., Metcalfe, J. C., Weissberg, P. L., Wade, D. P., & Lawn, R. M. (1993). Proliferation of human smooth muscle cells promoted by lipoprotein(a). *Science*, *260*(5114), 1655-1658. https://www.ncbi.nlm.nih.gov/pubmed/8503012

Guirguis-Blake, J. M., Evans, C. V., Senger, C. A., O'Connor, E. A., & Whitlock, E. P. (2016). Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force. *Ann Intern Med*, *164*(12), 804-813. https://doi.org/10.7326/m15-2113

Hajjar, K. A., Gavish, D., Breslow, J. L., & Nachman, R. L. (1989). Lipoprotein(a) modulation of endothelial cell surface fibrinolysis and its potential role in atherosclerosis. *Nature*, *339*(6222), 303-305. https://doi.org/10.1038/339303a0

Hancock, M. A., Boffa, M. B., Marcovina, S. M., Nesheim, M. E., & Koschinsky, M. L. (2003). Inhibition of plasminogen activation by lipoprotein(a): critical domains in apolipoprotein(a) and

mechanism of inhibition on fibrin and degraded fibrin surfaces. *J Biol Chem*, *278*(26), 23260-23269. https://doi.org/10.1074/jbc.M302780200

Handelsman, Y., Jellinger, P. S., Guerin, C. K., Bloomgarden, Z. T., Brinton, E. A., Budoff, M. J., Davidson, M. H., Einhorn, D., Fazio, S., Fonseca, V. A., Garber, A. J., Grunberger, G., Krauss, R. M., Mechanick, J. I., Rosenblit, P. D., Smith, D. A., & Wyne, K. L. (2020). Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm – 2020 Executive Summary. *Endocrine Practice*, *26*(10), 1196-1224. https://doi.org/10.4158/CS-2020-0490

Helgadottir, A., Gretarsdottir, S., Thorleifsson, G., Holm, H., Patel, R. S., Gudnason, T., Jones, G. T., van Rij, A. M., Eapen, D. J., Baas, A. F., Tregouet, D. A., Morange, P. E., Emmerich, J., Lindblad, B., Gottsater, A., Kiemeny, L. A., Lindholt, J. S., Sakalihasan, N., Ferrell, R. E., . . . Stefansson, K. (2012). Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. *J Am Coll Cardiol*, *60*(8), 722-729. https://doi.org/10.1016/j.jacc.2012.01.078

Hervio, L., Durlach, V., Girard-Globa, A., & Angles-Cano, E. (1995). Multiple binding with identical linkage: a mechanism that explains the effect of lipoprotein(a) on fibrinolysis. *Biochemistry*, *34*(41), 13353-13358. https://www.ncbi.nlm.nih.gov/pubmed/7577920

Jacobson, T. A., Ito, M. K., Maki, K. C., Orringer, C. E., Bays, H. E., Jones, P. H., McKenney, J. M., Grundy, S. M., Gill, E. A., Wild, R. A., Wilson, D. P., & Brown, W. V. (2015). National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol*, *9*(2), 129-169. https://doi.org/10.1016/j.jacl.2015.02.003

Jellinger, P. S., Handelsman, Y., Rosenblit, P. D., Bloomgarden, Z. T., Fonseca, V. A., Garber, A. J., Grunberger, G., Guerin, C. K., Bell, D. S. H., Mechanick, J. I., Pessah-Pollack, R., Wyne, K., Smith, D., Brinton, E. A., Fazio, S., & Davidson, M. (2017). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocr Pract*, *23*(Suppl 2), 1-87. https://doi.org/10.4158/ep171764.appgl

Lee, S. R., Prasad, A., Choi, Y. S., Xing, C., Clopton, P., Witztum, J. L., & Tsimikas, S. (2017). LPA Gene, Ethnicity, and Cardiovascular Events. *Circulation*, *135*(3), 251-263. https://doi.org/10.1161/CIRCULATIONAHA.116.024611

Lloyd-Jones, D. M., Morris, P. B., Ballantyne, C. M., Birtcher, K. K., Daly, D. D., Jr., DePalma, S. M., Minissian, M. B., Orringer, C. E., & Smith, S. C., Jr. (2016). 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*, *68*(1), 92-125. https://doi.org/10.1016/j.jacc.2016.03.519

Lu, W., Cheng, Y. C., Chen, K., Wang, H., Gerhard, G. S., Still, C. D., Chu, X., Yang, R., Parihar, A., O'Connell, J. R., Pollin, T. I., Angles-Cano, E., Quon, M. J., Mitchell, B. D., Shuldiner, A. R., & Fu, M. (2015). Evidence for several independent genetic variants affecting lipoprotein (a) cholesterol levels. *Hum Mol Genet*, *24*(8), 2390-2400. https://doi.org/10.1093/hmg/ddu731

Luke, M. M., Kane, J. P., Liu, D. M., Rowland, C. M., Shiffman, D., Cassano, J., Catanese, J. J., Pullinger, C. R., Leong, D. U., Arellano, A. R., Tong, C. H., Movsesyan, I., Naya-Vigne, J.,

Noordhof, C., Feric, N. T., Malloy, M. J., Topol, E. J., Koschinsky, M. L., Devlin, J. J., & Ellis, S. G. (2007). A polymorphism in the protease-like domain of apolipoprotein(a) is associated with severe coronary artery disease. *Arterioscler Thromb Vasc Biol*, *27*(9), 2030-2036. https://doi.org/10.1161/ATVBAHA.107.141291

Marcovina, S. M., Hobbs, H. H., & Albers, J. J. (1996). Relation between number of apolipoprotein(a) kringle 4 repeats and mobility of isoforms in agarose gel: basis for a standardized isoform nomenclature. *Clin Chem*, *42*(3), 436-439. https://www.ncbi.nlm.nih.gov/pubmed/8598109

Marcovina, S. M., & Koschinsky, M. L. (2003). Evaluation of lipoprotein(a) as a prothrombotic factor: progress from bench to bedside. *Curr Opin Lipidol*, *14*(4), 361-366. https://doi.org/10.1097/00041433-200308000-00004

McLean, J. W., Tomlinson, J. E., Kuang, W. J., Eaton, D. L., Chen, E. Y., Fless, G. M., Scanu, A. M., & Lawn, R. M. (1987). cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature*, *330*(6144), 132-137. https://doi.org/10.1038/330132a0

Moriarty, P. M., Varvel, S. A., Gordts, P. L., McConnell, J. P., & Tsimikas, S. (2017). Lipoprotein(a) Mass Levels Increase Significantly According to APOE Genotype: An Analysis of 431 239 Patients. *Arterioscler Thromb Vasc Biol*, *37*(3), 580-588. https://doi.org/10.1161/ATVBAHA.116.308704

Mu-Han-Ha-Li, D. L., Zhai, T. Y., Ling, Y., & Gao, X. (2018). LPA kringle IV type 2 is associated with type 2 diabetes in a Chinese population with very high cardiovascular risk. *J Lipid Res*, *59*(5), 884-891. https://doi.org/10.1194/jlr.P082792

Murdock, D. R., Venner, E., Muzny, D. M., Metcalf, G. A., Murugan, M., Hadley, T. D., Chander, V., de Vries, P. S., Jia, X., Hussain, A., Agha, A. M., Sabo, A., Li, S., Meng, Q., Hu, J., Tian, X., Cohen, M., Yi, V., Kovar, C. L., . . . Gibbs, R. A. (2021). Genetic testing in ambulatory cardiology clinics reveals high rate of findings with clinical management implications. *Genet Med*, *23*(12), 2404-2414. https://doi.org/10.1038/s41436-021-01294-8

Nagalla, S., & Bray, P. F. (2016). Personalized medicine in thrombosis: back to the future. *Blood*, *127*(22), 2665-2671. https://doi.org/10.1182/blood-2015-11-634832

NLA. (2022). *NLA Recommendations & Statements*. https://www.lipid.org/practicetools/documents

Ozkan, U., Ozcelik, F., Yildiz, M., & Budak, M. (2019). Lipoprotein(a) Gene Polymorphism Increases a Risk Factor for Aortic Valve Calcification. *J Cardiovasc Dev Dis*, *6*(3). https://doi.org/10.3390/jcdd6030031

Paré, G., Çaku, A., McQueen, M., Anand Sonia, S., Enas, E., Clarke, R., Boffa Michael, B., Koschinsky, M., Wang, X., Yusuf, S., & null, n. (2019). Lipoprotein(a) Levels and the Risk of Myocardial Infarction Among 7 Ethnic Groups. *Circulation*, *139*(12), 1472-1482. https://doi.org/10.1161/CIRCULATIONAHA.118.034311

Pechlivanis, S., Mahabadi, A. A., Hoffmann, P., Nöthen, M. M., Broecker-Preuss, M., Erbel, R., Moebus, S., Stang, A., & Jöckel, K.-H. (2020). Association between lipoprotein(a) (Lp(a)) levels and Lp(a) genetic variants with coronary artery calcification. *BMC Medical Genetics*, *21*(1), 62. https://doi.org/10.1186/s12881-020-01003-3

Quest Diagnostics. (2019). *Cardio IQ® LPA Aspirin Genotype*. https://testdirectory.questdiagnostics.com/test/test-detail/90553/cardio-iq-lpa-aspirin-genotype?cc=MASTER

Reyes-Soffer, G., Ginsberg, H. N., Berglund, L., Duell, P. B., Heffron, S. P., Kamstrup, P. R., Lloyd-Jones, D. M., Marcovina, S. M., Yeang, C., & Koschinsky, M. L. (2022). Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol*, *42*(1), e48-e60. https://doi.org/10.1161/atv.0000000000000147

Rosenson, R., Stein, J., & Durrington, P. (2022). *Lipoprotein(a)*. https://www.uptodate.com/contents/lipoprotein-a

Rowland, C. M., Pullinger, C. R., Luke, M. M., Shiffman, D., Green, L., Movsesyan, I., Devlin, J. J., Malloy, M. J., Kane, J. P., & Undas, A. (2014). Lipoprotein (a), LPA Ile4399Met, and fibrin clot properties. *Thromb Res*, *133*(5), 863-867. https://doi.org/10.1016/j.thromres.2014.01.024

Schmidt, K., Noureen, A., Kronenberg, F., & Utermann, G. (2016). Structure, function, and genetics of lipoprotein (a). *J Lipid Res*, *57*(8), 1339-1359. https://doi.org/10.1194/jlr.R067314

Scipione, C. A., McAiney, J. T., Simard, D. J., Bazzi, Z. A., Gemin, M., Romagnuolo, R., Macrae, F. L., Ariens, R. A., Hegele, R. A., Auld, J., Gauld, J. W., Boffa, M. B., & Koschinsky, M. L. (2017). Characterization of the I4399M variant of apolipoprotein(a): implications for altered prothrombotic properties of lipoprotein(a). *J Thromb Haemost*, *15*(9), 1834-1844. https://doi.org/10.1111/jth.13759

Shiffman, D., Slawsky, K., Fusfeld, L., Devlin, J. J., & Goss, T. F. (2012). Cost-effectiveness model of use of genetic testing as an aid in assessing the likely benefit of aspirin therapy for primary prevention of cardiovascular disease. *Clin Ther*, *34*(6), 1387-1394. https://doi.org/10.1016/j.clinthera.2012.04.004

Steyrer, E., Durovic, S., Frank, S., Giessauf, W., Burger, A., Dieplinger, H., Zechner, R., & Kostner, G. M. (1994). The role of lecithin: cholesterol acyltransferase for lipoprotein (a) assembly. Structural integrity of low density lipoproteins is a prerequisite for Lp(a) formation in human plasma. *J Clin Invest*, *94*(6), 2330-2340. https://doi.org/10.1172/JCI117598

Tregouet, D. A., Konig, I. R., Erdmann, J., Munteanu, A., Braund, P. S., Hall, A. S., Grosshennig, A., Linsel-Nitschke, P., Perret, C., DeSuremain, M., Meitinger, T., Wright, B. J., Preuss, M., Balmforth, A. J., Ball, S. G., Meisinger, C., Germain, C., Evans, A., Arveiler, D., . . . Samani, N. J. (2009). Genome-wide haplotype association study identifies the SLC22A3-LPAL2-LPA gene cluster as a risk locus for coronary artery disease. *Nat Genet*, *41*(3), 283-285. https://doi.org/10.1038/ng.314

Trinder, M., Uddin, M. M., Finneran, P., Aragam, K. G., & Natarajan, P. (2021). Clinical Utility of Lipoprotein(a) and LPA Genetic Risk Score in Risk Prediction of Incident Atherosclerotic Cardiovascular Disease. *JAMA Cardiology*, *6*(3), 287-295. https://doi.org/10.1001/jamacardio.2020.5398

Tsimikas, S., Fazio, S., Ferdinand, K. C., Ginsberg, H. N., Koschinsky, M. L., Marcovina, S. M., Moriarty, P. M., Rader, D. J., Remaley, A. T., Reyes-Soffer, G., Santos, R. D., Thanassoulis, G., Witztum, J. L., Danthi, S., Olive, M., & Liu, L. (2018). NHLBI Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis. *J Am Coll Cardiol*, *71*(2), 177-192. https://doi.org/10.1016/j.jacc.2017.11.014

Tuten, A., Gungor, Z., Ekmekci, H., Ekmekci, O. B., Kucur, M., Yilmaz, N., Donma, O., Sonmez, H., Acikgoz, A., & Madazli, R. (2019). Relationship between LPA SNPs and inflammatory burden in patients with preeclampsia to address future cardiovascular risk. *J Matern Fetal Neonatal Med*, 1-9. https://doi.org/10.1080/14767058.2019.1622667

USPSTF. (2022). *Aspirin Use to Prevent Cardiovascular Disease: Preventive Medication*. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/aspirin-to-prevent-cardiovascular-disease-preventive-medication

Wang, F. M., & Zhang, Y. (2019). High Lipoprotein(a) Level Is Independently Associated with Adverse Clinicopathological Features in Patients with Prostate Cancer. *Dis Markers*, *2019*, 9483935. https://doi.org/10.1155/2019/9483935

Wang, H., Hong, C. E., Lewis, J. P., Zhu, Y., Wang, X., Chu, X., Backman, J., Hu, Z., Yang, P., Still, C. D., Gerhard, G. S., & Fu, M. (2016). Effect of Two Lipoprotein (a)-Associated Genetic Variants on Plasminogen Levels and Fibrinolysis. *G3 (Bethesda)*, *6*(11), 3525-3532. https://doi.org/10.1534/g3.116.034702

Wilson, D. P., Jacobson, T. A., Jones, P. H., Koschinsky, M. L., McNeal, C. J., Nordestgaard, B. G., & Orringer, C. E. (2019). Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol*, *13*(3), 374-392. https://doi.org/10.1016/j.jacl.2019.04.010

Wilson, D. P., Jacobson, T. A., Jones, P. H., Koschinsky, M. L., McNeal, C. J., Nordestgaard, B. G., & Orringer, C. E. (2022). Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol*. https://doi.org/10.1016/j.jacl.2022.08.007

Yoon, Y. H., Ahn, J. M., Kang, D. Y., Lee, P. H., Kang, S. J., Park, D. W., Lee, S. W., Kim, Y. H., Han, K. H., Lee, C. W., Park, S. W., & Park, S. J. (2021). Association of Lipoprotein(a) With Recurrent Ischemic Events Following Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*, *14*(18), 2059-2068. https://doi.org/10.1016/j.jcin.2021.07.042

Zekavat, S. M., Ruotsalainen, S., Handsaker, R. E., Alver, M., Bloom, J., Poterba, T., Seed, C., Ernst, J., Chaffin, M., Engreitz, J., Peloso, G. M., Manichaikul, A., Yang, C., Ryan, K. A., Fu, M., Johnson, W. C., Tsai, M., Budoff, M., Vasan, R. S., . . . Group, N. T. L. W. (2018). Deep coverage whole genome sequences and plasma lipoprotein(a) in individuals of European and African ancestries. *Nat Commun*, *9*(1), 2606. https://doi.org/10.1038/s41467-018-04668-w

Zewinger, S., Kleber, M. E., Tragante, V., McCubrey, R. O., Schmidt, A. F., Direk, K., Laufs, U., Werner, C., Koenig, W., Rothenbacher, D., Mons, U., Breitling, L. P., Brenner, H., Jennings, R. T., Petrakis, I., Triem, S., Klug, M., Filips, A., Blankenberg, S., . . . Speer, T. (2017). Relations between lipoprotein(a) concentrations, LPA genetic variants, and the risk of mortality in patients with established coronary heart disease: a molecular and genetic association study. *Lancet Diabetes Endocrinol*, *5*(7), 534-543. https://doi.org/10.1016/S2213-8587(17)30096-7

Specialty Matched Consultant Advisory Panel review 4/2020

Medical Director review 4/2020

Specialty Matched Consultant Advisory Panel review 4/2021

Medical Director review 4/2021

Medical Director review 1/2022

Medical Director review 1/2023

Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will not provide coverage for genetic testing for lipoprotein A variant as a decision aid for aspirin treatment because it is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

For the policy titled: Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment

4/1/2019 Policy title changed throughout to reflect the addition of Lp(A) testing for CVD; description section, policy guidelines and references updated. Related Policies section added. Added 2nd policy statement "The use of genotyping of lipoprotein a (Lp(a)), including genetic testing for the rs3798220 single nucleotide polymorphism (SNP), the rs10455872 SNP, and/or the rs9457951 SNP, is considered investigational", to the When Not Covered section. Policy noticed 4/1/19, effective 6/1/19. Medical Director review 4/2019. (jd)

10/29/19 No change to policy statements. (hb)

2/11/20 Annual review by Avalon 4th Quarter 2019 CAB. No revisions and no change in policy intent. Medical Director review 12/2019. (jd)

4/28/20 Specialty Matched Consultant Advisory Panel review 4/2020. Medical Director review 4/2020. (jd)

2/9/21 Annual review by Avalon 4th Quarter 2020 CAB. Minor updates to description,policy guidelines and references. Medical Director review 1/2021. (jd)

5/4/21 Specialty Matched Consultant Advisory Panel review 4/2021. Medical Director review 4/2021. (jd)

2/8/22 Reviewed by Avalon 4th Quarter 2021 CAB. Description, policy guidelines, and references updated with minor revisions. Medical Director review 1/2022. (jd)

2/7/23 Reviewed by Avalon 4th Quarter 2022 CAB. Description, Policy Guidelines, and References updated with minor revisions, Related Policies section removed. Not Covered section edited for clarity, no change to policy statement. Medical Director review 1/2023. (tm)