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

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Line(s) of Business: HMO; PPO; QUEST; Medicare; FEP	**Precertification:** Refer to the GTM Utilization Review Matrix

I. Policy 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))[1,2] and has been associated with increased risk for cardiovascular disease (CVD).[3] Genetic variants of the Lp(a) gene, *LPA*, (rs3798220 and rs10455872) have been significantly associated with Lp(a) levels[1] and could serve as indicators of CVD risk.[4] 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.[5] As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment.[6]

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 AHS-G2050-Cardiovascular Disease Risk Assessment.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

1) Genetic testing for *LPA* variant(s) (e.g., LPA-Aspirin Check® and Cardio IQ® LPA Aspirin Genotype) **DOES NOT MEET COVERAGE CRITERIA**.

III. Table of Terminology

Term	Definition
AACE	American Association of Clinical Endocrinologists
ACC	American College of Cardiology
ACE	American College of Endocrinology
AHA	American Heart Association
apo(a)	Apolipoprotein(A)
APOE	*Apolipoprotein E*
AS	Aortic stenosis
ASCP	American Society for Clinical Pathology
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CAC	Coronary artery calcification
CAVD	Calcific aortic stenosis
CAVD	Calcific aortic valve disease
CHD	Coronary heart disease
CLIA ’88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
CNVs	Copy number variants
CV	Cardiovascular
CVD	Cardiovascular Disease
DNA	Deoxyribonucleic acid
EAS	European Atherosclerosis Society
ESC	The European Society for Cardiology
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
HDL	High-density lipoprotein
KIV	Kringle (five cysteine-rich domains) IV
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDT	Laboratory developed test
LDTs	Laboratory-developed tests
LPA	Lipoprotein(a)
Lp(a)	Lipoprotein(a)
MI	Myocardial infarctions
NHLBI	National Heart, Lung, and Blood Institute
NLA	The National Lipid Association
PCI	Percutaneous coronary intervention

PCSK9	Proprotein convertase subtilisin/kexin type 9
PSA	Prostate specific antigen
SNP	Single nucleotide polymorphism
SNPs	Single nucleotide polymorphisms
USPSTF	United States Preventive Services Task Force

IV. Scientific Background

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality; with over 9.9% of American adults (28.6 million) diagnosed with heart disease, it claims more lives each year than cancer and chronic lower respiratory disease combined. 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.[7] Lp(a) is also elevated in heterozygous familial hypercholesterolemia, further increasing atherosclerotic CVD risk in that disease setting.[7] 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.[8] Independent of any other risk factors, Lp(a) was positively associated with increased risk of myocardial infarctions (MI) as well.[9]

Since first described by Berg (1963) as a genetic trait increased in patients with coronary heart disease,[11] Lp(a) has been characterized as a type of LDL consisting of apolipoprotein B-100 covalently bound to apolipoprotein(a).[12] 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.[13] 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.[1,14,15] 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[16] of varying molecular weights.[7]

As it is genetically controlled, the concentration of Lp(a) is generally stable, correlates inversely with molecular size (smaller size correlates with higher serum levels), and is minimally influenced by age, weight, and diet.[17,18] Genetic variants of apo(a) have been found to have predictive value in coronary heart disease (CHD).[4,19-23] Beyond CHD, genetically lowered Lp(a) is also associated with a lower risk of peripheral vascular disease, stroke, heart failure, and aortic stenosis.[24]

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.[4] 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.[9]

Although its biology and pathophysiology are still incompletely understood,[3] Lp(a) is recognized as both atherogenic [19,25,26] and thrombogenic,[27,28] possibly due to its structural homology with plasminogen.[29,30] It is thought that Lp(a) could compete with plasminogen for fibrin binding, ultimately resulting in impaired fibrinolysis.[31]

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.[19,32,33] This amino acid substitution (I4399M) has been studied for its effects on coagulation, fibrinolysis, and overall fibrin cloth structure.[34]

Carriers of either the rs3798220 or rs10455872 variant were found to have no difference in plasminogen concentration or clot lysis time.[35] 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.[34] 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.[36] 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.[34]

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.[6] 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).[37]

Inflammatory genotypes, such as interleukin-1(+) clusters, significantly amplify cardiovascular risk among patients with elevated Lp(a) levels (>9.2 mg/dL). Individuals harboring these proinflammatory alleles demonstrate higher circulating cytokine levels and a markedly greater incidence of major CVD events compared with those carrying the interleaukin-1(-) genotype. These findings underscore the interplay between Lp(a)-mediated thrombosis and systemic inflammation, supporting combined assessment of Lp(a) and inflammatory biomarkers to refine aspirin treatment decisions.[38]

After a randomized trial of low-dose aspirin, the authors 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.[5]

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."[39] 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.[40]

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.[41] While a relationship between both Lp(a) variants has already been established regarding 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. 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.[41]

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.[42] 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 two 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 individuals. Tuten, et al. (2019) analyzed data from 200 pregnant Turkish individuals, 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.[43] 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 ≥ 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.[44] 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."[40]

Furthermore, population-based genome-wide association studies have identified multiple LPA and APOE variants that modulate Lp(a) concentrations and CVD risk across racial and ethnic groups. Variants such as rs7412 and rs405509 have been shown to alter Lp(a) metabolism and cardiovascular outcomes, with certain alleles conferring higher thrombogenic potential in African American populations. Including genetic testing for LPA and APOE polymorphisms could enhance precision in identifying individuals most likely to benefit from Lp(a)-guided preventive interventions such as aspirin therapy.[38]

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. A total of 3,747 (31.1%) patients had high Lp(a) (>30 mg/dL) and 8,317 (68.9%) patients had low Lp(a) (≤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-Lp(a) 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.[45]

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."[46] 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 dual 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)."[47]

Gu, et al. (2022) investigated whether elevated Lp(a) and two corresponding *LPA* polymorphisms played a role in the prediction of cardiovascular events. The authors enrolled 2766 individuals from Peking University People's Hospital. The study included a cohort with coronary heart disease and a separate

control group. The authors demonstrated that Lp(a) level and the amount of *LPA* SNPs were associated with the risk and severity of coronary heart disease. The rs6415084 and rs12194138 polymorphisms were particularly associated with serum Lp(a) levels. The authors concluded via univariate logistic regression analysis and multiple logistic regression analysis that, "These data together indicated that the level of Lp(a) and the prevalence of LPA SNPs rs6415084 (CT/TT) and rs12194138 (AT/TT) is positively correlated with the severity of CHD."[48]

Bhatia, et al. (2024) conducted a cohort study evaluating therapies to reduce cardiovascular disease risk among individuals with elevated lipoprotein(a). Their findings linked elevated Lp(a) levels (>50 mg/dL) with increased CVD risk, emphasizing its atherothrombotic and antifibrinolytic mechanisms, including apolipoprotein(a)'s interaction with platelets and inhibition of fibrinolysis. These mechanisms strengthen the biological plausibility of Lp(a) as both a genetic and biochemical target in CVD prevention and provide a mechanistic bridge between genetic predisposition (LPA variants) and phenotypic expression. Observational evidence further demonstrates that elevated Lp(a) independently predicts CHD events and that aspirin was associated with a 46% reduction in CHD risk among those with elevated Lp(a) (hazard ratio, 0.54; [95% CI, 0.32-0.94]; *P*=0.03).

V. 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 which state: [50]

"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.[51]

Genetic screening for Lp(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 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 Lp(a) variants is not mentioned.[3]

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

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)."[52]

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."[53]

Genetic screening for Lp(a) variants is not mentioned.[53]

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.[54] 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"

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]."[55]

In 2024, the NLA released a focused update to the 2019 NLA scientific statement that included recommendations for Lp(a) testing in clinical practice:[56]

1. "Adults (aged ≥18 y): Measurement of Lp(a) in all adults is reasonable to refine risk assessment for ASCVD events
2. Youth (aged <18 y): Selective screening of Lp(a) is recommended in high-risk patients (e.g., clinically suspected or genetically confirmed FH, ischemic stroke of unknown cause, first-degree relatives with a history of premature ASCVD [age <55 years in men, <65 years in women], or first-degree relatives with elevated Lp(a))
3. When Lp(a) levels are used for ASCVD risk assessment, it is reasonable to use measurements ≥125 nmol/L (≥50 mg/dL) as levels suggesting high risk, levels <75 nmol/L (<30 mg/dL) as low risk, and levels between as intermediate risk."[56]

Genetic screening for Lp(a) variants was mentioned in the most recent NLA guideline update.[56] "While genetic risk scores incorporating genetic variants at or near the LPA locus are increasingly accurate for identifying individuals likely to have elevated Lp(a) and to develop CVD, Lp(a) genetic risk score appears to add no incremental value for CVD risk classification compared with Lp(a) concentrations alone. Additionally, the generalizability of genetic risk scores to groups with non-White ancestry remains uncertain. Therefore, at this time, Lp(a) measurement is preferable for risk ascertainment; all the necessary information for appraisal of Lp(a)-attributable cardiovascular risk is embodied in the measurement of plasma Lp(a) concentration itself, mandating increased screening to identify individuals with elevated Lp(a) and high risk for CVD."[56]

The European Atherosclerosis Society (EAS)

In a 2022 update, the European Atherosclerosis Society recommends testing Lp(a) concentration at least once per lifetime in adults. The EAS also suggests measurement of Lp(a) in youth with a (1) history of ischemic stroke or a (2) family history of premature ASCVD or (3) elevated Lp(a) level and no other known risk factors.

The consensus statement suggests that other testing may have value under certain conditions. "Cascade testing has potential value in familial hypercholesterolaemia, or with family or personal history of (very)

high Lp(a) or premature ASCVD. Without specific Lp(a)-lowering therapies, early intensive risk factor management is recommended, targeted according to global cardiovascular risk and Lp(a) level."[57]

Under a subtitle posing the question "Is there a role for genetic testing?" the authors write: "Measurement of Lp(a) concentration is sufficient for Lp(a)-related risk estimation without the need for genotyping, polygenic risk scores, or investigation of expressed apo(a) isoform sizes."[57]

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

The ESC and EAS published a joint guideline for the Management of Dyslipidemias which recommends:

- "Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels > 180mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia (Level of Recommendation: C)
- Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk (Level of Recommendation: C)."[58]

Genetic screening for Lp(a) variants is not mentioned.[58]

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."[59]

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."[59]

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).[60,61]

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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.62
This test has not been cleared or approved by the FDA.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81479	Unlisted molecular pathology procedure

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

X. Policy History

Action Date	Action
June 01, 2023	Policy created
March 17, 2026	Policy approved by Medical Directors
March 27, 2026	Policy approved at UMC
August 1, 2026	Policy effective date following notification period