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 Integration; Medicare; FEP	Precertification: N/A

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

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 G2050 Cardiovascular Disease Risk Assessment.

For information on testing for salicylate resistance see G2107 Measurement of Thromboxane Metabolites for ASA Resistance.

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

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 a patient's illness.

1) The use of genetic testing for the rs3798220 allele (including proprietary testing such as LPA-Aspirin Check® and Cardio IQ® LPA Aspirin Genotype) **DOES NOT MEET COVERAGE CRITERIA** in patients who are being considered for treatment with aspirin to reduce risk of cardiovascular events.

2) 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, **DOES NOT MEET COVERAGE CRITERIA** in all situations.

III. Scientific 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. 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. Lp(a) is also elevated in heterozygous familial hypercholesterolemia, further increasing atherosclerotic CVD risk in that disease setting. 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. Independent of any other risk factors, Lp(a) was positively associated with increased risk of myocardial infarctions (MI) as well.

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). 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. 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. 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 of varying molecular weights.

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. Genetic variants of apo(a) have been found to have predictive value in coronary heart disease (CHD). Beyond CHD, genetically lowered Lp(a) is also associated with a lower risk of peripheral vascular disease, stroke, heart failure, and aortic stenosis.

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. 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.

Although its biology and pathophysiology are still incompletely understood, Lp(a) is recognized as both atherogenic and thrombogenic, possibly due to its structural homology with plasminogen. It is thought that Lp(a) could compete with plasminogen for fibrin binding, ultimately resulting in impaired fibrinolysis.

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. This amino acid substitution (I4399M) has been studied for its effects on coagulation, fibrinolysis, and overall fibrin cloth structure.

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

Clinical Validity and Utility

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. 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).

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.

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". 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.

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. 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.

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. 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. 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. 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."

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 7-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.

IV. 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:

“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.

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.

American College of Cardiology/American Heart Association

The ACC and AHA issued joint guidelines 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 refer to elevated lipoprotein(a) as an comorbidity that increased ASCVD risk.

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

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. 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 which lists Lipoprotein (a) >50mg/dL as an additional risk indicator that physicians could consider, partially in patients with moderate risk.

In a 2021 statement on Lipid Measurements in the Management of CV Diseases, the NLA confirmed that "Lipoprotein (a) measurement is reasonable for initial evaluation in patients with premature ASCVD, family history of premature ASCVD or of elevated Lp(a), history of LDL-C >190 mg/dL or suspected FH, or those with very high ASCVD risk."

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

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

The ESC and EAS published Guidelines for the Management of Dyslipidemias 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.

American Society for Clinical Pathology (ASCP)/Choosing Wisely

The American Society for Clinical Pathology, 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."

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".

U.S. Preventive Services Task Force (USPSTF)

U.S. Preventive Services Task Force (USPSTF) guidelines from 2016 recommendation for aspirin do not mention Lp(a) or genetic screening for Lp(a).

V. State and Federal Regulations, as applicable

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: http://www.cms.gov/medicare-coveragedatabase/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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

A search of the FDA Device database on 11/07/2021 for "lipoprotein a" yielded 35 results. Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VI. 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 Integration 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).

VII. Evidence-based Scientific References

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VIII. Policy History

Policy approved by Medical Directors	9/20/2022
Policy approved at UMC	12/16/2022
Policy effective	6/1/2023
Updated Lines of Business	12/18/2023