2.04.70	Genetic Testing for Lipoprotein(a) Variant(s) as a Decision Aid for Aspirin Treatment		
Original Policy Date:	October 30, 2015	**Effective Date:**	December 1, 2019
Section:	2.0 Medicine	**Page:**	Page 1 of 9

Policy Statement

The use of genetic testing for the *LPA* rs3798220 allele (*LPA*-Aspirin Genotype) is considered **investigational** in patients who are being considered for treatment with aspirin to reduce the risk of cardiovascular events.

Policy Guidelines

Genetic Counseling
Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding
There is no specific CPT code for this test. The following CPT code would be reported:

- **81479**: Unlisted molecular pathology procedure

Description

Lipoprotein(a) (LPA) is a lipid-rich particle similar to low-density lipoprotein and has been determined to be an independent risk factor for coronary artery disease. Patients with a positive test for the *LPA* genetic variant, rs3798220, have a higher risk for thrombosis and therefore may derive greater benefit from the antithrombotic properties of aspirin. As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment.

Related Policies

- Measurement of Lipoprotein-Associated Phospholipase A_2 in the Assessment of Cardiovascular Risk

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Berkeley HeartLab/Quest Diagnostics is certified under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Background

Lipoprotein(a)

Extensive epidemiologic evidence has determined that lipoprotein(a) (LPA) blood level is an independent risk factor for cardiovascular disease. The overall risk associated with LPA appears to be modest, and the degree of risk may be mediated by other factors such as low-density lipoprotein levels and/or hormonal status.

Over time, a person's LPA levels remain relatively stable; however, levels have been known to vary up to 1000-fold between different people, and this is most likely due to genetics. A single nucleotide variant in the *LPA* gene, *LPA* rs3798220, has been associated with both elevated LPA levels and an increased risk of cardiovascular disease. This variant substitutes methionine for isoleucine at amino acid position 4399 and is also called I4399M. Mendelian randomization studies have supported the hypothesis that this genetic variant, and the subsequent increase in LPA levels, are causative of cardiovascular disease.

Aspirin is a well-established treatment for patients with known coronary artery disease. It also is prescribed as primary prevention for some patients who are at increased risk of coronary artery disease. Current recommendations for primary prevention consider the future risk of cardiovascular events weighed against the bleeding risk of aspirin. The U.S. Preventive Services Task Force 2013 final guidelines recommended aspirin for men "age of 45 to 79 years when the potential benefit due to reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage"; the Task Force made the same recommendation for women between the ages of 55 and 79 years.[1,] Given such guidelines that recommend individualizing the risk-benefit ratio of aspirin therapy, additional tools that could aid in better defining the benefits of aspirin, and/or the risk of bleeding, have potential utility for clinicians who are making decisions about aspirin therapy.

The Cardio IQ® LPA Aspirin Genotype test is a commercially available genetic test (Berkeley HeartLab, a Quest Diagnostics service) that detects the presence of the rs3798220 allele. Patients with a positive test for rs3798220 have a higher risk for thrombosis and therefore may derive more benefit from the antithrombotic properties of aspirin. It has been proposed that the additional information obtained from the test may aid physicians in better estimating the benefit and risk of aspirin therapy and therefore may aid in deciding whether to prescribe aspirin for individual patients.

Literature Review

he primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain

of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Testing for the *LPA* rs3798220 Variant

Clinical Context and Test Purpose

The purpose of genetic testing for the lipoprotein(a) (*LPA*) rs3798220 variant in patients who have a high risk of thrombosis is to confirm a diagnosis of thrombosis and select appropriate therapy.

The question addressed in this evidence review is: Does testing for the *LPA* rs3798220 variant improve the net health outcome in patients at high risk of thrombosis?

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest is individuals at high risk of thrombosis.

Interventions

The test being considered is testing for the *LPA* rs3798220 variant, which would involve a laboratory-developed test provider and outpatient cardiology. Short-term follow-up for consultation would occur once laboratory test results have been received. Long-term follow-up would occur if a therapy change is warranted based on test findings.

Comparators

The following practice is currently being used to manage thrombosis: standard clinical management without genetic testing.

Outcomes

The general outcomes of interest test validity and reducing the risk of a coronary event. Short-term follow-up for consultation would take once laboratory test results have been received. Long-term follow-up would occur if a therapy change is warranted based on test findings.

Observational Studies Assessing the *LPA* rs3798220 Variant as a Risk Factor for Coronary Artery Disease

Several observational studies have evaluated whether *LPA* rs3798220 is an independent risk factor for coronary artery disease (CAD).

Wang et al (2014) conducted a case-control study and did not report an association between rs3798220 genotype and myocardial infarction risk in a Chinese population.[2,] Cases (n=2365) were patients who had experienced a first myocardial infarction, drawn from hospitals in 15 cities in China. (This was the Chinese cohort of the global INTERHEART study.[3,]) Age- and sex-matched controls (n=2678) were healthy adult visitors to the hospitals; these individuals had no history of cardiovascular disease. In logistic regression analysis adjusted for age, sex, and body

mass index, the odds for myocardial infarction in rs3798220 carriers compared with noncarriers was 1.12 (95% confidence interval [CI], 0.57 to 2.22; p=0.73).

In a case-control study, Koch et al (2013) evaluated 2136 cases and 1211 controls to determine whether single nucleotide variants (SNVs) rs3798220 and rs10455872 were associated with an increased risk of coronary disease.[4] Genotyping of these 2 SNVs and 7 other *LPA* variants believed to be associated with coronary disease was done using the TaqMan assay. After adjusting for conventional risk factors, the authors found an increased odds of myocardial infarction of 2.14 (95% CI, 1.37 to 3.33, p<0.001) for rs3798220 and 1.45 (95% CI, 1.36 to 2.24; p<0.001) for rs10455872. Two additional SNVs (rs3127599, rs9346818) also were found to be associated with risk of myocardial infarction, with an odds of 1.18 (95% CI, 1.06 to 1.32) and 0.88 (95% CI, 0.79 to 0.97), respectively.

Kamstrup et al (2013) followed a Danish cohort of 8720 participants for 10 years to determine whether *LPA* variants or LPA levels increased the risk of a first-time myocardial infarction or coronary heart disease (CHD) event.[5] Genotyping of rs3798220, rs10455872, and *LPA* kringle IV type 2 copy number variants was performed by polymerase chain reaction. The authors found that 27% of the total variation in LPA levels was explained by the rs10455872 genotype, 21% of the variation was explained by the *LPA* kringle IV type 2 copy number variant, and 5% of the variation was explained by the rs3798220 genotype. Hazard ratios (HRs) for rs3798220 carriers were 1.3 (95% CI, 0.8 to 2.1) for myocardial infarction and 1.4 (95% CI, 1.1 to 1.9) for CHD compared with noncarriers. *LPA* rs10455872 carriers had HRs of 1.3 (95% CI, 1.1 to 1.6) for myocardial infarction and 1.1 (95% CI, 0.9 to 1.3) for CHD compared with noncarriers, whereas homozygous rs10455872 patients had HRs of 1.2 (95% CI, 0.5 to 3.3) for myocardial infarction and 1.1 (95% CI, 0.5 to 2.1) for CHD compared with noncarriers.

Similarly, Anderson et al (2013) did not find an association between rs3798220 genotype and prevalence of CAD in 1235 patients in the Intermountain Heart Collaborative Study Registry who underwent coronary angiography.[6] CAD was defined as stenosis of 70% or more in coronary artery diameter, and non-CAD as stenosis less than 10% plus no history of CAD, myocardial infarction, or coronary artery revascularization. By these definitions, 801 (65%) patients had CAD, and 434 (35%) did not. In logistic regression analysis adjusted for age, sex, body mass index, hyperlipidemia, hypertension, diabetes, smoking history, and family history of premature CAD, the odds for CAD in rs3798220 carriers compared with noncarriers was 1.74 (95% CI, 0.84 to 3.59; p=0.36). In contrast, the rs10455872 genotype was significantly associated with CAD (odds ratio in rs10455872 carriers vs noncarriers, 1.77; 95% CI, 1.22 to 2.57; p=0.003).

Clarke et al (2009) used a case-control design to examine the association between the rs3798220 variant and CAD in 3145 case patients and 3352 controls from 4 European countries.[7] They initially examined 48,742 SNVs in 2100 genes that had some association with heart disease, including 40 SNVs from the *LPA* gene. The rs3798220 SNV was found in 2% of patients and had the strongest association with CAD, with an HR of 1.92 (95% CI, 1.48 to 2.49). This association was then replicated in 3 independent patient samples from cohort studies, with a total of 4846 patients and 4594 controls. In these patients, the rs3798220 variant remained an independent risk factor for CAD, with odds that was somewhat lower than in the derivation population (odds ratio, 1.68; 95% CI, 1.43 to 1.98).

In a similar case-control design, Shiffman et al (2008) examined the association between the rs3798220 allele and myocardial infarction in 3 case-control studies totaling 762 cases and 857 controls.[8] Starting from a total of 1949 SNVs associated with myocardial infarction, the authors identified 5 SNVs that were most strongly associated with myocardial infarction. One of these was rs3798220, which had odds in the 3 separate studies of 1.59 (95% CI, 1.03 to 2.48), 1.72 (95% CI, 1.19 to 2.49), and 3.52 (95% CI, 1.85 to 6.69).

The risk associated with genetic variants of *LPA* in diabetic patients may differ from that in the general population. A large prospective study performed by Qi et al (2012) evaluated LPA

variants in 2308 patients who had diabetes.[9] There was no significant association between genetic variants and cardiovascular risk or mortality. Odds ratios for CHD, cardiovascular disease, and cardiovascular death were 0.94 (95% CI, 0.69 to 1.28), 0.97 (95% CI, 0.72 to 1.29), and 1.23 (95% CI, 0.79 to 1.92), respectively. The authors also examined the degree of variability in risk between diabetic and nondiabetic patients and reported that there was significant heterogeneity between groups (p=0.006).

Shiffman et al (2008) used data from the Cardiovascular Health Study, a prospective cohort study of risk factors for myocardial infarction in 4522 subjects who were 65 years or older, to examine the association between the rs3798220 variant and myocardial infarction.[10] These authors tested 74 SNVs that had been genotyped as part of the Cardiovascular Health Study. After 13 years of follow-up, 539 (12%) patients had developed myocardial infarction. Eight SNVs were independent predictors of myocardial infarction, with HRs ranging from 1.13 to 1.62. The rs3798220 variant was one of the independent predictors and had the highest HR (1.62; 95% CI, 1.09 to 2.42). The authors calculated the false-positive reporting rate for each SNV and estimated the rate to be 1% for rs3798220.

Luke et al (2007) examined the association between SNVs and severe CAD as determined by coronary angiography.[11] They used patient samples from 3 case-control studies in sequence to determine the SNVs most strongly associated with severe CAD. Starting with more than 12,000 SNVs, the authors identified 302 SNVs associated with severe disease; after verification in the second study, 5 SNVs remained independent predictors; and after verification in the third study, only rs3798220 remained as the SNV most strongly associated with severe CAD. The adjusted odds for rs3798220 was 3.14 (95% CI, 1.51 to 6.56).

Section Summary: The *LPA* rs3798220 Variant as a Risk Factor for Coronary Artery Disease
The data on the clinical validity of testing for the *LPA* rs3798220 allele is sufficient to conclude that it is an independent risk factor for cardiovascular disease. It has not been determined whether detection of this genetic variant is superior to measurement of LPA levels as an independent risk factor for cardiovascular disease.

Prospective Studies Assessing Therapy Guided by the Presence of the *LPA* rs3798220 Variant
The Women's Health Study examined the comparative efficacy of aspirin and placebo for primary prevention of cardiovascular events in healthy women. Chasman et al (2009) published a post hoc analysis of 28,345 participants in the Women's Health Study who were genotyped for the presence of the *LPA* rs3798220 minor allele.[12] The allele was present in 3.7% of the population, 3.6% of which were heterozygotes and 0.06% who were homozygotes. As expected, LPA levels in carriers of the allele were markedly elevated compared with noncarriers, and carriers had a 2-fold increased risk for subsequent cardiovascular events compared with noncarriers.

The authors reported on an interaction between the presence of the *LPA* rs378220 allele and response to aspirin therapy. In carriers, a significant risk reduction was associated with aspirin treatment, with cardiovascular events occurring in 4.8% of patients in the placebo group compared with 2.1% in the aspirin group (HR=0.44; 95% CI, 0.20 to 0.94; p=0.03). For noncarriers of the allele, there was no significant reduction in cardiovascular events associated with aspirin treatment, with cardiovascular events occurring in 2.3% of the placebo group compared with 2.1% of the aspirin group (HR=0.91; 95% CI, 0.77 to 1.08; p=0.30).

Shiffman et al (2009) reported on the relation between the *LPA* rs3798220 variant and aspirin use from the Atherosclerosis Risk in Communities (ARIC) study.[13] The ARIC study assessed a prospective cohort of risk factors for CAD in 15,792 subjects. The subanalysis of ARIC included 6752 subjects who had data available for *LPA* genotype and aspirin use, including 221 subjects with the *LPA* rs3798220 genotype. Among carriers of rs3798220, the risk of cardiovascular events was compared in aspirin users and nonusers. The HR for nonaspirin users (n=168) was elevated at

1.57 but was not statistically significant (95% CI, 0.92 to 2.69); HR for aspirin users was not elevated at 0.86 (95% CI, 0.38 to 1.95).

Section Summary: Therapy Guided by the Presence of the *LPA* rs3798220 Variant
The data are supportive, but not conclusive, of the hypothesis that carriers of the rs3798220 allele may derive greater benefit from aspirin therapy than noncarriers. It is unclear how this information would be used in clinical care. For patients who are currently recommended to receive aspirin, a negative genetic test is probably insufficient to warrant withholding aspirin. Similarly, for patients who are not currently recommended to receive aspirin, a positive genetic test is probably insufficient to warrant starting aspirin. Therefore, it remains to be determined whether results of rs3798220 testing lead to changes in management and whether these management changes improve outcomes.

Summary of Evidence
For individuals who have a high risk of thrombosis who receive genetic testing for *LPA* rs3798220 variant, the evidence includes observational studies. Relevant outcomes are test validity, medication use, and morbid events. The *LPA* minor allele, rs3798220, is associated with higher levels of LPA and a higher risk for cardiovascular events. This allele is infrequent in the population and is associated with a modest increase in cardiovascular risk in the general population. Testing for this allele is commercially available, but performance characteristics are uncertain, and standardization of testing has not been demonstrated. Several observational studies have reported that this variant is an independent risk factor for cardiovascular disease, but some studies have not reported a significant association. Evidence from a post hoc analysis of the Women's Health Study reported that carriers of the allele might derive greater benefit from aspirin therapy compared with noncarriers. It is unclear whether this information, which derives from genetic testing, leads to changes in management; in particular, it cannot be determined from available evidence whether deviating from current guidelines on aspirin therapy based on *LPA* genetic testing improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements
A number of guidelines contain recommendations for testing of lipoprotein(a) serum levels, but none were identified with recommendations for genetic testing.[14,]

American College of Cardiology/American Heart Association
The American College of Cardiology and American Heart Association (2013) issued joint guidelines on the assessment of cardiovascular risk.[15,] The guidelines were based on a systematic review conducted by an expert panel appointed by the National Heart, Lung, and Blood Institute.[16,] The panel noted that lipoprotein(a) was considered a risk predictor, but its contribution to risk assessment "awaits further consideration at a later time."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in August 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

References

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	81479	Unlisted molecular pathology procedure
HCPCS	None	
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/30/2015	BCBSA Medical Policy adoption	Medical Policy Committee
04/01/2017	Policy revision without position change	Medical Policy Committee
12/01/2017	Policy revision without position change	Medical Policy Committee
12/01/2018	Policy revision without position change	Medical Policy Committee
12/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.