Genetic Testing for Lipoprotein(a) Variant(s) as a Decision Aid for Aspirin Treatment

Policy #  00300
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of genetic testing for the LPA rs3798220 allele (LPA-Aspirin Genotype) in patients who are being considered for treatment with aspirin (ASA) to reduce risk of cardiovascular events to be investigational.*

Background/Overview
Lipoprotein(a) (LPA) is a lipid-rich particle similar to low-density lipoprotein (LDL) and has been determined to be an independent risk factor for coronary artery disease (CAD). 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 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.

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

LPA levels are relatively stable in individuals over time but vary up to 1000-fold between individuals, presumably on a genetic basis. A single nucleotide polymorphism (SNP) in the LPA gene, LPA rs3798220, has been associated with both elevated LPA levels and an increased risk of CVD. This polymorphism 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 CVD.

Aspirin is a well-established treatment for patients with known CAD. It also is prescribed as primary prevention for some patients who are at increased risk of CAD. Current recommendations for primary prevention consider the future risk of cardiovascular events weighed against the bleeding risk of aspirin. U.S. Preventive Services Task Force (USPSTF) guidelines from 2009 recommend aspirin for men between the ages of 45-79 years when the benefit in reducing myocardial infarction (MI) exceeds the risk of bleeding, particularly gastrointestinal hemorrhage; and for women between the ages of 55-79 years when the benefit in reducing stroke exceeds the risk of gastrointestinal bleeding. Given guidelines such as these that recommend individualizing the risk/benefit ratio of aspirin therapy, additional tools that would 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.
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LPA-Aspirin Genotype 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 anti-thrombotic properties of aspirin. It has been proposed that the additional information obtained from the LPA-Aspirin Check test may aid physicians in better estimating the benefit/risk of aspirin therapy and therefore may aid in deciding whether to prescribe aspirin for individual patients.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
The LPA-Aspirin Genotype test has not been cleared or approved by the U.S. FDA. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. Berkeley HeartLab/Quest Diagnostics is a CLIA-certified laboratory.

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

Rationale/Source
This policy was created in 2011 and updated periodically with literature review. The most recent review covers the period through April 30, 2015.

Genetic testing for LPA rs3798220 can be evaluated in a similar framework as other novel cardiac risk factors. There are several conditions that must be met in order for a cardiovascular risk factor to demonstrate clinical utility. A 2002 Technology Evaluation Center (TEC) Assessment summarized 3 steps necessary for clinical utility:

- Standardization of measurement of the risk factor.
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor contributes independently to risk assessment compared with established risk factors.
- Determination of how the novel risk factor will be used in the management of the patient, compared with standard methods of assessing risk, and whether any subsequent changes in patient management lead to improved patient outcomes.

Is measurement of the LPA rs3798220 allele standardized?
Testing for the LPA rs3798220 allele is commercially available through Berkeley HeartLab under the name, LPA-Aspirin Check. DNA is extracted from a buccal swab sample taken from the inner cheek. Genetic testing is performed by real-time polymerase chain reaction (PCR) in conjunction with several control samples. Real-time PCR is expected to be more accurate than traditional PCR, because it preserves the exquisite sensitivity of PCR, while reducing the probability of cross-contamination that can result in false-positive results. The main limitations to real-time PCR accuracy are human factors such as improper assay
development, incorrect data analysis, or unwarranted interpretation: to ensure reliability of results, “real-time PCR primer sets must be designed and validated by stringent criteria.”

No published studies were identified that evaluated the accuracy of real-time PCR testing for the specific rs3798220 allele. Test performance (analytic validity) data are unavailable at the manufacturer web site.

**Section Summary**
This limited information is sufficient to conclude that real-time PCR is likely to be an accurate method for identifying genetic polymorphisms such as the rs3798220 allele but is not sufficient to conclude that the measurement of LPA rs3798220 is standardized.

**Is LPA rs3798220 an independent risk factor for coronary artery disease?**
Several observational studies have evaluated whether LPA rs3798220 is an independent risk factor for CAD. Shiffman et al (2008) used data from the Cardiovascular Health Study, a prospective cohort study of risk factors for MI in 4522 individuals who were 65 years or older, to examine the association of rs3798220 with MI. These authors tested 74 SNPs that had been genotyped as part of the Cardiovascular Health Study. After 13 years of follow-up, 539 patients (12%) had developed MI. There were 8 SNPs that were independent predictors of MI, with hazard ratios (HRs) varying from 1.13-1.62. The rs3798220 variant was one of the independent predictors and had the highest HR (1.62 [95% confidence interval (CI), 1.09 to 2.42]). The authors calculated the false-positive reporting rate for each SNP and estimated this to be 1% for rs3798220.

Clarke et al (2009) used a case-control design to examine the association of rs3798220 with CAD in 3145 case patients and 3352 controls from 4 European countries. They initially examined 48,742 SNPs in 2100 genes that had some association with heart disease, including 40 SNPs from the LPA gene. The rs3798220 SNP was found in 2% of patients and had the strongest association with CAD, with a 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 case patients and 4594 controls. In these patients, the rs3798220 variant remained an independent risk factor for CAD, with an odds ratio (OR) that was somewhat lower than in the derivation population (OR, 1.68 [95% CI, 1.43 to 1.98]).

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

In a similar case-control design, Shiffman et al (2008) examined the association between the rs3798220 allele and MI in 3 case-control studies totaling 762 cases and 857 controls. Starting from a total of 1949 SNPs associated with MI, the authors identified 5 SNPs that were mostly strongly associated with MI. One
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of these was rs3798220, which had ORs 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).

Risk associated with genetic variants of LPA in diabetic patients may be different from that in the general population. A large prospective study performed in 2011 evaluated LPA variants in 2308 patients who had diabetes. There was no significant association between genetic variants and cardiovascular risk or mortality. Odds ratios for coronary heart disease, 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 the 2 groups (p=0.006).

A 2013 case-control study of 2136 cases and 1211 controls evaluated whether SNPs rs3798220 and rs10455872 were associated with an increased risk of coronary disease. Genotyping of these 2 SNPs and 7 other LPA variants believed to be associated with coronary disease was done by Taqman assay. After adjusting for conventional risk factors, the authors found increased odds of MI of 2.14 (95% CI, 1.37 to 3.33, p<0.001) and 1.45 (95% CI, 1.36 to 2.24, p <0.001) for rs3798220 and rs10455872, respectively. Two additional SNPs, rs3127599 and rs9346818, also were found to be associated with risk of MI, with ORs 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 lipoprotein(a) levels increased the risk of a first-time MI or CHD event. Genotyping of rs3798220, rs10455872 and LPA-KIV-2 repeats was performed by PCR. The authors found that 27% of the total variation in lipoprotein(a) levels was explained by the rs10455872 genotype, 21% of the variation was explained by the LPA-KIV-2 repeat genotype, and 5% of the variation was explained by the rs3798220 genotype. Hazard ratios for rs3798220 carriers were 1.3 (95% CI, 0.8 to 2.1) for MI 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 MI and 1.1 (95% CI: 0.9-1.3) for CHD compared with noncarriers, whereas homozygous rs10455872 patients had HRs of 1.2 (95% CI, 0.5 to 3.3) for MI and 1.1 (95% CI, 0.5 to 2.1) for CHD compared with noncarriers.

Wang et al (2014) conducted a case-control study and did not find an association between rs3798220 genotype and MI risk in a Chinese population. Cases (n=2365) were patients who had experienced a first MI, drawn from hospitals in 15 cities in China. (This was the Chinese cohort of the global INTERHEART study.) Age- and sex-matched controls (n=2678) were healthy adult visitors to the hospitals and had no history of cardiovascular disease. In logistic regression analysis adjusted for age, sex, and body mass index, OR for MI in rs3798220 carriers compared with noncarriers was 1.12 (95% CI, 0.57 to 2.22; p=0.73).

Similarly, Anderson et al (2013) did not find an association between rs3798220 genotype and prevalent CAD in 1235 patients in the Intermountain Heart Collaborative Study Registry who underwent coronary angiography. CAD was defined as stenosis of 70% or more of coronary artery diameter, and non-CAD as stenosis less than 10% plus no history of CAD, MI, or coronary artery revascularization. By these definitions, 801 patients (65%) had CAD and 434 (35%) did not. In logistic regression analysis adjusted for age, sex, body mass index (natural log), hyperlipidemia, hypertension, diabetes, smoking history, and family
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history of premature CAD, OR 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 prevalent CAD; OR in rs10455872 carriers versus noncarriers was 1.77 (95% CI, 1.22 to 2.57; p=0.003).

Section Summary
This information is sufficient to conclude that the genetic variant, LPA rs3798220, is an independent risk factor for cardiovascular disease. It has not been determined whether measurement of the genetic variant is superior to measurement of LPA levels as an independent risk factor for cardiovascular disease.

Will identification of the rs3798220 variant lead to changes in management, and will these changes in management lead to improved patient outcomes?

The Women’s Health Study (WHS) examined the efficacy of aspirin versus placebo for primary prevention of cardiovascular events in healthy women. In 2009, Chasman et al published a post hoc analysis of 28,345 participants in the WHS who were genotyped for the presence of the LPA rs3798220 minor allele. The allele was present in 3.7% of the population, 3.6% who 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 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 interaction of the LPA rs3798220 variant and aspirin use from the Atherosclerosis Risk in Communities (ARIC) study. The ARIC study was a prospective cohort study of risk factors for CAD in 15,792 individuals. The LPA genetic substudy of ARIC included 6752 individuals who had data available for LPA genotype and aspirin use, including 221 individuals with the LPA rs3798220 genotype. Among carriers of rs3798220, the risk of cardiovascular events was compared in aspirin users and non-users. The HR for non-aspirin users (n=168) was elevated at 1.57 but did not reach statistical significance (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
These data are supportive, but not conclusive, of the hypothesis that carriers of the rs3798220 allele may derive greater benefit from aspirin therapy compared with 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 leads to changes in management and whether these changes in management improve outcomes.
Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov on May 1, 2015, did not identify any ongoing or unpublished trials that would likely impact this policy.

Summary
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 genetic 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 WHS reported that carriers of the allele may derive greater benefit from aspirin treatment compared with noncarriers. It is unclear whether this information derived from genetic testing leads to changes in management. In particular, it cannot be determined from available evidence whether deviating from current guidelines on aspirin treatment based on LPA genetic testing improves outcomes. Therefore, measurement of the LPA rs3798220 variant as a decision aid for aspirin treatment is considered investigational.

References
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). C-Reactive Protein as a Cardiac Risk Marker (Special Report). TEC Assessments 2002; Volume17, Tab 23.
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06/02/2011 Medical Policy Committee review
06/15/2011 Medical Policy Implementation Committee approval. New policy.
06/14/2012 Medical Policy Committee review
06/20/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013 Coding updated
06/06/2013 Medical Policy Committee review
06/05/2014 Medical Policy Committee review
06/18/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015 Medical Policy Committee review
06/17/2015 Medical Policy Implementation Committee approval. Updated test name to LPA-Aspirin Genotype. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016 Medical Policy Committee review
06/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017 Medical Policy Committee review
06/21/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2018

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