KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

Policy # 00284
Original Effective Date: 02/16/2011
Current Effective Date: 10/12/2020

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 kinesin-like protein 6 (*KIF6*) genotyping for predicting cardiovascular risk and/or the effectiveness of statin therapy to be **investigational.***

Background/Overview

Kinesin-like protein 6 (*KIF6*) belongs to the kinesin superfamily of proteins involved in intracellular transport. The exact function of the *KIF6* gene product is as yet undetermined. It has been reported that the gene is not expressed in the vasculature, the primary site of atherosclerosis, but is expressed in low levels in the brain, connective tissue, colon, eye, pharynx, skin, and testes. In contrast, a study presented at a 2010 American Heart Association scientific session reported on data derived from tissue immunohistochemistry, locating KIF6 protein in macrophages surrounding neovessels and in foam cells in human atherosclerotic lesions. Nevertheless, there is no strong evidence that KIF6 protein plays a direct biologic role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction.

Analyses of prospective observational studies of cardiovascular health and the placebo arm of randomized controlled trials of statin interventions in at risk populations have suggested a significant association between the arginine-to-tryptophan substitution at position 719 (Trp719Arg) single nucleotide variant (rs20455) in *KIF6* and the development of clinical CAD. Approximately 60% of the population carries the putative *KIF6* high-risk 719Arg allele. Moreover, carriers of the 719Arg allele in the treatment arms of the statin trials appeared to be at no increased or decreased risk of CAD or recurrent myocardial infarction, depending on the intensity of the statin therapy. These

results have supported the development of a *KIF6* Trp719Arg genotyping test for use as a predictor of CAD risk and the likely effectiveness of statin therapy.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

In January 2011, Celera Corp. submitted a premarket approval application to FDA for its *KIF6* Genotyping Assay performed using Abbott's m2000™‡ instrument system. In April, FDA informed Celera that its application was not approvable "without major amendment." The data and publications submitted were deemed "…insufficient to demonstrate the safety and effectiveness of the device for its proposed intended use." FDA indicated that additional data on clinical utility might be required, which could include conducting a randomized controlled trial.

Now a wholly owned subsidiary of Quest Diagnostics, Celera holds a U.S. patent on methods of determining coronary heart disease risk through detection of the *KIF6* gene variant and reduction of such increased risk by atorvastatin and pravastatin therapy and offers the Cardio IQ™‡ *KIF6* Genotype.

Rationale/Source

Genetic testing to determine kinesin-like protein 6 (*KIF6*) Trp719Arg variant status is being evaluated as a test to predict the risk of future cardiovascular events and as a test to predict response to statin therapy, particularly in high-risk patients.

For individuals who are asymptomatic with risk of cardiovascular disease and undergoing treatment with statin therapy who receive testing for *KIF6* Trp719Arg variant status, the evidence includes secondary analyses of randomized controlled trials, case-control studies, and a quasi-experimental single-arm study. Relevant outcomes are overall survival, test accuracy and validity, change in disease status, morbid events, and medication use. Data supporting the association

between *KIF6* variant status and coronary artery disease outcomes are contradictory. The most recent evidence from large populations with different vascular disease risk levels has not supported a significant association between coronary artery disease risk and the presence of the variant. Further, studies of the association between response to statin therapy and *KIF6* variant status are mixed. However, a large meta-analysis has shown that carriers of the *KIF6* variant derive greater clinical benefit from low-density lipoprotein cholesterol reduction (a 13% reduction in the risk of coronary artery disease outcomes) compared with noncarriers. Currently, no prospective randomized controlled trials have evaluated the impact of testing for *KIF6* variants on changes in clinical management (eg, intensifying the statin treatment in carriers, use of alternative approaches for lipid management in noncarriers) or outcomes. One nonrandomized study has suggested that subjects with *KIF6* genotype results showed greater adherence to statin therapy, but, overall, it is uncertain whether testing for *KIF 6* variants will alter the clinical management decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

In 2019, the American College of Cardiology and American Heart Association issued a joint guideline on use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease, which made no reference to *KIF6* genotyping.

In 2013, the American College of Cardiology and the American Heart Association issued joint guidelines on the assessment of cardiovascular risk that did not address *KIF6* genotyping.

In 2010, the joint American College of Cardiology Foundation and American Heart Association practice guideline on the assessment of cardiovascular risk in asymptomatic adults made no reference to *KIF6* genotyping.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for *KIF6* genotyping in coronary heart disease risk or use of *KIF6* genotyping to guide the selection or use of statin therapy have been identified.

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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 April 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

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Policy History

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02/03/2011 Medical Policy Committee review

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02/16/2011	Medical Policy Implementation Committee approval. New policy.
02/02/2012	Medical Policy Committee review
02/15/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/07/2013	Medical Policy Committee review
02/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2021

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.