BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

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

Policy #: 466
Category: Laboratory

Latest Review Date: June 2020
Policy Grade: C

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after April 12, 2011:

Blue Advantage will treat **KIF6 Genotyping for predicting cardiovascular risk and/or the effectiveness of statin therapy** as a non-covered benefit and investigational.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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

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 the American Heart Association Scientific Sessions 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 biological role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction (MI).

Analyses of prospective observational studies of cardiovascular health, and of 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 polymorphism (rs20455) in KIF6 and the development of clinical coronary artery disease (CAD). Approximately 60 percent 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 risk, or at decreased risk of CAD or recurrent myocardial infarction (MI), 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 of the likely effectiveness of statin therapy.

KEY POINTS:

The most recent literature review was performed through March 20, 2019.

Summary of Evidence

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 (RCTs), case-control studies, and one 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 (CAD) outcomes are contradictory. The most recent evidence from large populations with different vascular disease risk levels has not supported a significant association between CAD risk and 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 CAD outcomes) compared with noncarriers. However, no prospective randomized clinical trials (RCTs) have evaluated the impact of testing for KIF6 variants on changes in clinical management (e.g., intensifying the statin treatment in carriers, use of alternate approaches for lipid management in non-carriers) or outcomes. One nonrandomized study suggested that subjects who received KIF6 genotype results had greater adherence to statin therapy, but overall it is uncertain if testing for KIF6 variants alters the clinical management decisions. The clinical utility of KIF6 testing has not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

No reference to KIF6 genotyping was found in the 2010 joint American College of Cardiology Foundation/American Heart Association Practice Guidelines on the Assessment of Cardiovascular Risk in Asymptomatic Adults.

In 2013, ACC/AHA issued joint guidelines on the assessment of cardiovascular risk that does not address KIF6 genotyping.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force (USPSTF) recommendations for KIF6 genotyping in CHD risk or use of KIF6 genotyping to guide the selection or use of statin therapy have been identified.

KEY WORDS:

Cardiovascular genotyping, Genetic testing, cardiovascular risk, Statin pharmacogenetics, KIF6 genotyping, Pharmacogenetic testing, statins, Celera

APPROVED BY GOVERNING BODIES:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (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. On April 7, 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. An online search in 2017 found no update.

Now a wholly owned subsidiary of Quest Diagnostics, Celera Corp, holds a U.S. patent on methods of determining coronary heart disease (CHD) 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."

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT codes:

81479	Unlisted molecular pathology procedure

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POLICY HISTORY:

Adopted for Blue Advantage, February 2011
Available for comment February 24th through April 11, 2011
Medical Policy Group, February 2012

Medical Policy Group, January 2013
Medical Policy Group, February 2013
Medical Policy Group, February 2014
Medical Policy Group, February 2015
Medical Policy Group, February 2016
Medical Policy Group, June 2017
Medical Policy Group, August 2017
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Medical Policy Group, June 2020
