This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

### Populations

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<th>Individuals:</th>
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<th>Comparators</th>
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<tr>
<td>- Who are asymptomatic with risk of cardiovascular disease</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<td>- KIF6 genotyping</td>
<td>- Standard management with clinical risk factors</td>
<td>- Overall survival</td>
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</table>

### Description

Genetic testing to determine KIF6 Trp719Arg variant status is being evaluated as a prognostic test to predict risk of future cardiovascular events and/or as a pharmacogenetic test to predict response to statin therapy, particularly in high-risk patients.

### Summary of Evidence

The evidence for use of KIF6 genotyping for individuals who are asymptomatic with risk of cardiovascular disease and/or undergoing treatment with statin therapy includes secondary analyses of randomized controlled trials (RCTs), case-control studies, and one quasi-experimental single-arm study. Relevant outcomes include overall survival, test accuracy and validity, change in disease status, morbid events, and medication use. Data supporting the association of the KIF6 rs20455 single-nucleotide polymorphism, corresponding to an arginine-to-tryptophan substitution at position 719 (Trp719Arg), with coronary artery disease (CAD) outcomes are contradictory. The most recent evidence from large populations at different levels of vascular risk does not
support a significant association with future CAD outcomes. Moreover, the biologic function of the KIF6 gene product is currently unknown. Thus, the clinical validity for the KIF6 genotyping test has not been shown. The most recent analyses of treatment trials indicate that the efficacy of statin therapy appears to be similar among carriers and noncarriers of the mutation. A large meta-analysis shows that carriers of the KIF6 variant derive greater clinical benefit from low-density lipoprotein cholesterol reduction compared with noncarriers by about 13%. One nonrandomized study suggested that subjects who received KIF6 genotype results had greater adherence to statin therapy, but methodologic limitations are present in this study, and the findings have not been evaluated in randomized trials. Further, it has not been determined whether knowledge of carrier status can be used to improve patient management decisions and improve outcomes in other ways. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Policy**

*KIF6* genotyping is considered *investigational* for predicting cardiovascular risk and/or the effectiveness of statin therapy.

**Policy Guidelines**

*Genetic Counseling*

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Background**

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 2010 American Heart Association Arteriosclerosis, Thrombosis and Vascular Biology Scientific Sessions reported data derived from tissue immunohistochemistry, locating KIF6 protein in macrophages surrounding neovessels and in foam cells in human atherosclerotic lesions. Nevertheless, there is as yet no strong evidence that KIF6 protein plays a direct biological role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction (MI).

Analysis of prospective observational studies of cardiovascular health and of the placebo arm of randomized controlled trials (RCTs) of statin intervention in at-risk populations has 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 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 risk, or at decreased risk, of CAD or recurrent MI, depending on the intensity of the statin therapy. These results 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.
Celera Corp., now a wholly owned subsidiary of Quest Diagnostics, holds a U.S. patent related to methods of determining heart attack risk through detection of the KIF6 gene variant and reduction of such increased risk by statin therapy, and offers the “Cardio IQ™ KIF6 Genotype.” Celera’s Berkeley HeartLab subsidiary has been offering KIF6 genotyping (KIF6-StatinCheck™ Genotype Test) since July 2008, and now offers it as part of a comprehensive cardiovascular risk screening program with other serum-based tests. San Francisco General Hospital’s Clinical Chemistry Laboratory, is the only non-Celera lab to obtain a license to develop a KIF6 laboratory-developed test; a small number of clinical labs/health care groups have negotiated with Celera to offer the test by sending it to Berkeley HeartLab (e.g., Aurora Health Care of Milwaukee, WI).

Regulatory Status

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 Act (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 submitted a premarket approval application to FDA for its KIF6 Genotyping Assay performed using Abbott’s m2000™ instrument system. On April 7, FDA sent a letter to Celera indicating 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 may be required, which could include conducting a randomized controlled trial. An online search in February 2016 found no update.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


30. National Government Services, Inc. Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 04/01/2016.