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

Policy # 00284
Original Effective Date: 02/16/2011
Current Effective Date: 09/19/2018

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
Genetic testing to determine the 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.

The KIF6 protein 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. Rather, it 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 Arteriosclerosis, Thrombosis and Vascular Biology 2010 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 Trp719Arg single nucleotide polymorphism (SNP; 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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
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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. 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 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.

Now a wholly owned subsidiary of Quest Diagnostics, Celera 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.

Centers for Medicare and Medicaid Services (CMS)  
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada, and Hawaii). Palmetto GBA’s decisions apply for all molecular diagnostic tests for Medicare. In 2015, Palmetto GBA completed a review on the KIF6 genotype test, and concluded, “To date, there is insufficient evidence to support the required clinical utility for the established Medicare benefit category. Therefore, the KIF6 genotype test is a statutorily excluded test.”

Rationale/Source
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.
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KIF6 GENOTYPING

Clinical Context and Test Purpose
The purpose of testing for KIF6 gene variants in patients receiving statins therapy for CAD is to inform a decision whether an individual who has a variant is at a higher risk of a future cardiovascular event, and therefore statin treatment should be initiated or the existing statin dose should be increased.

The questions addressed in this evidence review are: (1) Is there evidence that testing for variants in the KIF6 gene has clinical validity?; and (2) Does patient management change in a way that would improve outcomes as a result of testing?

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

Patients
The population of interest includes patients who require or are being treated with statins for primary or secondary prevention of cardiovascular disease.

Interventions
The test being considered is genetic testing for variants in the KIF6 gene to guide initiation or intensification of statin therapy.

Comparators
The following practice is currently being used: standard clinical care without genetic testing, in which decisions about medical therapy are based on standard lipid levels and risk factors for CAD (eg, smoking, weight, diet, diabetes, family history of CAD). The intensity of therapies is based on a continued monitoring of response to treatment (eg, achieving target low-density lipoprotein [LDL] reduction).

Outcomes
The primary outcomes of interest for this review are CAD events and mortality over a 10-year period. The potential harmful outcomes are those resulting from a false test result. False-positive test results can lead to the initiation of unnecessary treatment and adverse events from that treatment. False-negative test results could also lead to undertreatment.

Timing
Decisions about choosing statin therapy are primarily driven by risks of CAD over a 10-year horizon.

Setting
Patients being treated with statins for primary prophylaxis of CAD are typically treated by primary care providers; those requiring statin therapy for secondary prevention may be treated by specialists or primary care providers. Consultations generally occur in outpatient care.
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Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Multiple studies have reported on the association between the KIF6 Trp719Arg single nucleotide variant (SNV) and the risks of CAD and response to statin therapy, with varying results about the strength and direction of the association. These studies include early retrospective evaluations of prospective, observational studies (see Table 1, part 1); retrospective evaluations of the placebo arms of RCTs of statin therapy (see Table 1, part 2); large meta-analysis of 19 case-control studies (see Table 1, part 3); and a retrospective evaluation of more recently conducted RCTs (see Table 1, part 4).

Patient populations in these studies included relatively unselected prevention cohorts and those with a higher risk of a CAD event. In prospective, observational studies and the placebo arms of RCTs, the Trp719Arg variant was positively associated with some CAD-related outcomes. In some RCTs, 719Arg variant carriers had larger decreases in CHD risk in association with statin treatment than noncarriers.

However, a large meta-analysis of 19 case-control studies found no association between the Trp719Arg SNV and nonfatal CAD. A major limitation of this meta-analysis was the exclusion of fatal coronary disease events and inability to examine whether the effect on risk was modified by statin therapy. In addition to the findings of the meta-analysis, none of several, large genome-wide association studies evaluating CAD or myocardial infarction reported any SNVs at the KIF6 locus as significant. Retrospective analyses of data from major RCTs published from 2011 to 2012 were consistent with the meta-analytic results, and statins were equally effective at reducing cardiovascular event rates among carriers and noncarriers of the KIF6 variant.

In a retrospective analysis of 2 prospective trials, Arsenault et al (2012) investigated whether KIF6 variant carriers obtain more benefit from high-dose statin therapy. The benefit was similar across all groups, except for those with homozygous variants, in whom there was a statistically significant benefit with a higher statin dose. However, the genotype by treatment interaction was not significant.

The conflicting results on the KIF6 variant, CHD, and treatment outcomes might have been explained in the meta-analysis by Ference et al (2011). Reviewers selected 37 case-control studies, prospective cohort studies, or randomized trial treatment allocation arms (each considered as a separate cohort), which together enrolled 144,931 participants and reported 27,465 CHD events. The KIF6 genotype, particularly
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the Trp719Arg SNV carrier status, was not associated with increased risk of CHD event. However, for each millimole per liter increase in low-density lipoprotein cholesterol (LDL-C), KIF6 variant carriers experienced a 15% greater increase in the relative risk of CHD compared with noncarriers (ratio of relative risk, 1.15; 95% confidence interval [CI], 1.06 to 1.25, p=0.001). Similarly, the decrease in risk for each millimole per liter decrease in LDL was 13% higher for variant carriers. Also included in the meta-analysis were 8 randomized trials assessing statin therapy in 50,060 participants with 7307 CHD events. KIF6 variant carriers derived a greater clinical benefit for each millimole per liter reduction in LDL-C during treatment with a statin than did noncarriers (ratio of relative risk, 0.87; 95% CI, 0.77 to 0.99; p=0.038). Thus, the results suggested that the KIF6 Trp719Arg variant increases vulnerability to LDL-C. This result might explain why KIF6 variant carriers appear to derive greater clinical benefit from a statin even though the variant itself does not appear to affect the ability of the statin to lower LDL-C, nor does it appear to be independently associated with the risk of CHD on average. However, “the association between the KIF6 variant and the risk of CHD will vary according to the average LDL cholesterol level of the population(s) under study.” This association might also explain some of the conflicting reports of KIF6 genotype association with CHD.

Table 1. Results of Studies Investigating the Differential Effects of KIF6 Genotype on CV Outcomes and a Meta-Analysis of the Association Between KIF6 Genotype and CAD Outcomes

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Patients Evaluated</th>
<th>KIF6 Association Evaluated</th>
<th>Observational Study or Placebo Arm, KIF6 Variant Carriers vs Noncarriers (95% CI)</th>
<th>Statin Arm vs Placebo Arm (unless otherwise stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part 1. KIF6 variant association with CAD outcomes in retrospective evaluations of prospective, observational studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morrison et al (2007) Retrospective evaluation of ARIC study cohort</td>
<td>U.S. individuals ages 45-64 y</td>
<td>MI, CHD death, or coronary revascularization</td>
<td>HR=1.09 (1.00 to 1.19)</td>
<td>NA</td>
</tr>
<tr>
<td>Shiffman et al (2008) Retrospective evaluation of CHS</td>
<td>Adults ages ≥65 y</td>
<td>Incident MI</td>
<td>HR=1.29 (90% CI, 1.1 to 1.52)* (95% CI, 1.06 to 1.6)*</td>
<td>NA</td>
</tr>
<tr>
<td>Shiffman et al (2008) Retrospective evaluation of WHS</td>
<td>Healthy white American women</td>
<td>Incident CHD event (MI, coronary revascularization, or CV-related death) or incident ischemic stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Part 2. KIF6 variant association with CAD outcomes in retrospective evaluations of RCTs of statin therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lakoubova et al (2008) Retrospective evaluation of CARE study</td>
<td>White MI survivors with total cholesterol &lt;240 mg/dL</td>
<td>Recurrent fatal or nonfatal MI</td>
<td>HR=1.50 (1.05 to 2.15)</td>
<td>KIF6 variant carriers: HR=0.63 (0.46 to 0.87)</td>
</tr>
<tr>
<td>Shiffman et al (2010) Retrospective evaluation of CARE study</td>
<td>MI survivors with total cholesterol &lt;240 mg/dL</td>
<td>Recurrent fatal or nonfatal MI</td>
<td>Adjusted for self-reported ethnicity among: KIF6 variant carriers: HR=0.63 (0.49 to 0.83)</td>
<td>Noncarriers: HR=0.80 (0.52 to 1.24)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Patients Evaluated</th>
<th>KIF6 Association Evaluated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iakoubova et al (2008) Nested case-control study from WOSCOPS trial</td>
<td>Men with hypercholesterolemia but no history of MI</td>
<td>Nonfatal MI, revascularization procedures, or death from CHD</td>
<td>OR=1.55 (1.14 to 2.09)</td>
</tr>
<tr>
<td>Iakoubova et al (2008) Retrospective evaluation of PROVE IT-TIMI 22</td>
<td>Patients hospitalized for MI or high-risk unstable angina</td>
<td>Composite: all-cause mortality, MI, unstable angina, or stroke</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Iakoubova et al (2010) Retrospective evaluation of PROSPER study</td>
<td>Older patients with: • preexisting vascular disease • increased risk for vascular disease</td>
<td>Composite: death from CHD, nonfatal MI, or fatal/nonfatal stroke</td>
<td>HR=1.28 (0.98 to 1.69)</td>
</tr>
</tbody>
</table>

Part 3. Meta-analysis of KIF6 variant association with CAD outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>CAD cases with and without diagnosis of nonfatal MI</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assimes et al (2010) Meta-analysis of 19 case-control studies</td>
<td>17,000 cases, 39,369 controls</td>
<td>OR=0.98 (0.95 to 1.02)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Part 4. Recent publications: KIF6 variant association with CAD outcomes in retrospective evaluations of RCTs of statin therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>Composite: CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or arterial revascularization</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffmann et al (2011) Retrospective evaluation of 4D prospective study (atorvastatin vs placebo)</td>
<td>Patients with T2D and &lt;2 y prior hemodialysis treatment</td>
<td>Composite: death from cardiac causes, MI, or stroke</td>
<td>HR=0.83 (0.66 to 1.05)</td>
</tr>
</tbody>
</table>

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<th>Study; Trial</th>
<th>Patients Evaluated</th>
<th>KIF6 Association Evaluated</th>
<th>Results</th>
</tr>
</thead>
</table>
| Akao et al (2012)  
Retrospective study of participants in PROSPER trial, randomized to pravastatin 40 mg/d or placebo | Individuals with history of, or risk factors for, vascular disease | MI or stroke | • Homozygote  
HR=0.47 (p=0.03)  
• For women on pravastin only: not significant after correction for multiple comparisons | NA |

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ARIC: Atherosclerosis Risk in Communities; CAD: coronary artery disease; CARE: Cholesterol and Recurrent Events trial; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CI: confidence interval; CV: cardiovascular; CVD: cardiovascular disease; HPS: Heart Protection Study; HR: hazard ratio; IDEAL: Incremental Decrease in End Points Through Aggressive Lipid-Lowering; JUPITER: Justification for Use of Statins in Primary Prevention, An Intervention Trial Evaluating Rosuvastatin; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; NA: not applicable; OR: odds ratio; PROSPER: PROspective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI 22: Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction 22 trial; RCT: randomized controlled trial; TNT: Treating to New Targets; T2D: type 2 diabetes; WHS: Women's Health Study; WOSCOPS: West of Scotland Coronary Prevention Study.

* Published.  
* Calculated from published data.

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**Section Summary: Clinically Valid**

There is uncertainty about the clinical validity of genetic testing for KIF6 Trp719Arg SNV due to conflicting results on the association between KIF6 variant carrier status and the risks of CAD and to conflicting results of the association between KIF6 variant carrier status and response to statin therapy.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The potential clinical utility of genetic testing for KIF6 includes confirming a diagnosis and evaluating whether there is a modifiable treatment option that would lower the risk of CAD for that individual.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Charland et al (2014) reported on the results of a prospective, nonrandomized, open-label, single-center trial designed to compare statin adherence at 6 months in those who learned about their KIF6 carrier status with those who did not. Patients older than 18 years of age who were new to statin therapy (with no...
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pharmacy electronic claims for statins in prior 6 months before the index date) were enrolled, and KIF6 genotyping was performed. KIF6 carrier status results were mailed to all individuals, including information on the association between KIF6 carriers and higher coronary heart disease risk reduction with statins. Patients not contacted for study participation were matched 1:1 with the final KIF6-tested group based on age, sex, index statin prescription fill channel (mail or retail pharmacy), and a number of unique chronic medications within 180 days of the statin index date to serve as controls. A secondary control cohort was created from patients who were contacted about the trial and made aware that their statin adherence might be routinely monitored but who declined study participation with KIF6 testing. The primary outcomes were statin prescription adherence and persistence, assessed using prescription claims records. Adherence was calculated as the proportion of days covered; subjects were adherent if they had 80% or more of the days covered. The proportion of patients categorized as adherent to statin therapy was 18.4% higher for the KIF6-tested group (63.4%; 95% CI, 59.6% to 67.1%) than for the matched controls (45.0%; 95% CI, 41.1% to 48.8%; p<0.001) and 12.7% higher than for the secondary control group (50.7%; 95% CI, 47.7% to 52.6%; p<0.001). While this trial reported an association between receipt of KIF6-genotype testing results and higher statin adherence, the nonrandomized trial design and the baseline differences between groups limit the validity of the results. The potential for bias in the self-selection of healthier patients for KIF6 genotyping and the inability to isolate the incremental effects of receiving the KIF6 genotype results over other aspects of trial participation restrict the conclusions that can be drawn about the effect of KIF6 genotyping on adherence.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The conflicting evidence on clinical validity does not permit conclusions on clinical utility.

**Section Summary: Clinically Useful**
The clinical utility of genetic testing for the KIF6 variant has not been established. It is unclear whether genetic testing for the KIF6 variant alters the clinical management decisions. One nonrandomized trial suggested that subjects who received KIF6 genotype results exhibited greater adherence to statin therapy, but the nonrandomized trial design and the baseline group differences limit the validity of the results. The potential for selection bias of healthier patients who volunteered for KIF6 genotyping and the inability to isolate the incremental effects of receiving the KIF6 genotype results over other aspects of trial participation restrict the conclusions that can be drawn about the effect of KIF6 genotyping on adherence. More importantly, no study has demonstrated whether KIF6 testing leads to changes in clinical management that reduce the risk of CAD.

**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
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analyses of RCTs, 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 RCTs 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 KIF6 variants will alter the clinical management decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

Policy History
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02/03/2011 Medical Policy Committee review
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
04/02/2015 Medical Policy Committee review
04/20/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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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.
Next Scheduled Review Date: 09/2019

Coding
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<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81479</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
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</table>

*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. 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:

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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.

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