Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/15/2017

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.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing for hereditary pancreatitis (HP) for patients aged 18 years and younger with unexplained acute recurrent (>1 episode) or chronic pancreatitis (CP) with documented elevated amylase or lipase levels to be eligible for coverage.

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 genetic testing for hereditary pancreatitis (HP) in all other situations to be investigational.*

Background/Overview

PANCREATITIS
Acute and CP are caused by trypsin activation within the pancreas, resulting in autodigestion, inflammation, elevation of pancreatic enzymes in serum, and abdominal pain. CP is defined as a state of ongoing inflammation associated with chronic or recurrent symptoms and progression to exocrine and endocrine pancreatic insufficiency.

Alcohol is the major etiologic factor in 80% of CP, which has a peak incidence in the fourth and fifth decades of life. Gall stones, hypercalcemia, inflammatory bowel disease, autoimmune pancreatitis, and peptic ulcer disease can also cause CP. About 20% of CP is idiopathic.

A small percentage of CP is categorized as HP, which usually begins with recurrent episodes of acute pancreatitis in childhood and evolves into CP by age 20 years. Multiple family members may be affected over several generations, and pedigree analysis often reveals an autosomal dominant pattern of inheritance. Clinical presentation and family history alone are sometimes insufficient to distinguish between idiopathic CP and HP, especially early in the course of the disease. Individuals with HP have an estimated 40% to 55% lifetime risk of developing pancreatic cancer.
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Genetic Determinants

*PRSS1 Variants*
Whitcomb et al discovered that disease-associated variants of protease, serine, 1 (trypsin 1) (*PRSS1*) on chromosome 7q35 cause HP. *PRSS1* encodes cationic trypsinogen. Gain of function variants of the *PRSS1* gene cause HP by prematurely and excessively converting trypsinogen to trypsin, which results in pancreatic autodigestion. Between 60% and 80% of people who have a disease-associated *PRSS1* variant will experience pancreatitis in their lifetimes; 30% to 40% will develop CP. Most, but not all, people with a disease-associated variant of *PRSS1* will have inherited it from one of their parents. The proportion of HP caused by a de novo variant of *PRSS1* is unknown. In families with 2 or more affected individuals in 2 or more generations, genetic testing have shown that most have a demonstrable disease-associated *PRSS1* variant. In 60% to 100%, the variant is detected by sequencing technology (Sanger or next-generation), and duplications of exons or the whole *PRSS1* gene are seen in about 6%. Two *PRSS1* point variants (p.Arg122His, p.Asn29Ile) are most common, accounting for 90% of disease-associated variants in affected individuals. Over 40 other *PRSS1* sequence variants have been found, but their clinical significance is uncertain. Pathogenic *PRSS1* variants are present in 10% or less of individuals with CP.

Targeted analysis of exons 2 and 3, where the common disease-associated variants are found, or *PRSS1* sequencing, are first-line tests, followed by duplication analysis. The general indications for *PRSS1* testing and emphasis on pre- and posttest genetic counseling have remained central features of reviews and guidelines. However, several other genes have emerged as significant contributors to both HP and CP. They include the cystic fibrosis (CF) transmembrane conductance regulator (*CFTR*) gene, serine peptidase inhibitor, Kazal type 1 (*SPINK1*) gene, chymotrypsin C (*CTRC*) gene, and claudin-2 (*CLDN-2*) gene.

*CFTR Variants*
Autosomal recessive variants of *CFTR* cause CF, a chronic disease with onset in childhood that causes severe sinopulmonary disease and numerous gastrointestinal abnormalities. The signs and symptoms of CF can vary widely. On rare occasions, an affected individual may have mild pulmonary disease, pancreatic exocrine sufficiency, and may present with acute, recurrent acute, or CP. Individuals with heterozygous variants of the *CFTR* gene (CF carriers) have a 3- to 4-fold increased risk for CP. Individuals with 2 *CFTR* pathogenic variants (homozygotes or compound heterozygotes) will benefit from CF-specific evaluations, therapies, and genetic counseling.

*SPINK Variants*
The *SPINK* gene encodes a protein that binds to trypsin and thereby inhibits its activity. Variants in *SPINK* are not associated with acute pancreatitis but are found, primarily as modifiers, in acute recurrent pancreatitis and seem to promote the development of CP, including for individuals with compound heterozygous variants of the *CFTR* gene. Autosomal recessive familial pancreatitis may be caused by homozygous or compound heterozygous *SPINK* variants.
CTRC Variants
CTRC is important for the degradation of trypsin and trypsinogen, and 2 variants (p.R254W, p.K247_R254del) are associated with increased risk for idiopathic CP (odds ratio [OR], 4.6), alcoholic pancreatitis (OR=4.2), and tropical pancreatitis (OR=13.6).

CLDN2 Variants
CLDN2 encodes a member of the claudin protein family, which acts as an integral membrane protein at tight junctions and has tissue-specific expression. Several single-nucleotide variants in CLDN2 have been associated with CP.

Genetic Testing for Variants
Testing for variants associated with HP is typically done by direct sequence analysis or next-generation sequencing (NGS). A number of laboratories offer testing for the relevant genes, either individually or as panels. For example, ARUP Laboratories (Salt Lake City, UT) offers a Pancreatitis Panel, which includes direct (Sanger) sequencing of CFTR, CTRC, PRSS1, and SPINK. Prevention Genetics (Marshfield, WI) offers a Chronic Pancreatitis Sequencing Panel, which includes NGS of 5 genes: CASR, CFTR, CTRC, PRSS1, and SPINK1. Ambry Genetics (Aliso Viejo, CA) offers a Pancreatitis Panel, which includes NGS of PRSS1, SPINK1, CTRC, and CFTR. Ambry’s PancNext™ panel consists of NGS of 13 genes: APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53.

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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for hereditary pancreatitis is available under the auspices of 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.

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.

Rationale/Source
Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). Following is a summary of the key literature.
GENETIC TESTING FOR HEREDITARY PANCREATITIS IN PATIENTS WITH CHRONIC PANCREATITIS OR RECURRENT ACUTE PANCREATITIS

Clinical Context and Test Purpose
The purpose of genetic testing of patients who have CP or acute recurrent pancreatitis (ARP) is to confirm a diagnosis and inform management decisions.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals with CP or ARP?

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

Patients
The relevant population of interest is patients with chronic pancreatitis or recurrent acute pancreatitis.

Interventions
Genetic testing for HP.

Comparators
Standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are test accuracy, symptoms, change in disease status, morbid events and hospitalizations.

Time
The time frame for outcome measurement varies from short-term development of symptoms to long-term survival outcomes. There are no clear established frameworks to use for outcome timeframes.

Setting
Patients are generally referred by a family practice physician or gastroenterologist to a medical geneticist. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
Testing for variants in the protease, serine, 1 (trypsin 1) (PRSS1), serine peptidase inhibitor (SPINK), and cystic fibrosis (CF) transmembrane conductance regulator (CFTR) genes is usually done by direct sequence analysis, which is the criterion standard for detecting a variant that is present and/or excluding a variant that is absent. Testing can also be done by next-generation sequencing, which has an accuracy that approaches that of direct sequencing. In patients who test negative by either of these methods,
duplication/deletion analysis may be performed to detect copy number variations. These genetic testing methods are considered to have high analytic validity.

**Clinical Validity**

The clinical validity of genetic testing for HP refers to the variant detection rate in patients who have known HP.

There is a lack of published evidence on the percentage of patients who are first identified as having clinically defined HP and then tested for genetic variants. Most studies that examined disease-associated variant detection rates use a population of patients with idiopathic CP and do not necessarily require that patients have a family history of CP. In other studies, cohorts of patients with HP were defined by the presence of genetic variants or family history, which therefore may include patients with genetic variants who do not have a family history of CP.

A summary of representative studies reporting rates of detecting disease-associated variants in patients with symptoms of pancreatitis is included in Table 1.

**Table 1. Summary of Studies Reporting the Clinical Validity of HP Gene Testing**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>Genes Tested</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applebaum-Shapiro (2001) (U.S.)</td>
<td>115 patients with HP defined clinically</td>
<td>PRSS1</td>
<td>52% (60/115)</td>
</tr>
<tr>
<td>Ceppa (2013) (U.S.)</td>
<td>87 patients with HP, defined by known pathogenic variant or family history</td>
<td>PRSS1, SPINK, CFTR</td>
<td>62% (54/87)</td>
</tr>
<tr>
<td>Patients with CP and/or ARP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vue (2016) (U.S.)</td>
<td>91 children with ARP (n=77) or CP (n=14)</td>
<td>SPINK, CFTR, PRSS1</td>
<td>33/69 (48%) tested had at least 1 disease-associated variant</td>
</tr>
<tr>
<td>Saito (2016) (Japan)</td>
<td>128 children with CP or ARP</td>
<td>PRSS1, SPINK, CPA1, SPINK, CFTR, CTRC</td>
<td>39.1% (50/128) had at least 1 abnormal variant</td>
</tr>
<tr>
<td>Koziel (2015) (Poland)</td>
<td>221 patients with AP and 345 healthy controls</td>
<td>SPINK, CFTR, CTRC</td>
<td></td>
</tr>
<tr>
<td>Schwarzenberg (2015) (international)</td>
<td>170 children, 76 with CP and 94 with ARP</td>
<td>PRSS1, SPINK, CFTR, CTRC</td>
<td>67% (51/76) with CP</td>
</tr>
<tr>
<td>Poddar (2015) (India)</td>
<td>68 children with pancreatitis (35.3% AP, 32.3% ARP, 32.3% CP); 25</td>
<td>PRSS1, SPINK, CFTR</td>
<td>44% (38/86)</td>
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Page 6 of 13

Masson (2013) (France)  
253 patients with idiopathic CP  
PRSS1, SPINK, CFTR, CTRC  
• 23.7% (60/253) “causal” variant  
• 24.5% (62/253) “contributory” variant

Wang (2013) (China)  
75 children with idiopathic CP  
PRSS1, SPINK, CFTR, CTRC, CLDN2  
• 66.7% (50/75) (with PRSS1 or SPINK variants)

Sultan (2012) (U.S.)  
29 children with ARP or CP  
PRSS1, SPINK, CFTR  
79% (23/29)

Gasiorowska (2011) (Poland)  
14 patients with idiopathic CP; 46 control patients without pancreatitis  
PRSS1, SPINK  
50% (7/14)

Joergensen (2010) (Denmark)  
122 patients with idiopathic pancreatitis  
PRSS1, SPINK, CFTR  
40% (49/122)

Rebours (2009) (France)  
200 patients with CP  
PRSS1  
68% (136/200)

Keiles (2006) (U.S.)  
389 patients with recurrent or CP referred for genetic testing  
PRSS1, SPINK, CFTR  
49% (185/381)

Truninger (2001) (Germany)  
104 patients with CP  
PRSS1  
8% (8/104)

healthy controls

AP: acute pancreatitis; ARP: acute recurrent pancreatitis; CP: chronic pancreatitis; HP: hereditary pancreatitis.

Only 2 studies were identified that included patients with known HP. Applebaum-Shapiro et al (2001) identified PRSS1 variants in 52% of patients with HP; other patients may have had different disease-associated variants not addressed in this study. Ceppa et al (2013) identified PRSS1, SPINK, or CFTR disease-associated variants in 62% of patients with HP. Again, other patients may have had different, rarer, variants.

The true clinical sensitivity and specificity for genetic testing in cases of HP are uncertain for a number of reasons. First, the populations in published studies have been defined differently, with most not consisting of patients with clinically defined HP. The populations are from different geographic regions, in which the prevalence of genetic variants may vary. Some of the studies have mixed adult and pediatric populations, while others have reported on either adults or children. Finally, genes tested for in these studies have differed, with many studies not including all of the known genes associated with HP.

At least 1 study (2015) found that the proportion of patients with acute pancreatitis attributable to genetic causes is higher among younger patients. In a group of 309 subjects with acute pancreatitis, patients ages 35 and younger (n=66) were more likely to have a genetic cause of pancreatitis identified (10%) than older patients (1.5%; p=0.003).
Section Summary: Clinical Validity for Testing for Variants Associated With HP

A number of studies have reported variant detection rates in various populations of patients with CP, but few studies have enrolled a population of patients with known HP. Studies that tested patients with known HP reported detection rates between 52% and 62%; studies may not have tested for all relevant genetic variants. For other studies that tested patients with CP or ARP, disease-associated variant detection rates varied widely across studies.

Clinical Utility

Direct Evidence
There are no direct outcome data on the clinical utility of testing for confirmation of HP (ie, no studies have reported outcomes data for patients tested and not tested for HP).

Chain of Evidence
A chain of evidence would evidence that genetic testing can identify individuals with HP who would not otherwise be identified, that treatments are available for these patients that would not otherwise be given to patients with CP or ARP, and that these treatments improve health outcomes.

There is some evidence that testing patients with HP, or patients with CP or ARP, can identify individuals with disease-associated variants (see Clinical Validity section). However, it is unclear whether patient management would differ for patients with CP depending on whether or not a variant associated with HP is found. Conservative therapy for CP includes a low-fat diet with multiple small meals, maintenance of good hydration, use of antioxidants, and avoidance of smoking and alcohol use. While all of these interventions may alter the natural history of the disease, there is no evidence that the impact differs for HP compared with other etiologies of CP.

Moreover, there is a lack of evidence that treatments (eg, for CP-related pain) would differ depending on whether or not patients had HP. Total pancreatectomy with islet cell transplantation (or total pancreatectomy with islet autotransplantation [TP-IAT]) has been investigated in CP or ARP, particularly as a treatment for intractable pain in patients with impaired quality of life in whom medical, endoscopic, or prior surgical treatment have failed. However, questions remain about the best timing of surgery, selection of candidates, evaluation of outcomes, and follow-up. Chinnakotla et al (2014) retrospectively compared outcomes after TP-IAT for patients with HP or familial pancreatitis compared with other causes of CP among 484 patients treated at a single institution from 1977 to 2012, 80 of whom had HP. Genetic testing was not available for all patients with suspected HP. Multiple causes of HP or familial pancreatitis were included: 38 with PRSS1 variants; 9 with SPINK1 variants; 14 with CFTR variants; and 19 with familial pancreatitis without a variant specified. Patients with HP were younger at the time of TP-IAT (mean age, 21.9 years vs 37.9 years in nonhereditary CP, p<0.001), but had a longer history of pancreatitis (mean, 10.1 years vs 6.4 years in nonhereditary CP, p=0.001). Pain scores significantly improved after TP-IAT (p<0.001), with no significant differences between HP and nonhereditary CP.
Several studies were identified that examined whether the severity and/or natural history of CP differs in patients with and without disease-associated variants. Some have reported that patients with HP have an earlier age of onset compared with patients with other etiologies of CP. Other studies have examined whether the severity and natural history differ for patients with HP, but findings have been inconsistent. Some studies have reported that disease progression is slower in patients with HP and that surgical intervention is required less often for patients with HP. However, 1 study also reported that the cumulative risk for exocrine failure was more than twice as high for patients with disease-associated variants compared with patients without disease-associated variants. In another small study (1998) that compared the clinical course of patients with HP to those with alcoholic CP, most clinical manifestations were similar, but patients with HP had a higher rate of pseudocysts.

Section Summary: Clinical Utility for Testing for Variants Associated With HP
The evidence on clinical utility does not support an improvement in health outcomes associated with genetic testing. For diagnostic testing, there is a lack of direct evidence that genetic testing leads to management changes. A chain of evidence does not indicate that treatment would differ for patients with HP compared to other patients with CP. In addition, the evidence to date is insufficient to determine whether patients with HP respond differently to treatments such as TP-IAT than other patients with CP. However, there is a suggestion that patients with HP have earlier onset of disease and inconsistent evidence on disease severity in patients with HP versus other types of CP.

TARGETED TESTING ASYMPTOMATIC RELATIVES OF PATIENTS WITH HP

Clinical Context and Test Purpose
The purpose of genetic testing of asymptomatic relatives of patients with HP is to determine the likelihood that the individual will develop CP.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in asymptomatic relatives of patients with HP?

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

Patients
The relevant population of interest is patients who are asymptomatic with a relative or relatives who have been diagnosed with HP.

Interventions
Genetic testing for HP.

Comparators
Standard clinical management without genetic testing.
Outcomes
The general outcomes of interest are test accuracy, symptoms, change in disease status, morbid events, and hospitalizations.

Time
There are no clinical guidelines with recommendations for monitoring asymptomatic individuals found to have variants associated with HP. The timeframe for outcome measurement varies from short-term development of symptoms to long-term survival outcomes. There are no clear established frameworks to use for outcome timeframes.

Setting
Asymptomatic patients might be referred by a family practice physician to a medical geneticist. Referral for genetic counseling is important for explanation of genetic disease, heritability, and genetic risk.

Analytic Validity
Same as previous section for patients with CP or ARP.

Clinical Validity
Same as previous section for patients with CP or ARP.

Clinical Utility
Predictive testing can be performed in asymptomatic relatives of patients with known HP to determine the likelihood of CP. For this population, no direct evidence was identified that compared outcomes in patients who did and did not undergo genetic testing. It is possible that at-risk relatives who are identified with disease-associated variants might alter lifestyle factors (eg, diet, smoking, alcohol use), and this might delay or prevent CP onset. However, evidence on this question is lacking, so that conclusions cannot be made on whether genetic testing of asymptomatic family members of patients with HP improves outcomes.

Section Summary: Targeted Testing Asymptomatic Relatives of Patients With HP
There is a lack of evidence that genetic testing of asymptomatic relatives of patients with HP leads to interventions that delay or prevent pancreatitis onset. It is possible that patients might alter lifestyle factors that increase risk of pancreatitis, but studies are lacking.

SUMMARY OF EVIDENCE
For individuals who have CP or ARP who receive testing for genes associated with HP, the evidence includes cohort studies on variant detection rates. Relevant outcomes are test accuracy, symptoms, change in disease status, morbid events, and hospitalizations. There are studies on the detection rate of HP-associated genes in various populations. Few studies have enrolled patients with known HP; those doing so have reported detection rates for disease-associated variants between 52% and 62%. For other studies that tested patients with CP or ARP, disease-associated variant detection rates varied widely across studies. There is a lack of direct evidence that testing for HP improves health outcomes, and insufficient chain of
Genetic Testing for Hereditary Pancreatitis

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Original Effective Date: 11/20/2013
Current Effective Date: 11/15/2017

Evidence that, in patients with CP or ARP, management would change after genetic testing in a manner likely to improve health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic with family members with HP who receive testing for a known familial variant associated with HP, the evidence includes a very limited number of studies. Relevant outcomes are test accuracy, symptoms, change in disease status, morbid events, and hospitalizations. No direct evidence was identified comparing outcomes in patients tested or not tested for a familial variant. It is possible that at-risk relatives who are identified with a familial variant may alter lifestyle factors (eg, diet, smoking, alcohol use), and this may delay or prevent CP onset. However, studies evaluating behavioral changes and impact on disease are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/15/2017


Policy History
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Current Effective Date: 11/15/2017

11/07/2013 Medical Policy Committee review
11/06/2014 Medical Policy Committee review
11/21/2014 Medical Policy Implementation Committee approval. No change to coverage.
Genetic Testing for Hereditary Pancreatitis

Policy #  00394
Original Effective Date:  11/20/2013
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08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. Added “Based on review of available data, the Company may consider genetic testing for hereditary pancreatitis for patients aged 18 years and younger with unexplained recurrent (>1 episode) acute or chronic pancreatitis with documented elevated amylase or lipase to be eligible for coverage.”
11/03/2016 Medical Policy Committee review
11/16/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review
11/15/2017 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date:  11/2018

Coding

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<th>Code Type</th>
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<td>CPT</td>
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<td>HCPCS</td>
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<td>ICD-10 Diagnosis</td>
<td>K86.0-K86.1</td>
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*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

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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.

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   A. In accordance with nationally accepted standards of medical practice;
   B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
   C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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