



Louisiana

Saturation Biopsy for Diagnosis, Staging, and Management of Prostate Cancer

Policy # 00639

Original Effective Date: 01/01/2019

Current Effective Date: 01/01/2019

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.

Note: Whole Gland Cryoablation of Prostate Cancer is addressed separately in medical policy 00022.

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 saturation biopsy in the diagnosis, staging, and management of prostate cancer to be **investigational**.*

Policy Guidelines

Saturation biopsy is generally considered obtaining more than 20 biopsy tissue cores from the prostate in a systematic manner; it is occasionally defined as obtaining more than 18 biopsy tissue cores.

Background/Overview

PROSTATE CANCER

Prostate cancer is common and is the second leading cause of cancer-related deaths in men in the United States.

Diagnosis

The diagnosis of prostate cancer is made by biopsy of the prostate gland. The approach to biopsy has changed over time, especially with the advent of prostate-specific antigen screening programs that identify cancer in prostates that are normal to palpation and to transrectal ultrasound. For patients with an elevated prostate-specific antigen level but with a normal biopsy, questions exist about subsequent evaluation, because repeat biopsy specimens may be positive for cancer in a substantial percentage of patients.

In the early 1990s, use of sextant biopsies involving 6 random, evenly distributed biopsies became the standard approach to diagnose prostate cancer. In the late 1990s, as studies showed high false-negative rates for this strategy (missed cancers), approaches were developed to increase the total number of biopsies and to change the location of the biopsies. While there is disagreement about the optimal strategy, most would agree that initial prostate biopsy strategies should include at least 10 to 14 cores. Additional concerns have been raised about drawing conclusions about the stage (grade) of prostate cancer based on limited biopsy specimens. Use of multiple biopsies has also been discussed as an approach to identify tumors that may be eligible for subtotal cryoablation therapy.

At present, many practitioners use a 12- to 14-core "extended" biopsy strategy for patients undergoing initial biopsy. This extended biopsy is done in an office setting and allows for more extensive sampling of the

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lateral peripheral zone; a sampling of the lateral horn might increase the cancer detection rate by approximately 25%.

Another approach to increasing the number of biopsy tissue cores is “saturation” biopsy. In general, saturation biopsy is considered as more than 20 cores taken from the prostate, with an improved sampling of the anterior zones of the gland, which may be undersampled in standard peripheral zone biopsy strategies and might lead to missed cancers. Saturation biopsy might be performed transrectally or transperineally; the transperineal approach is generally performed as a stereotactic template-guided procedure with general anesthesia.

Surveillance

In addition to the diagnosis of prostate cancer, some have suggested that saturation biopsy could be a part of active surveillance (a treatment approach that involves surveillance with prostate-specific antigen, digital rectal exam, and routine prostate biopsies in men whose cancers are small and expected to behave indolently). Saturation biopsy has the potential to identify tumor grade more accurately than standard biopsy.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Saturation biopsy is a surgical procedure and, as such, is not subject to regulation by the U.S. FDA.

Centers for Medicare and Medicaid Services (CMS)

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.

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.

INITIAL OR REPEAT SATURATION BIOPSY

Clinical Context and Proposed Clinical Utility

The proposed clinical utility of saturation biopsy for diagnosis of prostate cancer is to improve health outcomes by detecting more clinically significant cancers and intervening appropriately. To evaluate the

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impact of saturation biopsy on the net health outcome, studies are needed that compare rates of clinically significant prostate cancers detected using saturation biopsy vs other biopsy methods.

The question addressed in this evidence review is: In individuals with suspected prostate cancer, does initial or repeat saturation biopsy improve the diagnosis of patients with clinically significant prostate cancer and lead to improved patient management decisions and health outcomes?

The following PICOTS were used to select literature to inform this review. They apply to the first 2 indications—initial or repeat saturation biopsy.

Patients

The relevant population of interest is patients with suspected prostate cancer.

Interventions

The therapy being considered is initial or repeat saturation biopsy.

Comparators

The following practice is currently being used: standard biopsy.

Outcomes

Change in detection rate alone is not sufficient to determine the impact of saturation biopsy on health outcomes compared with other biopsy methods. With higher detection rates, there is the possibility of detecting clinically insignificant cancers, which could lead to unnecessary treatment. In addition, studies would ideally evaluate the impact of saturation biopsy on health outcomes such as disease progression or mortality.

Timing

Diagnostic accuracy is a short-term outcome. Survival outcomes would be measured over the long term (e.g., 5- or 10-year survival).

Setting

Patients would be tested in the primary or specialty care setting.

Initial Saturation Biopsy

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.

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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).

The literature on diagnostic accuracy consists of studies reporting prostate cancer detection rates or diagnostic yields as a primary outcome. These data were summarized in a systematic review by Jiang et al (2013) on the utility of an initial transrectal saturation biopsy compared with an extended biopsy strategy. Eight studies (total N=11,997 participants) met eligibility criteria (i.e., compared 2 biopsy strategies on initial biopsy). Two of the studies were randomized controlled trials, one used a paired design, and 5 were nonrandomized trials. Overall, prostate cancer was diagnosed in 2328 (42.4%) of 5486 men who underwent saturation biopsy compared with 2562 (39.3%) of 6511 men who had an extended biopsy. The detection rate was statistically significantly higher in the saturation biopsy group (risk difference, 0.004; 95% confidence interval [CI], 0.01 to 0.008; $p=0.002$). When only the higher quality studies were analyzed (i.e., the randomized controlled trials and prospective paired design), the detection rate remained statistically significantly higher for saturation biopsy (risk difference, 0.03; 95% CI, 0.01 to 0.05; $p=0.01$). Subgroup analysis found that the difference in detection rates between saturation and extended biopsy strategies was limited to the subgroup of men with prostate-specific antigen (PSA) levels less than 10 ng/mL. Within this group, prostate cancer was diagnosed in 998 (38%) of 2597 men who had saturation biopsies and in 1135 (34%) of 3322 men with extended biopsies (risk difference, 0.04; 95% CI, 0.01 to 0.07; $p=0.002$). Although the subgroup analyses included individual risk factors such as PSA level, they did not differentiate between detection of lower and higher risk prostate cancers. In addition, differences in health outcomes (e.g., progression-free survival, overall survival) were not reported.

A related meta-analysis was published by Xue et al (2017). Reviewers evaluated the literature comparing transrectal and transperineal biopsy approaches for the detection of prostate cancer. In an analysis stratified by the number of biopsy cores, there was no significant difference in the prostate cancer detection rate with the transrectal strategy or the transperineal biopsy strategy in studies using extended biopsy (odds ratio, 1.14; 95% CI, 0.89 to 1.45) or studies using saturation biopsy (odds ratio, 1.11; 95% CI, 0.92 to 1.34).

A retrospective nonrandomized study by Li et al (2014) reviewed data on 438 men who received an initial saturation biopsy and 3338 men who had an initial extended prostate biopsy. In an analysis stratified by PSA levels, there was a statistically significant higher rate of prostate cancer detection using a saturation biopsy strategy in men with a PSA level less than 10 ng/mL. Detection rates among men with a PSA level less than 4 ng/mL were 47.1% (40/85) with saturation biopsy and 32.8% (288/878) with extended biopsy ($p=0.008$). Rates among men with PSA levels between 4 ng/mL and 9.9 ng/mL were 50.9% (144/283) with saturation biopsy and 42.9% (867/2022) with extended biopsy ($p=0.011$). There was no statistically significant difference in detection rates between groups when PSA levels were greater than 10 ng/mL. Detection rates at PSA levels greater than 10 ng/mL were 60% (42/70) with saturation biopsy and 61% (267/438) with extended biopsy ($p=0.879$).

A related study by Li et al (2014) evaluated the potential benefit of saturation biopsy as the initial prostate biopsy strategy by examining the yield of repeat saturation biopsy in men with initial negative findings by

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either saturation or extended prostate biopsy. A total of 561 men were included in the study; the initial strategy was saturation biopsy in 81 men and extended biopsy in 480 men. In all cases, saturation biopsy was used for the first repeat biopsy. The overall prostate cancer detection rates were 19.8% in the group with initial saturation biopsy and 34.8% in the group with initial extended biopsy ($p=0.008$). Low-risk prostate cancer was defined using the Epstein criteria (i.e., Gleason score ≤ 6 , PSA density of ≤ 0.15 g/mL per gram, <3 positive cores, and $>50\%$ cancer involvement in a single core). The number of intermediate- and/or high-risk prostate cancers (i.e., not low-risk) identified at first repeat biopsy was 4 (4.9%) of 81 in the initial saturation biopsy group and 85 (17.3%) of 490 in the initial extended biopsy group ($p=0.048$). The statistically significantly lower prostate cancer detection rate among men who initially underwent saturation biopsy would suggest that initial saturation biopsy might be less likely to miss prostate cancer than extended biopsy, and, in this study, prostate cancer diagnosed by repeat saturation after negative initial saturation biopsy was more likely to be clinically insignificant. However, the study indirectly evaluated the initial biopsy, and the number of events in men who underwent an initial saturation biopsy was relatively small.

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.

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.

No direct evidence from studies comparing the impact of saturation biopsy with standard biopsy for patient management decisions or health outcomes in patients with suspected prostate cancer was identified.

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.

Because the evidence is insufficient to demonstrate the detection of clinically significant cancers with saturation biopsy, no inferences can be made about clinical utility.

Subsection Summary: Initial Saturation Biopsy

Studies on saturation biopsy as the initial prostate biopsy strategy were summarized in a 2013 systematic review of 8 studies (2 were randomized controlled trials). The prostate cancer detection rate was significantly higher in men with saturation biopsy than in men with standard biopsy. In a subgroup analysis, the systematic review found that the higher detection rate was limited to men with PSA levels less than 10 ng/mL. Health outcomes (e.g., survival rate) were not reported. Although several studies were published

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after the systematic review, none showed that initial saturation biopsy detected more clinically significant cancers and none reported progression or survival outcomes.

Repeat Saturation Biopsy

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).

Eichler et al (2006) published a systematic review of cancer detection rates and complications of various prostate biopsy strategies. They pooled data that compared various extended biopsy schemes for studies involving 20,698 patients. Reviewers concluded that prostate biopsy schemes consisting of 12 cores that add laterally directed cores to the standard sextant scheme seem to have the right balance between the cancer detection rate and adverse events and that taking more than 12 cores added no significant benefit.

Representative studies of saturation biopsy in repeat prostate biopsies follow. These studies focused on cancer detection rates and did not report health outcomes (e.g., overall survival, progression-free survival).

Mabjeesh et al (2012) reported on a high-risk group of men with at least 2 previous negative transrectal biopsies who then underwent transperineal template-guided saturation biopsy. Prostate cancer was detected in 24 (26%) of the 92 patients, predominantly in the anterior zones. A median of 30 cores was taken in the saturation biopsies. Gleason scores of 7 or higher were detected in 11 (46%) of the diagnosed men. Most tumors (83.3%) were found in the anterior zones of the gland, with a significantly higher number of positive cores than in the posterior zones (mean, 4.9 vs 1.5, $p=0.015$).

Lee et al (2011) evaluated the role of transrectal saturation biopsy for cancer detection in men with high-grade prostatic intraepithelial neoplasia diagnosed by extended biopsy. From 1999 to 2009, 314 men had at least 1 or more repeat biopsies due to the presence of exclusive high-grade prostatic intraepithelial neoplasia (without any other pathologic finding) in a previous extended biopsy. They were divided into 2 groups according to the initial follow-up biopsy scheme; 178 men were followed using a second standard extended biopsy scheme, and 136 were followed using the saturation biopsy scheme. In the standard repeat biopsy group, 35 (19.7%) of 178 men had cancer on initial repeat biopsy. In the saturation biopsy group, 42 (30.9%) of 136 had cancer on initial repeat biopsy (overall, $p=0.04$). Multivariate analysis demonstrated that the biopsy scheme on repeat biopsy was an independent predictor of prostate cancer detection (odds ratio, 1.85; 95% CI, 1.03 to 3.29), exclusive of age, PSA level, days from initial biopsy, digital rectal exam status, and multifocal prostatic epithelial neoplasia. Pathologic findings on repeat

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biopsies demonstrated similar Gleason scores, regardless of biopsy technique: a Gleason score of 6 was present in 74.3% and 73.1% of specimens in the standard and saturation schemes, respectively. The presence of a Gleason score of 8 or higher was 8.6% and 9.5%, respectively.

Zaytoun et al (2011) reported on the results of a prospective, nonrandomized comparative study of extended biopsy vs office-based transrectal saturation biopsy in a repeat biopsy population. After an initially negative biopsy, 1056 men underwent a repeat 12- to 14-core biopsy (n=393) or a 20- to 24-core repeat biopsy (n=663) at the discretion of the attending urologist's practice pattern. Indications for the second biopsy included a previous suspicious pathologic finding and/or clinical indications such as an abnormal digital rectal exam, persistently increased PSA level, and PSA level increasing more than 0.75 ng/mL annually. Prostate cancer was detected in 29.8% (n=315) of repeat biopsies. The saturation biopsy group had a detection rate of 32.7% vs 24.9% in the extended biopsy group (p=0.008). Of the 315 positive biopsies, 119 (37.8%) revealed clinically insignificant cancer (defined as Gleason score <7, a total of ≤3 positive cores, and maximum of ≤50% of cancer in any positive core). There was a trend toward increased clinically insignificant cancer detection for saturation biopsy (40.1%) vs extended biopsy (32.6%; p=0.02).

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.

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.

No direct evidence from studies comparing the impact of saturation biopsy with standard biopsy for patient management decisions or health outcomes in patients with suspected prostate cancer was identified.

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.

Because the evidence is insufficient to demonstrate the detection of clinically significant cancers with saturation biopsy, no inferences can be made about clinical utility.

Subsection Summary: Repeat Saturation Biopsy

Several studies have compared saturation with standard prostate biopsies in the repeat biopsy setting and have found significantly higher detection rates with saturation biopsy. However, at least 1 study found that about one-third of the positive findings with saturation biopsy were clinically insignificant cancers. Moreover, studies of saturation biopsy as the repeat prostate biopsy strategy focused on cancer detection rates and did not report health outcomes (e.g., progression or survival).

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ACTIVE SURVEILLANCE

Clinical Context and Proposed Clinical Utility

The proposed clinical utility of saturation biopsy is to improve health outcomes by better identifying patients with prostate cancer who are appropriate candidates for active surveillance through more accurate determination of the Gleason score.

The question addressed in this evidence review is: In individuals with prostate cancer who are candidates for active surveillance, does saturation biopsy improve the identification of tumor grade and improve health outcomes compared with standard biopsy?

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

Patients

The relevant population of interest is patients with prostate cancer who are potential candidates for active surveillance.

Interventions

The test being considered is saturation biopsy.

Comparators

The following practice is currently being used: standard biopsy.

Outcomes

Gleason score is a criterion used to select men for active surveillance. More accurate selection of patients for active surveillance could lead to better health outcomes by reducing misclassification of patients as being sufficiently low risk that active surveillance is an appropriate approach to patient management.

Timing

Diagnostic accuracy is a short-term outcome. Survival outcomes would be measured over the long term (e.g., 5- or 10-year survival).

Setting

Patients would be tested in the primary or specialty care setting.

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).

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Several studies have evaluated the accuracy of saturation biopsy for identifying patients who might be suitable candidates for active surveillance. Linder et al (2013) reviewed data on 500 consecutive patients who underwent standard template prostate biopsy (12 cores) or saturation biopsy (at least 18 cores) before radical prostatectomy. They identified 218 patients who would have been candidates for active surveillance. Criteria were a Gleason score no greater than 6, clinical stage T1 or T2a, PSA level less than 10 ng/mL, and involvement of no more than 33% of cores. Among these 218 patients, 124 had undergone standard biopsy and 94 underwent saturation biopsy. In a multivariate analysis, biopsy method was not a significant predictor of upstaging on analysis of pathologic findings ($p=0.26$). In addition, the 5-year biochemical failure-free survival rates (defined as PSA level of at least 0.4 ng/mL) did not differ significantly between groups: rates were 97% for standard biopsy and 95% for saturation biopsy ($p=0.11$).

Quintana et al (2016) compared 12-core biopsy with saturation biopsy (18-33 cores; median, 20 cores) in 375 patients to determine the Gleason score accurately. The authors stated that patients with Gleason scores of 4 or higher were generally not considered candidates for active surveillance. Gleason score was confirmed by pathologic analysis of prostate specimens. For detecting a high Gleason grade (i.e., ≥ 4), there were no statistically significant differences in the sensitivity, specificity, negative predictive value, or positive predictive value of 12-core vs saturation biopsies. The areas under the receiver operating characteristic curve were 0.82 for saturation biopsy and 0.84 for 12-core biopsy (p value not reported).

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.

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.

No direct evidence from studies comparing the impact of saturation biopsy with standard biopsy for patient management decisions or health outcomes in patients with prostate cancer being considered for active surveillance was identified.

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.

Because the evidence is insufficient to demonstrate that saturation biopsy improves the identification of tumor grade, no inferences can be made about clinical utility.

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SUMMARY OF EVIDENCE

For individuals who have suspected prostate cancer who receive initial saturation biopsy, the evidence includes randomized controlled trials, observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and treatment-related morbidity. A 2013 systematic review found higher rates of cancer detection with saturation biopsy than with extended biopsy overall, but, in the subgroup of men with prostate-specific antigen levels less than 10 ng/mL, the degree of difference was small and possibly not clinically significant. Health outcomes (e.g., survival rate) were not reported. Although several studies were published after the systematic review, none showed that initial saturation biopsy improved the detection of clinically significant cancers and none reported progression or survival outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have suspected prostate cancer who receive repeat saturation biopsy, the evidence includes observational studies and a systematic review. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and treatment-related morbidity. Several studies have compared saturation with standard prostate biopsies in the repeat biopsy setting and have found significantly higher detection rates with saturation biopsy. However, at least 1 study found that about one-third of the positive findings with saturation biopsy were clinically insignificant cancers. Moreover, studies of saturation biopsy as the repeat prostate biopsy strategy focused on cancer detection rates and did not report health outcomes (e.g., progression or survival). Evidence is lacking as to whether saturation biopsy leads to improved health outcomes, including the possibility of detecting clinically insignificant cancers, which could lead to unnecessary treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have prostate cancer and are candidates for active surveillance who receive saturation biopsy, the evidence includes 2 nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and treatment-related morbidity. Both studies retrospectively compared standard biopsy with saturation biopsy for selecting patients for active surveillance; neither found that saturation biopsy improved the ability to select patients. In 1 study, biopsy method was not a significant predictor of upstaging and, in the other study, biopsy method was not significantly associated with selecting patients with a high Gleason score. The evidence is insufficient to determine the effects of the technology on health outcomes.

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10/04/2018 Medical Policy Committee review

10/17/2018 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 10/2019

Coding

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Louisiana

Saturation Biopsy for Diagnosis, Staging, and Management of Prostate Cancer

Policy # 00639

Original Effective Date: 01/01/2019

Current Effective Date: 01/01/2019

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

Code Type	Code
CPT	55706
HCPCS	No codes
ICD-10 Diagnosis	C61, D07.5, D40.0

*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.

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