Navigated Transcranial Magnetic Stimulation

Policy # 00407
Original Effective Date: 03/19/2014
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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: Magnetoencephalography/Magnetic Source Imaging is addressed separately in medical policy 00082.

Note: Functional Magnetic Resonance Imaging of the Brain is addressed separately in medical policy 00447.

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 navigated transcranial magnetic stimulation (nTMS) for all purposes, including but not limited to the preoperative evaluation of patients being considered for brain surgery, when localization of eloquent areas of the brain (e.g., controlling verbal or motor function) is an important consideration in surgical planning to be **investigational.***

Background/Overview

MANAGEMENT OF BRAIN TUMORS

Surgical management of brain tumors involves resecting the brain tumor and preserving essential brain function. "Mapping" of brain functions, such as body movement and language, is most accurately achieved with direct cortical stimulation (DCS), an intraoperative procedure that lengthens operating times and requires a wide surgical opening. Even if not completely accurate compared with DCS, preoperative techniques that map brain functions may aid in planning the extent of resection and the surgical approach. Although DCS is still usually performed to confirm the brain locations associated with specific functions, preoperative mapping techniques may provide useful information that improves patient outcomes.

Noninvasive Mapping Techniques

The most commonly used tool for the noninvasive localization of brain functions is functional magnetic resonance imaging (fMRI). fMRI identifies regions of the brain where there are changes in localized cortical blood oxygenation, which correlate with neuronal activity associated with a specific motor or speech task being performed as the image is obtained. The accuracy and precision of fMRI depend on the patient's ability to perform the isolated motor task, such as moving the single assigned muscle without moving others. This may be difficult in patients in whom brain tumors have caused partial or complete paresis. The reliability of fMRI in mapping language areas has been questioned. Guissani et al (2010) reviewed several studies comparing fMRI with DCS of language areas and found large variability in the sensitivity and specificity rates of fMRI. Reviewers also pointed out a major conceptual point in how fMRI and DCS "map" language areas: fMRI identifies regional oxygenation changes, which show that a particular region of the brain is involved in the capacity of interest, whereas DCS locates specific areas in which the activity of interest is disrupted. Regions of the brain involved in a certain activity may not necessarily be required for that activity and could theoretically be safely resected.

Magnetoencephalography (MEG) is also used to map brain activity. In this procedure, electromagnetic recorders are attached to the scalp. Unlike electroencephalography, MEG records magnetic fields generated by electric currents in the brain, rather than the electric currents themselves. Magnetic fields tend to be less distorted by the skull and scalp than electric currents, yielding an improved spatial resolution. MEG is conducted in a magnetically shielded room to screen out environmental electric or magnetic noises that could interfere with the MEG recording. (See medical policy 00082 for additional information on MEG and magnetic resonance imaging (MRI).)

nTMS is a noninvasive imaging method for evaluating eloquent brain areas. Transcranial magnetic pulses are delivered to the patient as a navigation system calculates the strength, location, and direction of the stimulating magnetic field. The locations of these pulses are registered to a magnetic resonance image of the patient's brain. Surface electromyography electrodes are attached to various limb muscles of the patient. Moving the magnetic stimulation source to various parts of the brain causes electromyography electrodes to respond, indicating the part of the cortex involved in particular muscle movements. For evaluation of language areas, magnetic stimulation areas that disrupt specific speech tasks are thought to identify parts of the brain involved in speech function. Navigated TMS can be considered a noninvasive alternative to DCS, in which electrodes are directly applied to the surface of the cortex during craniotomy. Navigated TMS is being evaluated as an alternative to other noninvasive cortical mapping techniques (e.g., fMRI, MEG) for presurgical identification of cortical areas involved in motor and language functions. Navigated TMS, used for cortical language area mapping, is also being investigated in combination with diffusion tensor imaging tractography for subcortical white matter tract mapping.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2009, the eXimia Navigated Brain Stimulation System (Nexstim) was cleared for marketing by the U.S. FDA through the 510(k) process for noninvasive mapping of the primary motor cortex of the brain to its cortical gyrus for preprocedural planning.

Similarly, in May 2012, the Nexstim Navigated Brain Stimulation System 4 and Navigated Brain Stimulation System 4 with NexSpeech®‡ were cleared for marketing by the U.S. FDA through the 510(k) process for noninvasive mapping of the primary motor cortex and for localization of cortical areas that do not contain speech function for preprocedural planning.

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.

PREOPERATIVE LOCALIZATION OF ELOQUENT AREAS OF THE BRAIN

Clinical Context and Test Purpose
The purpose of nTMS in patients who have brain lesions is to aid in the localization of eloquent areas of the brain to reduce damage to verbal and motor functions during surgery.

The question addressed in this evidence review is: Does nTMS improve health outcomes in patients who have brain lesions and are about to undergo surgery that could harm eloquent areas of the brain?

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

Patients
The relevant population of interest is individuals who have brain lesions and are undergoing surgery that could harm eloquent areas of the brain.

Interventions
The intervention of interest is nTMS.

Comparators
Several tools are used for the noninvasive localization of brain functions. They include fMRI and MEG. Whether noninvasive presurgical tools are used, DCS is usually performed during surgery to confirm the brain locations associated with specific functions.

Outcomes
The outcomes of interest are surgical improvement in survival or in functional measures such as speaking and walking or in a reduction in morbidity.

Timing
Navigated TMS is performed during preoperative surgical planning.

Setting
Navigated TMS is done in a specialty setting (i.e., neurology).

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).

Most studies of nTMS are small case series evaluating patients with brain tumors, cavernous angiomas, arteriovenous malformations, or other brain lesions; case series are not ideal studies to ascertain diagnostic characteristics. A number of small nTMS studies have also evaluated healthy volunteers, but they do not add substantially to the evidence base. Studies comparing nTMS with DCS, MEG, and/or fMRI and/or using DCS as the reference standard are described next.

Distance Between nTMS and DCS Hotspots
Picht et al (2011) evaluated 17 patients with brain tumors using nTMS and DCS. Both techniques were used to elicit “hotspots,” the point at which either nTMS or DCS produced the largest electromyographic response in the target muscles. Target muscles were selected based on the needs of each patient concerning tumor location and clinical findings. Intraoperative DCS locations were chosen independently of nTMS, and the surgeon was unaware of the nTMS hotspots. For 37 muscles in 17 patients, nTMS and DCS data were both available. Mean distance between nTMS and DCS hotspots was 7.83 mm (standard error, 1.18) for the abductor pollicis brevis muscle (95% confidence interval, 5.31 to 10.36 mm) and 7.07 mm (standard error, 0.88) for the tibialis anterior muscle. When DCS was performed during surgery, there were large variations in the numbers of stimulation points, and the distance between nTMS and DCS was much smaller when a larger number of points were stimulated.

Forster et al (2011) performed a similar study in 11 patients. Functional MRI also was performed in this study. The distance between corresponding nTMS and DCS hotspots was 10.49 mm (standard deviation [SD], 5.67). The distance between the centroid of fMRI activation and DCS hotspots was 15.03 mm (SD=7.59). However, it was unclear whether hotspots elicited by 1 device could be elicited by the other and vice versa. In at least 2 excluded patients, hotspots were elicited by DCS but not by nTMS.

Tarapore et al (2012) evaluated the distance between nTMS and DCS hotspots. Among 24 patients who underwent nTMS, 18 of whom also underwent DCS, 8 motor sites in 5 patients corresponded. The median distance between nTMS and DCS hotspots was 2.13 mm (standard error of the mean [SEM], 0.29). In the craniotomy field where DCS mapping was performed, DCS elicited the same motor sites as nTMS. The study also evaluated MEG; the median distance between MEG motor sites and DCS sites was 12.1 mm (8.2).

Mangravati et al (2013) evaluated the distance between nTMS and DCS hotspots in 7 patients. It is unclear how many hotspots were compared or how many potential comparisons were unavailable due to a failure of either device to find a particular hotspot. It appears that the mean distance between hotspots was based on locations of hotspots for 3 different muscles. The overall mean difference between nTMS and DCS was 8.47 mm, which was less than the mean difference between the fMRI centroid of activation and DCS hotspots (12.9 mm).

Krieg et al (2012) compared nTMS with DCS in 14 patients. Interpreting this study is difficult because the navigation device employed appeared to differ from the FDA–approved device. Additionally, the comparison of nTMS to DCS used a different methodology. Both nTMS and DCS were used to map the whole volume of the motor cortex, and a mean difference between the borders of the mapped motor cortex was calculated. The mean distance between the 2 methods was 4.4 mm (SD=3.4).

Language Mapping

A study by Picht et al (2013) evaluated the accuracy of nTMS in identifying language areas. Twenty patients underwent evaluation of language areas over the whole left hemisphere, which was divided into 37 regions. DCS was performed only in areas accessible in the craniotomy site. Data for both methods were available in 160 regions for the 20 patients. Using DCS as the reference standard, there were 46 true-positive, 83 false-positive, 26 true-negative, and 5 false-negative findings. Considering the analysis as 160 independent data points for each brain region, nTMS had a sensitivity of 90%, specificity of 24%, positive predictive value (PPV) of 36%, and negative predictive value of 84%. An analysis of regions considered to be in the classic Broca area (involved in speech production) showed a sensitivity of 100%, specificity of 13%, PPV of 57%, and negative predictive factor of 100%. This study, which found a high rate of false-positives, raises concerns about the utility of nTMS for identifying language areas. Even if nTMS were used to rule out areas in which language areas are unlikely, the sensitivity of 90% might result in some language areas not appropriately identified.

Tarapore et al (2013) also evaluated the use of nTMS and MEG to identify language areas (N=12). A total of 183 regions were evaluated with both nTMS and DCS. In these 183 regions, using DCS as the reference standard, there were 9 true-positives, 4 false-positives, 169 true-negatives, and 1 false-negative, translating to a sensitivity of 90%, specificity of 98%, PPV of 69%, and negative predictive factor of 99%.

Section Summary: Clinically Valid

The studies assessing the distance between nTMS and DCS hotspots appear to show that stimulation sites eliciting responses from both techniques tended to be mapped within 10 mm of each other. This distance tends to be less than the distance between fMRI centers of activation and DCS hotspots. It is difficult to assess the clinical significance of these data for presurgical planning. The available studies of the diagnostic accuracy nTMS evaluating language areas have shown a sensitivity of 90% and variable specificity in 2 studies (range, 24%-98%). The PPVs were relatively low in both of the studies (range, 57%-69%). Even if nTMS were used to rule out areas in which language areas are unlikely, the sensitivity of 90% might result in some language areas not appropriately identified.

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 (RCTs).

The ideal study to determine whether nTMS improves health outcomes in patients being considered for surgical resection of brain tumors would be an RCT comparing nTMS with strategies that do not use nTMS. There are challenges in the design and interpretation of such studies. Given that results of diagnostic workups of brain tumor patients may determine which patients undergo surgery, the counseling given to patients, and the type of surgery performed, it would be difficult to compare outcomes for groups of patients with qualitatively different outcomes. For example, it is difficult to compare the health outcomes of a patient who ends up not having surgery, who conceivably has a shorter overall lifespan but a short period of very high quality of life, with a patient who undergoes surgery and has some moderate postoperative disability, but a much longer lifespan.

No RCTs were identified. However, controlled observational studies are available. Several studies have matched patients who underwent presurgical nTMS with similar historical controls who did not. Hendrix et al (2017) reported on 20 consecutive patients with malignant brain tumors and lesions in language-eloquent areas who underwent preoperative nTMS and matched them to patients treated in the pre-nTMS era. Patients were matched on tumor location, tumor and edema volume, preoperative language deficits, and histopathology. The primary efficacy outcome was not specified. Patients underwent clinical language assessments before and after surgery at postoperative day 1 and weeks 1, 6, and 12 postsurgery. Language performance status was characterized as no language deficit (grade 0), mild deficit (grade 1), medium deficit (grade 2); and severe deficit (grade 3). The complication rates, gross resection rates, and residual tumor volumes on fMRI did not differ significantly between groups. The group that had presurgical nTMS had shorter surgery durations than patients treated pre-nTMS (mean, 104 minutes and 135 minutes, respectively, p=0.039) and a shorter inpatient stay (mean, 9.9 days vs 15 days, p=0.001). Language deficits did not differ between groups preoperatively, or at postoperative day 1, week 1, or week 12. For example, at week 12, 15 patients in the nTMS group and 14 patients in the pre-TMS group had a grade 0 deficit (p=0.551). There was a statistically significant difference at week 6 (p=0.048); the p value was not adjusted for multiple comparisons (i.e., assessment at multiple time points). Groups might have differed in other ways that affected outcomes and procedures might have changed over time in ways that affected surgical duration, complication rates, and inpatient stays.

Krieg et al (2014) enrolled 100 consecutive patients who underwent nTMS preoperative mapping and identified 100 historical controls who were matched by tumor location, preoperative paresis, and histology. Most patients had glioblastoma (37%), brain metastasis (24%), or astrocytoma (29%). Data analysis was performed blinded to group assignment. The primary efficacy outcome was not specified. Median follow-up was 7.1 months (range, 0.2-27.2 months) in the nTMS group and 6.2 months (range, 0.1-79.4 months) in controls. Incidence of residual tumor by postoperative fMRI was lower in the nTMS group (22%) compared with controls (42%; odds ratio, 0.38; 95% confidence interval, 0.21 to 0.71). The incidence of new surgery-related transient or permanent paresis did not differ between groups. However, "when also including neurological improvement [undefined] in the analysis," more patients in the nTMS group improved (12% nTMS vs 1% controls), and similar proportions of patients worsened (13% nTMS vs 18% controls) or remained unchanged (75% nTMS vs 81% controls; p=0.006). Limitations of this study included the use of historical controls, uncertain outcome assessments (e.g., "neurological improvement" was not defined), and uncertain validity of statistical analyses because the primary outcome was not specified and there was no correction for multiple testing.

A second study by Krieg et al (2015) had some overlap in enrolled patients. It prospectively enrolled 70 patients who underwent nTMS and matched them with a historical control group of 70 patients who did not have preoperative nTMS. All patients had motor eloquently located supratentorial high-grade gliomas and all underwent craniotomy by the same surgeons. As in the 2014 Krieg study, patients were matched by tumor location, preoperative paresis, and histology; the primary outcome was not specified. Outcome assessment was blinded. Craniotomy size was 25.3 cm^2 (SD=9.7) in the nTMS group and 30.8 cm^2 (SD=13.2) in the non-nTMS group; the size difference was statistically significant (p=0.006). There were no statistically significant differences between groups in rates of surgery-related paresis, rates of surgery-related complications on MRI, or degrees of motor impairment during follow-up. Median overall survival was 15.7 months (SD=10.9) in the nTMS group and 11.9 months (SD=10.3) in the non-nTMS group, which did not differ significantly between groups (p=0.131). Mean survival at 3, 6, and, 9 months was significantly higher in the nTMS group than in the non-nTMS group but did not differ statistically between groups at 12 months.

Frey et al (2014) enrolled 250 consecutive patients who underwent nTMS preoperative mapping and identified 115 historical controls who met the same eligibility criteria. Criteria included being evaluated for surgery for a tumor in a motor eloquent area and without seizures more than once a week or cranial implants. Fifty-one percent of the nTMS group and 48% of controls had World Health Organization grade II, III, or IV gliomas; remaining patients had brain metastases from other primary cancers or other lesions. Intraoperative motor cortical stimulation to confirm nTMS findings was performed in 66% of the nTMS group. The Medical Research Council scale and Karnofsky Performance Status were used to assess muscle strength and performance status, respectively. Outcomes were assessed at postoperative day 7 and then at 3-month intervals. At the 3-month follow-up, 6.1% of the nTMS group and 8.5% of controls had new postoperative motor deficits (not significantly different); changes in performance status postoperatively also were similar between groups. Other outcomes were reported for patients with glioma only (128 nTMS patients, 55 controls). Based on postoperative MRI, gross total resection was achieved in 59% of nTMS patients and 42% of controls (p<0.05). At mean follow-up of 22 months (range, 6-62 months) in the nTMS group and 25 months (range, 9-57 months) in controls, mean progression-free survival (PFS) was similar between groups (mean PFS, 15.5 months [range, 3-51 months] for nTMS vs 12.4 months [range, 3-38 months] for controls; not significantly different). In the subgroup of patients with low-grade (grade II) glioma

(38 nTMS patients, 18 controls), mean PFS was longer in the nTMS group (mean PFS, 22.4 months; range, 11-50 months) than in the control group (15.4 months; range, 6-42 months; p<0.05), and new postoperative motor deficits were similar (7.5% vs 9.5%, respectively; not significantly different). Overall survival did not differ statistically between treatment groups.

One nonrandomized study used concurrent controls. Sollmann et al (2015) matched 25 prospectively enrolled patients who underwent preoperative nTMS but whose results were not available to the surgeon during the procedure (group 1) to 25 patients who underwent preoperative nTMS whose results were available to the surgeon (group 2). All patients had language eloquently located brain lesions within the left hemisphere. Primary outcomes were not specified. Three months postsurgery, 21 patients in group 1 had no or mild language impairment, and 4 patients had moderate-to-severe language deficits. In group 2, 23 patients had no or mild language impairment, and 2 patients had moderate-to-severe deficits. The difference between groups in postoperative language deficits was statistically significant (p=0.015). Other outcomes, including duration of surgery, postoperative Karnofsky Performance Status scores, the percentage of residual tumor, and peri- and postoperative complication rates did not differ significantly between groups.

Picht et al (2012) assessed whether a change in management occurred as a result of knowledge of nTMS findings. In this study, surgeons first made a plan based on all known information without nTMS findings. After being informed of nTMS findings, the surgical plan was reformulated if necessary. Among 73 patients with brain tumors in or near the motor cortex, nTMS was judged to have changed the surgical indication in 2.7%, changed the planned extent of resection in 8.2%, modified the approach in 16.4%, added awareness of high-risk areas in 27.4%, added knowledge not used in 23.3%, and only confirmed the expected anatomy in 21.9%. The first 3 surgical categories, judged to have been altered because of nTMS findings, were summed to determine “objective benefit” of 27.4%.

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. Current evidence on clinical validity does not permit construction of a chain of evidence to support the use of nTMS for presurgical mapping of eloquent areas of the brain.

Section Summary: Clinically Useful

No RCTs have compared health outcomes in patients who did and did not have presurgical nTMS before brain surgery. There is direct evidence from several nonrandomized comparative studies of patients undergoing nTMS, mainly compared with historical controls. Findings were mixed; outcomes were not consistently better in patients who underwent presurgical nTMS. Complication rates did not differ significantly between groups. In 2 of 3 studies, residual tumor volume did not differ between groups. Two studies reported survival rates. In both, overall survival did not differ significantly between groups. One of the studies found significantly higher mean survival rates in the nTMS group at 3, 6, and 9 months postsurgery, but not at 12 months. One of 2 studies, reporting postoperative language deficits, found significantly fewer deficits in the group that received presurgical nTMS. Limitations of all studies discussed in this section include the single-center settings (because nTMS is an operator-dependent technology, applicability may be limited), lack of randomization and/or use of historical controls (surgeon technique and practice likely improved over time), selective outcomes reporting (survival outcomes in glioma patients only), and uncertain validity of statistical analyses (primary outcome not identified and no correction for multiple testing). Additionally, studies either matched patients to controls on a few variables or used controls who met similar eligibility criteria. These techniques may not adequately control for differences in patient groups that may affect outcomes.

SUMMARY OF EVIDENCE

For individuals who have brain lesion(s) undergoing preoperative evaluation for localization of eloquent areas of the brain who receive nTMS, the evidence includes controlled observational studies and case series. Relevant outcomes are overall survival, test accuracy, morbid events, and functional outcomes. Several small studies have evaluated the distance between nTMS hotspots and DCS hotspots for the same muscle. Although the average distance in most studies is 10 mm or less, this does not take into account the error margin in this average distance or whether hotspots are missed. It is difficult to verify nTMS hotspots fully because only exposed cortical areas can be verified with DCS. Limited studies of nTMS evaluating language areas have shown high false-positive rates (low specificity) and sensitivity that may be insufficient for clinical use. Several controlled observational studies have compared outcomes in patients undergoing nTMS with those (generally pre-TMS historical controls) who did not undergo nTMS. Findings of the studies were mixed; outcomes were not consistently better in patients who underwent presurgical nTMS. For example, overall survival did not differ significantly between groups in 2 studies and one reporting postoperative language deficits found significantly fewer deficits in the group that had presurgical nTMS. The controlled observational studies had various methodologic limitations and, being nonrandomized, might not have adequately controlled for differences in patient groups, which could have biased outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

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03/06/2014	Medical Policy Committee review
03/19/2014	Medical Policy Implementation Committee approval. New policy.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Updated rationale and references. Coverage eligibility unchanged.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2018	Coding update
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2019

Coding

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

Code Type	Code
CPT	Code deleted eff 1/1/18: 0310T Code added 1/1/18: 64999
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*****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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