Navigated Transcranial Magnetic Stimulation (nTMS)

Policy # 00407
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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.

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 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 (eg, controlling verbal or motor function) is an important consideration in surgical planning to be investigational.*

Background/Overview
Navigated transcranial magnetic stimulation (nTMS) is a noninvasive imaging method for the evaluation of 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 imaging (MRI) image of the patient’s brain. Surface electromyography (EMG) electrodes are attached to various limb muscles of the patient. Moving the magnetic stimulation source to various parts of the brain causes the EMG 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. nTMS can be considered a noninvasive alternative to direct cortical stimulation (DCS), in which electrodes are directly applied to the surface of the cortex during craniotomy.

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 considered to be most accurately achieved with DCS, an intraoperative procedure that increases operating time and requires a wide surgical opening. Even if not completely accurate compared to DCS, preoperative techniques that map brain functions may aid in planning the extent of resection and the operative 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.

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 correlates with neuronal activity associated with a specific motor or speech task being performed as the image is obtained. The accuracy and precision of fMRI is dependent 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 reviewed several studies comparing fMRI and DCS of language areas and found large variability in sensitivity and specificity of fMRI. The discussion also points out a major conceptual point in how fMRI and DCS “map” language areas. fMRI findings reflect regional oxygenation changes which show that a particular region of
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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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
The Nexstim® Navigated Brain Stimulation (NBS) System 4 and NBS System 4 with NexSpeech® received 510(k) clearance in May 2012 for noninvasive mapping of the primary motor cortex and for localization of cortical areas that do not contain speech function, for the purposes of preprocedural planning.

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
Test-Retest Reliability in Healthy Volunteers
In some studies, nTMS has been repeated in subjects over a relatively short interval in time to evaluate whether the test is reliable; that is, produces a similar result. In these studies, it is assumed that nothing in the subject has changed, and any difference in result is due to variations in the testing procedure and any natural variability in the subject.

In a study by Forster et al, 12 healthy participants underwent nTMS in 2 different sessions, separated in time an average of 10 days. Five muscle groups in the upper and lower extremity in each subject were stimulated, and the hotspots (points of optimal stimulation) and center of gravity (amplitude-weighted center of area sensitive to stimulation) for each subject were identified. The mean distance between these points between sessions for each muscle were calculated. The intraclass coefficient in the x axis (mediolateral) and the y axis (anteroposterior) for each muscle was calculated. Overall, across all muscles, the mean difference (SD) in hotspot location between sessions was 0.79 (0.47) cm. The mean difference in center of gravity location was 0.57 (0.32) cm. The intraclass coefficients in the anteroposterior axis ranged from 0.54 to 0.89, consistent with moderate to excellent reliability. In the mediolateral axis, intraclass coefficients ranged from 0.11 to 0.89, with several of the coefficients less than 0.49, which is generally regarded as poor reliability.

A study by Weiss et al also evaluated the reliability of nTMS and functional MRI in 10 healthy subjects. Muscles in the hand, foot and face were evaluated. nTMS was not feasible in a high proportion of subjects for evaluating the face and tongue due to technical constraints and other artifacts. Functional magnetic resonance imaging (fMRI) on the other hand, produced interpretable findings for all muscle groups in all sessions. The mean difference (SD) in hotspot location, as identified by nTMS between sessions was 10.8 (1.9) mm. The mean difference in maximum activation, as identified by fMRI between sessions was 6.2 mm, thus showing that fMRI was more reliable than nTMS in locating a specific point associated with a particular muscle. In another type of analysis in which the spatial extent of a particular muscle activity was mapped by either nTMS or fMRI, neither technique yielded reliable results. The extent of spatial overlap between
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sessions was very low for either technique (less than 32% for both) and the intraclass correlation coefficients were also both less than 50%, indicating poor reliability.

Studies of nTMS in Brain Tumor Patients
Most studies of nTMS are small case series of brain tumor patients, which are not ideal studies to ascertain diagnostic characteristics. Due to the use of nTMS and/or other methods to identify the motor or language centers in the cortex and determine the surgical approach, the reference standard of DCS may be biased. The DCS procedure may be limited or altered because of the tumor resection or other surgical factors. It is not possible to verify all the nTMS sites identified, because the surgical field is limited. Because of this necessarily limited verification, it is difficult to ascertain diagnostic characteristics of nTMS.

Comparisons to Direct Cortical Stimulation
Picht et al evaluated 17 patients with brain tumors with both 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 particular patient in regard to tumor location and clinical findings. The intraoperative DCS locations were chosen independently of nTMS, and the surgeon was not aware of the nTMS hotspots. There were 37 muscles in the 17 patients for which both nTMS and DCS data were available. The mean (SE) distance between the nTMS and DCS hotspots was 7.83 (1.18) mm for the abductor pollicis brevis muscle and 7.07 (0.88) mm for the tibialis anterior muscle. The 95% confidence interval for the mean distance was 5.31 to 10.36 mm. When DCS was performed during surgery, there was large variation in the number of stimulation points, and the distance between nTMS and DCS was much less when a larger number of points were stimulated.

Forster et al performed a similar study in 11 patients. fMRI was also performed in these patients. The distance between corresponding nTMS and DCS hotspots was 10.49 (5.67) mm. The distance between the centroid of fMRI activation and DCS hotspots was 15.03 (7.59) mm. However, it is not clear whether there were hotspots with either device that cannot be elicited with the other. There were at least 2 excluded patients in whom nTMS hotspots could not be elicited in which DCS elicited a response.

Another study by Tarapore et al evaluated distance between nTMS and DCS hotspots. Among 24 patients who underwent nTMS, 18 of whom underwent DCS, 8 motor sites in 5 patients were corresponding. The median distance between nTMS and DCS hotspots was 2.13 (0.29) mm. In the craniotomy field in which DCS mapping was performed, DCS did not find any new motor sites that TMS failed to identify. The study also evaluated magnetoencephalography (MEG); the median distance between MEG motor sites and DCS was 12.1 (8.2) mm.

Mangravati et al also evaluated the distance between nTMS and DCS hotspots in 7 patients. It cannot be determined from the study report how many hotspots are compared and how many potential comparisons are not available due to failure of either device to find a particular hotspot. It appears that the mean distance between hotspots is based on the locations of hotspots for 3 different muscles. The overall mean difference between nTMS and DCS was 8.47 mm. This was smaller than the mean difference between the centroid of fMRI activation and DCS hotspots of 12.9 (5.7) mm.
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Krieg et al also evaluated nTMS in comparison to DCS in a study of 14 patients. However, the navigation device employed appears to be different than the FDA-approved device. In addition, the comparison of nTMS to DCS uses a different methodology. Both nTMS and DCS were used to map out the whole volume of the motor cortex, and a mean difference between the borders of the edge of the mapped motor cortex was calculated. The mean distance between the two methods was 4.4 (3.4) mm.

These studies assessing the distance between nTMS and DCS hotspots appear to show that stimulation sites in which responses can be elicited from both techniques tend to be mapped within 1 cm 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, in terms of the utility of the information, on presurgical planning.

Language Mapping Compared With Direct Cortical Stimulation

A study by Picht et al attempted to evaluate the accuracy of nTMS for identifying language areas. Twenty patients underwent evaluation of language areas over the whole left hemisphere, which was divided into 37 regions. DCS was necessarily performed only in areas accessible in the craniotomy site. In a total of 160 regions in the 20 patients, data for both methods were available. Using DCS as the reference standard, there were 46 true positives, 83 false positives, 26 true negatives, and 5 false negatives. Considering the analysis as 160 independent data points for each brain region, nTMS had a sensitivity of 90.2%, specificity of 23.8%, positive predictive value of 35.6% and negative predictive value of 83.9%. An analysis of regions considered to be in the classic Broca’s area showed a sensitivity of 100%, specificity 13.0%, positive predictive value of 56.5%, and negative predictive value of 100%.

Another study by Tarapore et al of 12 subjects also evaluated nTMS for identifying language areas. In addition to nTMS, MEG was also evaluated. 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. This translates to a sensitivity of 90%, specificity of 98%, a positive predictive value of 69% and a negative predictive value of 99%.

The study by Picht et al showing the very high number of false positives raises concerns about the utility of nTMS for identifying language areas. Even if nTMS is used to rule out areas in which language areas are unlikely, the sensitivity of 90.2% may result in some language areas not appropriately identified.

Studies of Clinical Utility

There are no formal comparison studies evaluating nTMS versus other strategies without nTMS in affecting health outcomes in patients being considered for surgical resection of brain tumors. Such studies would be difficult to design and may not be practical or ethical to carry out. Given that results of diagnostic workups of brain tumor patients may result in differences in which patients are operated on, the counseling given to patients, and the type of surgery performed, it would be difficult to compare outcomes of groups of patients with very qualitatively different outcomes. For example, it is difficult to compare the health outcome of a patient who ends up not being operated on, who conceivably has a shorter overall lifespan but a short period of very high quality of life, to a patient who undergoes operation but has some moderate disability afterward, but a much longer overall lifespan.
A study by Picht et al attempts to determine the clinical utility of nTMS by assessing whether a change in management occurred as a result of knowledge of nTMS findings. In this study, surgeons first made a surgical plan based on all known information without nTMS findings. After being made aware of nTMS findings, the surgical plan was reformulated if necessary. According to this protocol, in 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 that was not used in 23.3%, and only confirmed the expected anatomy in 21.9%. The first 3 categories in which it was judged that the surgery was altered because of nTMS findings were summed up to determine “objective benefit,” which was 27.4%.

**Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2013

In response to requests, input was received from 1 physician specialty society (2 reviewers) and 2 academic medical centers while this policy was under review in 2013. The majority of reviewers considered nTMS to be investigational.

**Summary**

Overall, the literature on nTMS is at a very preliminary stage of demonstrating effectiveness. Relatively small studies have demonstrated the distance between nTMS hotspots and DCS hotspots for the same muscle. Although the average distance in most studies is 1 cm or less, this does not take into account the degree of error in this average distance, or whether there are missed hotspots. It is difficult to fully verify nTMS hotspots because only exposed cortical areas can be verified with DCS. Limited studies of nTMS to evaluate language areas show a very high rate of false positives, at least in one study. One study has attempted to demonstrate how clinical decision making has been changed as a result of nTMS results. This type of study does not provide strong evidence of the efficacy of nTMS. Based on the limited evidence available and the results of clinical vetting, nTMS is considered investigational for all indications.

**References**

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Coding

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

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Policy History

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03/06/2014  Medical Policy Committee review
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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

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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