Navigated Transcranial Magnetic Stimulation

Policy # 00407
Original Effective Date: 03/19/2014
Current Effective Date: 08/23/2017

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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
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.

The most commonly used tool for the noninvasive localization of brain functions is functional magnetic resonance imaging (fMRI). Functional MRI 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 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.

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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 (eg, 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, Helsinki, Finland) 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 pre-procedural 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**

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical performance (test-retest reliability or interrater reliability); (2) diagnostic accuracy (sensitivity, specificity, and positive [PPV] and negative predictive value [NPV]) in relevant populations of patients; and (3) demonstration that the diagnostic information can be used to improve patient outcomes. Following is a summary of the key literature to date.

**PREOPERATIVE NAVIGATED TRANSCRANIAL MAGNETIC STIMULATION TO LOCALIZE 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.
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The question addressed in this evidence review is: Does the evidence indicate that nTMS improves 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**
There are several other tools 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 for technical performance are test-retest reliability or interrater reliability. The relevant outcomes for diagnostic accuracy are sensitivity, specificity, predictive values, and related measures of diagnostic accuracy. Effects on health outcomes would be supported by improvement in survival or in functional measures such as speaking and walking or in a reduction in morbidity. Alternatively, evidence of clinical utility may be derived from a chain of evidence linking an improvement in diagnostic accuracy with treatment guided by a correct diagnosis.

**Timing**
nTMS for preoperative planning is performed before surgery.

**Setting**
nTMS is done in a specialty setting (i.e., neurology).

**Technical Performance**
In 2013, Sollman et al published a study on intra- and interobserver variability of language mapping using brain nTMS. In healthy volunteers, nTMS test-retest reliability varied across error type (e.g., neologism, semantic error) and cortical region (i.e., anterior, posterior), but, overall, both intra- and interobserver reliability were low (range of concordance correlation coefficients: intraobserver, -0.222 to 0.505; interobserver, -0.135 to 0.588).

**Section Summary: Technical Performance**
In a study of healthy volunteers, intra- and interobserver reliability of nTMS were both relatively low.
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Diagnostic Accuracy
Most studies of nTMS are small case series of patients with brain tumors, cavernous angiomas, arteriovenous malformations, or other brain lesions; case series are not ideal studies to ascertain diagnostic characteristics. There are also a number of small nTMS studies evaluating healthy volunteers, but they do not add substantially to the evidence base. Studies comparing nTMS to 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 about 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 [SE]=1.18) for the abductor pollicis brevis muscle (95% confidence interval [CI], 5.31 to 10.36 mm) and 7.07 mm (SE=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 lower 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.

A 2012 study by Tarapore et al evaluated the 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 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 (SEM=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 in 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 2013 study by Picht et al evaluated 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 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%, PPV of 36%, and NPV 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 NPV 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, sensitivity of 90% might result in some language areas not appropriately identified.

A 2013 study by Tarapore et al also evaluated nTMS for identifying language areas (N=12). 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, translating to a sensitivity of 90%, specificity of 98%, PPV of 69%, and NPV of 99%.

Section Summary: Diagnostic Accuracy
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 regarding the utility of the information for presurgical planning. The available studies of the diagnostic accuracy nTMS evaluating language areas have shown a sensitivity of 90% and variable specificity (24% in 1 study, 98% in another study). The PPVs were relatively low in both of the studies (57% and 69%, respectively). 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.

Clinical Utility
The ideal study to determine whether nTMS improves health outcomes in patients being considered for surgical resection of brain tumors would be a randomized controlled trial 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.
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No randomized controlled trials were identified. However, controlled observational are available. Several studies have matched patients who underwent presurgical nTMS with similar historical controls who did not. Most recently in 2017, Hendrix et al 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 at 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 stays (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 (ie, assessment at multiple time points). Groups may have differed in other ways that affected outcomes and procedures may have changed over time in ways that affected surgical duration, complication rates, and inpatient stays.

Previously, 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% CI, 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 (“neurological improvement” were 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 this research group, which had some overlap in enrolled patients, was published in 2015. 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 cm² (SD=9.7) in the nTMS group and 30.8 cm² (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 to 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 in 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; p=NS). Overall survival did not differ statistically between treatment groups.

One nonrandomized study used concurrent controls. Sollman 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, percentage of residual tumor, and peri- and postoperative complication rates did not differ significantly between groups.

One study (2012) identified 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
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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%.

Section Summary: Clinical Utility
No randomized controlled trials 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 pre-surgical 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 outcome 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 degree of error 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, may not have adequately controlled for differences in patient groups, which may have biased outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.
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References


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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.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017 Medical Policy Committee review
01/01/2018 Coding update
Next Scheduled Review Date: 08/2018

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