

# TRANSCRANIAL MAGNETIC STIMULATION

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## Related Policies

- [Deep Brain and Cortical Stimulation](#)
- [Vagus Nerve Stimulation](#)

## Related Optum Guideline

- [Transcranial Magnetic Stimulation \(TMS\)](#)

## INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

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## APPLICABLE LINES OF BUSINESS/PRODUCTS

This policy applies to Oxford Commercial plan membership.

## BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

### **Essential Health Benefits for Individual and Small Group**

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

## NON-COVERAGE RATIONALE

### **Transcranial magnetic stimulation is unproven and/or not medically necessary for treating all medical (i.e., non-behavioral) conditions including but not limited to:**

- Alzheimer's disease
- Chronic neuropathic pain
- Dystonia
- Epilepsy
- Headaches
- Parkinson's disease
- Stroke
- Tinnitus

For Behavioral Disorders, refer to the Optum Behavioral Solutions Coverage Determination Guideline titled *Transcranial Magnetic Stimulation (TMS)* at [Optum Provider Express > Clinical Resources > Guidelines/Policies/Manuals > Coverage Determination Guidelines](#).

Some studies have examined the use of transcranial magnetic stimulation for treating disorders such as pain, dystonia, epilepsy, headaches, Parkinson's disease, stroke, and tinnitus. However, because of limited studies and small sample size there is insufficient data to conclude that transcranial magnetic stimulation is beneficial for treating these conditions.

### **Navigated transcranial magnetic stimulation (nTMS) is unproven and/or not medically necessary for treatment planning or for diagnosing motor neuron diseases or neurological disorders.**

There is limited information from the peer-reviewed published medical literature to conclude that navigated transcranial magnetic stimulation is an effective clinical diagnostic test. Most published studies involve a small number of patients. Randomized controlled trials with large populations are needed to evaluate how this test can reduce clinical diagnostic uncertainty or impact treatment planning.

## APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
64999	Unlisted procedure, nervous system
90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
90868	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session
90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management

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## DESCRIPTION OF SERVICES

Single-pulse transcranial magnetic stimulation (TMS) was originally introduced in 1985 as a noninvasive and safe way to stimulate the cerebral cortex. Activation of the motor cortex by transcranial magnetic stimulation produces contralateral muscular-evoked potentials (MEPs), thus providing a valuable tool for functional mapping of the motor cortex. Technological advances introduced generators capable of producing rapid, repetitive pulses of magnetic stimulation. The magnetic field pulses pass unimpeded through the hair, skin, and skull and into the brain where they induce an electrical current to flow inside the brain without seizures or need for anesthesia. The amount of electricity created is very small and cannot be felt by the patient, but the electric charges cause the neurons to become active and are thought to lead to the release of neurotransmitters such as serotonin, norepinephrine and dopamine. Repetitive TMS (rTMS) is also currently under investigation as a treatment for several disorders originating in the cerebral cortex including pain, dystonia, epilepsy, headaches, Parkinson's disease, stroke, and tinnitus. TMS is delivered by various available devices, and treatment has been tested using a variety of protocols, including high frequency delivered over the left dorsolateral prefrontal cortex, low frequency delivered over the right or left dorsolateral prefrontal cortex, bi-lateral delivery, and deep TMS in which deeper prefrontal regions are stimulated.

Navigated transcranial magnetic stimulation (nTMS) is being studied as a diagnostic tool to stimulate functional cortical areas at precise anatomical locations to induce measurable responses. This technology is being investigated to map functionally essential motor areas for diagnostic purposes and for treatment planning.

## CLINICAL EVIDENCE

### **Therapeutic Transcranial Magnetic Stimulation**

#### ***Systematic Review and Meta-Analyses for Parkinson's Disease***

Goodwill et al. (2017) conducted a meta-analysis that quantified the effectiveness of repetitive transcranial magnetic stimulation (rTMS) to improve motor and cognitive dysfunction in Parkinson's disease (PD). A total of 24 rTMS with a sham control group were included in the analyses. The results showed an overall positive effect in favor of rTMS compared with sham stimulation on motor function. The use of rTMS did not improve cognition. No effects for stimulation parameters on motor or cognitive function were observed. The authors acknowledged several limitations. Studies evaluating rTMS demonstrated modest effect sizes (0.4–0.6) and large heterogeneity between studies. Clinical and lifestyle variables including PD-related comorbidity, physical activity levels and other mental health conditions were not accounted for in the subgroup analyses, which may have influenced the responsiveness to non-invasive brain stimulation (NBS).

In a systematic review and meta-analysis, Wagle Shukla et al. (2016) reviewed the literature on clinical repetitive transcranial magnetic stimulation (rTMS) trials in Parkinson's disease to quantify the overall efficacy of this treatment. Prospective clinical trials were included that had an active arm and a control arm and change in motor scores on Unified Parkinson's Disease Rating Scale as the primary outcome. The authors pooled data from 21 studies that met these criteria and analyzed separately the effects of low- and high-frequency rTMS on clinical motor improvements. Repetitive transcranial magnetic stimulation therapy demonstrated benefits at short-term follow-up (immediately after a treatment protocol) with a pooled mean difference of 3.4 points as well as at long-term follow-up (average follow-up 6 weeks) with mean difference of 4.1 points. The authors concluded that rTMS therapy results in mild-to-moderate motor improvements and has the potential to be used as an adjunct therapy for the treatment of Parkinson's disease. According to the authors, future large, sample studies should be designed to isolate the specific clinical features of Parkinson's disease that respond well to rTMS therapy. The authors indicated that the literature on the use of rTMS for levodopa-induced dyskinesia, objective bradykinesia, and gait measures is sparse and that on the basis of the current available information, the results are conflicting, and no clear treatment protocol has yet been defined.

Chung and Mak (2016) conducted a systematic review to examine the efficacy of rTMS on improving physical function and motor signs over the short- and long-terms in people with Parkinson's disease (PD). Twenty-two randomized placebo-controlled trials comprising 555 people with PD were included. Pooled estimates of effect of rTMS indicated significantly improved short-term upper limb function, short-term and long-term walking performance, short-term and long-term unified Parkinson's disease rating scale (UPDRS) III scores. Subgroup analyses suggest a more prominent effect for primary motor cortex (M1) stimulation. Meta-regression revealed that a greater number of total stimulation pulses were associated with more UPDRS III improvements over the long-term. The authors concluded that the pooled evidence suggests that rTMS improves upper limb function in the short-term, and walking performance and UPDRS III in the short- and long-terms in PD sufferers. According to the authors, the limitations of this review included the following: the insignificant long-term effect of rTMS on upper limb bradykinesia results should be interpreted with caution due to small number of studies. Second, the effects of rTMS targeting frontal areas other than M1, low frequency rTMS and TBS remain inconclusive due to an insufficient number of research studies. Third, the followup period for the included trials was relatively short considering that PD is a chronic degenerative disease. The lack of studies with a longer duration of follow-up, such as 6–12 months, limited this analysis.

In a systematic review and meta-analysis, Chou et al. (2015) evaluated the repetitive transcranial magnetic stimulation (rTMS) effects on motor dysfunction in patients with Parkinson's disease (PD). Eligible studies included sham-controlled, randomized clinical trials of rTMS intervention for motor dysfunction in patients with PD. Relevant measures were extracted independently by 2 investigators. Standardized mean differences (SMDs) were calculated with random-effects models. Twenty studies with a total of 470 patients were included. Random-effects analysis revealed a pooled SMD of 0.46, indicating an overall medium effect size favoring active rTMS over sham rTMS in the reduction of motor symptoms. Subgroup analysis showed that the effect sizes estimated from high-frequency rTMS targeting the primary motor cortex and low-frequency rTMS applied over other frontal regions were significant. Using the Grading of Recommendations, Assessment, Development, and Evaluation criteria, the authors characterized the quality of evidence presented in this meta-analysis as moderate quality. The authors concluded that the pooled evidence suggests that rTMS improves motor symptoms for patients with PD. According to the authors, one of the limitations of this meta-analysis was that the results could be constrained by the unclear risk of bias on certain domains owing to incomplete data in a few studies. In addition, several uncontrolled variables, such as medication use, disease stage, side of onset, side of rTMS stimulation, age, and sex, existed and may have confounded the results of the analysis.

## **Systematic Review and Meta-Analyses for Pain**

Saltychev and Laimi (2017) investigated whether there is evidence of repetitive transcranial magnetic stimulation (rTMS) being effective in decreasing the severity of pain among patients with fibromyalgia. Seven trials were included in the meta-analysis. The risk of bias was considered low for seven studies. Pain severity before and after the last stimulation decreased by -1.2 points on 0-10 numeric rating scale. Pain severity before and 1 week to 1 month after the last stimulation decreased by -0.7 points. Both pooled results were below the minimal clinically important difference of 1.5 points. The authors did not find evidence of clinically significant effectiveness of rTMS in decreasing the severity of fibromyalgia pain immediately after the treatment as well as in short-term follow-up.

Goudra et al. (2017) evaluated the role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of chronic pain. Studies comparing rTMS and conventional treatment for chronic pain were searched. The comparison was made for decrease in the pain scores with and without (sham) the use of rTMS after a follow-up interval of 4-8 weeks. All reported pain scores were converted into a common scale ranging from "0" (no pain) to "10" (worst pain). Nine trials with 183 patients in each of the groups were included in the analysis. The decrease in pain scores with rTMS was 1.12 and in sham-rTMS was 0.28. The pooled mean drop in pain scores with rTMS therapy was higher by 0.79. The duration and frequency of rTMS were highly variable across trials. Publication bias was unlikely. The authors concluded that the use of rTMS improves the efficacy of conventional medical treatment in chronic pain patients. This treatment is not associated with any direct adverse effects. However, according to the authors, the duration and frequency of rTMS therapy is presently highly variable and needs standardization. According to the authors, availability of a limited number of trials examining the usefulness of rTMS is an important drawback of the current meta-analysis.

In a systematic review of controlled clinical trials, Shirahige et al. (2016) evaluated the efficacy of noninvasive brain stimulation (NIBS) on pain control in migraine patients. Eight studies were included in the quantitative analysis with 153 migraine patients who received NIBS and 143 patients who received sham NIBS. In the overall meta-analysis, the authors did not find significant results for pain intensity, for migraine attacks, and for painkiller intake. However, subgroup analysis considering only transcranial direct current stimulation (tDCS) effects demonstrated a decrease for pain intensity, migraine attacks, and painkiller intake. Subgroup analysis for TMS did not reveal significant effects for any outcome. The authors concluded that this review failed to find support for the superiority of NIBS over sham treatment. According to the authors, there is a need for larger controlled trials with methodological rigor, which could increase the power of result inference.

Jin et al. (2015) conducted a meta-analysis that examined clinical trials (randomized sham-controlled or self-controlled trials; double-blind or single-blind; parallel or cross-over study designs) involving the analgesic efficacy of high frequency repetitive transcranial magnetic stimulation (HF-rTMS) for neuropathic pain (NP). Twenty-five studies (including 32 trials and 589 patients) were selected for the meta-analysis. All 3 HF-rTMS treatments (5, 10, and 20 Hz) produced pain reduction, while there were no differences between them, with the maximal pain reduction found after one and 5 sessions of rTMS treatment. Further, this significant analgesic effect remained for one month after 5 sessions of rTMS treatment. There are limitations of this meta-analysis. For example, the long-term analgesic effects of different HF-rTMS and low frequency (LF) rTMS sessions, including the single session of rTMS on different NP of varying origins have yet not been evaluated; the full degree of pain relief is still unclear for many rTMS studies. The authors concluded that HF-rTMS stimulation on primary motor cortex is effective in relieving pain in NP patients. Although 5 sessions of rTMS treatment produced a maximal analgesic effect and may be maintained for at least one month, further large-scale and well-controlled trials are needed to determine if this enhanced effect is specific to certain types of NP such as post-stroke related central NP. According to the authors, there is not enough clinical evidence to determine the long-term effect of rTMS therapy (longer than 2 months post-treatment).

In a meta-analysis, Galhardoni et al. (2015) reviewed the literature on the analgesic effects of repetitive transcranial magnetic stimulation (rTMS) in chronic pain according to different pain syndromes and stimulation parameters. A total of 33 randomized trials were found. Many studies reported significant pain relief by rTMS, especially high-frequency stimulation over the primary motor cortex performed in consecutive treatment sessions. Pain relief was frequently >30% compared with control treatment. Neuropathic pain, fibromyalgia, and complex regional pain syndrome were the pain syndromes more frequently studied. However, among all published studies, only a few performed repetitive sessions of rTMS. The authors concluded that TMS has potential utility in the management of chronic pain; however, studies using maintenance sessions of rTMS and assessing the effects of rTMS on the different aspects of chronic pain are needed to provide a more solid basis for its clinical application for pain relief.

In an updated version of the original Cochrane review published in 2010, O'Connell et al. (2014) evaluated the efficacy of non-invasive brain stimulation techniques in chronic pain. The update included a total of 30 rTMS studies. Meta-analysis of studies of rTMS (involving 528 participants) demonstrated significant heterogeneity. Pre-specified subgroup analyses suggested that low-frequency stimulation is ineffective (low-quality evidence) and that rTMS applied to the dorsolateral prefrontal cortex is ineffective (very low-quality evidence). The authors found a short-term

effect on pain of active high-frequency stimulation of the motor cortex in single-dose studies (low-quality evidence). This equates to a 12% reduction in pain, which does not exceed the pre-established criteria for a minimal clinically important difference. Evidence for multiple-dose studies was heterogenous but did not demonstrate a significant effect (very low-quality evidence). The authors concluded that single doses of high-frequency rTMS of the motor cortex may have small short-term effects on chronic pain. However, it is likely that multiple sources of bias may exaggerate this observed effect. The authors state that the effects do not meet the predetermined threshold of minimal clinical significance and multiple-dose studies do not consistently demonstrate effectiveness. According to the authors, the available evidence suggests that low-frequency rTMS and rTMS applied to the pre-frontal cortex are not effective in the treatment of chronic pain.

### **Systematic Review and Meta-Analyses for Stroke**

In a systematic review, Sebastianelli et al. (2017) summarized the evidence for the effectiveness of low-frequency (LF) repetitive transcranial magnetic stimulation (rTMS) in promoting functional recovery after stroke. Sixty-seven studies were included in the review. The authors observed considerable heterogeneity across studies in the stimulation protocols. According to the authors, the use of different patient populations, regardless of lesion site and stroke etiology, different stimulation parameters and outcome measures means that the studies were not readily comparable, and estimating real effectiveness or reproducibility was very difficult. The authors concluded that LF rTMS over unaffected hemisphere may have therapeutic utility, but the evidence is still preliminary and the findings need to be confirmed in further randomized controlled trials.

Dionísio et al. (2017) conducted a systematic review to provide information regarding the application of repetitive transcranial magnetic stimulation (rTMS) in stroke patients and to assess its effectiveness in clinical rehabilitation of motor function. Seventy trials were included in the review. The majority of the articles reported rTMS showing potential in improving motor function, although some negative reports, all from randomized controlled trials, contradicted this claim. According to the authors, future studies are needed because there is a possibility that a bias for non-publication of negative results may be present.

In a meta-analysis and systematic review, McIntyre et al. (2017) evaluated the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in improving spasticity after stroke. A literature search of multiple databases was conducted for articles published in English from January 1980 to April 2015 using select keywords. Studies were included if: 1) the population included was >50% stroke patients; 2) the sample size included  $\geq 4$  subjects; 3) the intervention applied was rTMS; and 4) upper extremity spasticity was assessed pre and post intervention. Randomized controlled trials (RCTs) were assessed for methodological quality using the Physiotherapy Evidence Database (PEDro) tool. The main outcome measurement was the Modified Ashworth Scale (MAS). Ten studies met the inclusion criteria: two RCTs (PEDro scores 8-9) and eight pre-post studies. Meta-analyses of primarily uncontrolled pre-post studies found significant improvements in MAS for elbow, wrist, and finger flexors. However, a meta-analysis of the two available RCTs failed to find a significant rTMS treatment effect on MAS for the wrist. The authors concluded that there is limited available evidence to support the use of rTMS in improving spasticity post stroke. Despite the positive findings reported, better powered and appropriately controlled trials are necessary.

In a systematic review and meta-analysis, Zhang et al. (2017) evaluated the short- and long-term effects as well as other parameters of repetitive transcranial magnetic stimulation (rTMS) on upper limb motor functional recovery after stroke. Thirty-four studies with 904 participants were included in the systematic review. Pooled estimates show that rTMS significantly improved short-term and long-term manual dexterity. More pronounced effects were found for rTMS administered in the acute phase of stroke, subcortical stroke, 5-session rTMS treatment and intermittent theta burst stimulation. Only three studies reported mild adverse events such as headache and increased anxiety. The authors concluded that five-session rTMS treatment could best improve stroke-induced upper limb dyskinesia acutely in a long-lasting manner and intermittent theta burst stimulation is more beneficial than continuous theta burst stimulation. Studies with larger sample sizes are needed to further investigate the use of rTMS for upper limb motor functional recovery after stroke.

Pisegna et al. (2016) conducted a systematic review and meta-analysis of randomized controlled trials to evaluate the effects of non-invasive brain stimulation, including transcranial magnetic stimulation on post-stroke dysphagia. Eight randomized controlled trials were included in the review. This review found evidence for the efficacy of non-invasive brain stimulation on post-stroke dysphagia. A significant effect size resulted when stimulating the unaffected rather than the affected hemisphere. This finding is in agreement with previous studies implicating the plasticity of cortical neurons in the unaffected hemisphere. According to the authors, non-invasive brain stimulation appears to assist cortical reorganization in post-stroke dysphagia but emerging factors highlight the need for more data. The authors indicated that based on this preliminary review, non-invasive brain stimulation facilitated recovery in post-stroke dysphagia but should not yet be considered for clinical use outside of clinical trials.

Li et al. (2015a) performed a meta-analysis of studies investigating the effects of low-frequency repetitive transcranial magnetic stimulation on post-stroke aphasia. Of the 879 articles identified, 4 RCTs were included in the final analysis.

Data synthesis showed that low-frequency repetitive transcranial magnetic stimulation was beneficial for post-stroke patients in terms of naming and changes in brain excitability. However, the changes in repetition and comprehension after stimulation were not significant. No adverse effects were reported. The included studies were of high methodological quality. The authors concluded that these findings indicate that low-frequency repetitive transcranial magnetic stimulation is an effective treatment for recovery of naming. According to the authors, due to the limited number of included studies, as well as the small sample sizes, the statistical power of the meta-analysis was moderate. The authors also indicated that although rTMS is considered a promising therapy, the specific mechanism underlying its success is unknown. Further investigations should evaluate the different types and phases of aphasia.

### ***Systematic Review and Meta-Analyses for Other Conditions***

In a Cochrane review, Chen et al. (2016) assessed the evidence for the use of TMS in individuals with drug-resistant epilepsy compared with other available treatments in reducing seizure frequency and improving quality of life. Seven randomized controlled trials that were double-blinded, single-blinded or unblinded, and placebo, no treatment, or active controlled were included in the analysis. The total number of participants in the seven trials was 230. Two of the seven studies analyzed showed a statistically significant reduction in seizure rate from baseline (72% and 78.9% reduction of seizures per week from the baseline rate, respectively). The other five studies showed no statistically significant difference in seizure frequency following rTMS treatment compared with controls. The authors judged the quality of evidence for the primary outcomes of this review to be low. According to the authors, there is evidence that rTMS is safe and not associated with any adverse events, but given the variability in technique and outcome reporting that prevented meta-analysis, the evidence for efficacy of rTMS for seizure reduction is still lacking despite reasonable evidence that it is effective at reducing epileptiform discharges.

Soleimani et al. (2016) conducted a systematic literature review and meta-analysis on the effect of repetitive transcranial magnetic stimulation (rTMS) compared with sham in chronic tinnitus patients. For the meta-analysis weighted mean differences (and standard deviations) of Tinnitus Questionnaire (TQ) and Tinnitus Handicap Inventory (THI) scores were determined. Therapeutic success was defined as difference of at least 7 points in the THI score between baseline and the follow-up assessment after treatment. Results from 15 RCTs were analyzed. For THI, the data of mean difference score in two groups, 1 and 6 month after intervention, was 6.71 and 12.89, respectively. According to the authors, these data underscore the clinical effect of rTMS in the treatment of tinnitus. The authors reported that there is high variability of studies design and reported outcomes. Replication of data in multicenter trials with a large number of patients and long-term follow-up is needed before further conclusions can be drawn.

In a Cochrane review, Fang et al. (2013) evaluated the clinical efficacy and safety of rTMS for treating amyotrophic lateral sclerosis (ALS). Three randomized, placebo-controlled trials with a total of 50 participants were included in the review. All the trials were of poor methodological quality and were insufficiently homogeneous to allow the pooling of results. The authors concluded that there is currently insufficient evidence to draw conclusions about the efficacy and safety of rTMS in the treatment of ALS.

### **Randomized Controlled Trials and Other Technology Assessments**

Several randomized controlled trial and comparative studies with small patient populations evaluated whether TMS improves conditions such as the following:

- Stroke (Zheng et al., 2015, n=108; Chieffo et al., 2014, n=10; Kim et al., 2014, n=32)
- Alzheimer's disease (Eliasova et al., 2014, n=10; Ahmed et al., 2012, n=45; Rabey et al., 2013, n=15; Lee et al., 2016, n=26)
- Aphasic stroke (Du et al., 2016; Rubi-Fessen et al., 2015; Tsai et al., 2014, n=56; Barwood et al. 2011, n=12; Park et al., 2017, n=35)
- Cigarette consumption, dependence and craving (Dinur-Klein et al., 2014, n=115)
- Headaches (Rocha et al., 2015, n=19; Misra et al., 2013, n=50)
- Multiple sclerosis (Elzamarany et al., 2016, n=24)
- Parkinson's disease (Brys et al., 2016; Li et al., 2015b)

The limited data from these studies do not allow definitive conclusion regarding the possible benefits of TMS. Many of these studies were feasibility studies with methodological limitations including small patient populations and short-term follow-up. The findings of these studies need to be validated by randomized trials with larger patient numbers and long-term follow-up.

Other randomized trials have found that TMS may be not be as effective as or superior to placebo or that TMS has no significant effect on symptoms for various conditions (Seynaeve et al., 2016; Cincotta et al., 2015; de Oliveira et al., 2014; Benninger et al., 2012; Seniów et al., 2012; Shirota et al., 2013; Langguth et al., 2012; Plewnia et al., 2012; Wrigley et al., 2013; Conforto et al., 2014).

According to the National Institute for Health and Care Excellence (NICE) Guideline for transcranial magnetic stimulation for treating and preventing migraine (2014), evidence on the efficacy of TMS for the treatment of migraine

is limited in quantity and for the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate but there is uncertainty about the safety of long-term or frequent use of TMS. Therefore, according to NICE, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

In an Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review for the evaluation and treatment of tinnitus, the evidence was rated as insufficient for repetitive transcranial magnetic stimulation (Pichora-Fuller et al., 2013).

### **Professional Societies**

#### ***European Academy of Neurology (EAN)***

Cruccu et al. (2016) conducted a systematic review and meta-analysis of trials to update previous European Federation of Neurological Societies guidelines on neurostimulation for neuropathic pain. The GRADE system was used to assess quality of evidence and propose recommendations. Weak recommendations were given for the use of primary motor cortex (M1) rTMS in neuropathic pain and fibromyalgia and inconclusive recommendations were given regarding complex regional pain syndrome (CRPS). There were inconclusive recommendations regarding rTMS of the dorsolateral prefrontal cortex (DLPFC) in fibromyalgia and neuropathic pain.

#### ***European Headache Federation***

In a position statement for neuromodulation of chronic headaches, the European Headache Federation states that application of the noninvasive rTMS in chronic headaches is not yet evidence based, given the poor amount of controlled data (Martelletti et al. 2013).

#### ***American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)***

In a clinical practice guideline for tinnitus, the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) Guideline Development Panel indicated that clinicians should not recommend TMS for the treatment of patients with persistent, bothersome tinnitus (Tunkel et al., 2014).

### **Diagnostic Transcranial Magnetic Stimulation**

Takahashi et al. (2013) conducted a systematic review to evaluate spatial accuracy and clinical usefulness of navigated transcranial magnetic stimulation (nTMS) in brain tumor surgery in or near the motor cortex. A total of 11 studies that evaluated nTMS prior to surgery in adults were included in the review. Quality criteria consisted of documentation of the influence of nTMS brain mapping on clinical decision making in a standardized prospective manner and/or performance of intraoperative direct electrical stimulation (DES) and comparison with nTMS results. Cross-observational assessment of nTMS accuracy was established by calculating a weighted mean distance between nTMS and DES. All studies reviewed concluded that nTMS correlated well with the "gold standard" of DES. The mean distance between motor cortex identified on nTMS and DES by using the mean distance in 81 patients described in 6 quantitatively evaluated studies was 6.18 mm. The nTMS results changed the surgical strategy based on anatomical imaging alone in 25.3% of all patients, based on the data obtained in 87 patients in 2 studies. The authors conclude that the nTMS technique spatially correlates well with the gold standard of DES. Its functional information benefits surgical decision making and changes the treatment strategy in one-fourth of cases. The studies include in the review were limited by small sample sizes.

### **Primary Studies Not Included in the Systematic Review**

Hendrix et al. (2016) evaluated preoperative navigated transcranial magnetic stimulation (nTMS) in cortical motor eloquent lesions with emphasis on metastasis. A total of 61 patients underwent nTMS before undergoing surgery for a motor eloquent brain lesion. Thirty patients (49.2%) presented with a preoperative motor deficit. One week after surgery, paresis had resolved or improved in 56.7% of the patients. Out of the patients with postoperative paresis, 89.5% experienced an improvement of motor status at follow-up. All metastatic lesions were completely resected compared to 78.9% of non-metastatic lesions. Only 4.3% of patients with a metastatic lesion, but 26.3% of patients with a non-metastatic lesion experienced deterioration of motor function after surgery. The authors concluded that preoperative nTMS is suitable for mapping of a variety of motor eloquent brain lesions resulting in favorable neurological outcome. Particularly in metastatic motor eloquent lesion, motor function appears to be preserved after surgery. The findings of this study need to be validated with a randomized trial comparing navigated transcranial magnetic stimulation with the gold standard of direct cortical stimulation intraoperative mapping.

Sollmann et al. (2015) enrolled 25 patients with language eloquently located brain lesions undergoing preoperative rTMS language mapping (GROUP 1), with the mapping results not being available for the surgeon, and matched those patients with 25 subjects who also underwent preoperative rTMS (GROUP 2), but the mapping results were taken into account during tumor resection. Additionally, cortical language maps were generated by analyzing preoperative rTMS and intraoperative direct cortical stimulation (DCS) data. Mean anterior-posterior craniotomy extents and overall craniotomy sizes were significantly smaller for the patients in GROUP 2. Postoperative language deficits were found

significantly more frequently for the patients in GROUP 1, although the preoperative language status did not differ between groups. Additionally, there was a trend towards fewer unexpected tumor residuals, shorter surgery duration, less peri- or postoperative complications, shorter inpatient stay, and higher postoperative Karnofsky performance status scale for the patients in GROUP 2. According to the authors, this study provides a first hint that the clinical course of patients suffering from brain tumors might be improved by preoperative rTMS language mapping. However, a significant difference between both groups was only found for craniotomy extents and postoperative deficits, but not for other clinical parameters, which only showed a trend toward better results in GROUP 2. The authors indicated that multicenter trials with larger sample sizes are needed to further investigate the distinct impact of rTMS language mapping on the clinical course of brain tumor patients.

Krieg et al. (2015) prospectively enrolled 70 patients with supratentorial motor eloquently located high-grade glioma (HGG) undergoing preoperative nTMS and matched these patients with 70 HGG patients who did not undergo preoperative nTMS. On average, the overall size of the craniotomy was significantly smaller for nTMS patients when compared to the non-nTMS group. Furthermore, residual tumor tissue (nTMS: 34.3%; non-nTMS: 54.3%) and unexpected tumor residuals (nTMS: 15.7%; non-nTMS: 32.9%) were less frequent in nTMS patients. Regarding the further clinical course, median inpatient stay was 12 days for the nTMS and 14 days for the non-nTMS group. Sixty percent of patients of the nTMS group and 54.3% of patients of the non-nTMS group were eligible for postoperative chemotherapy, while 67.1% of nTMS patients and 48.6% of non-nTMS patients received radiotherapy. Moreover, 3, 6, and 9 months survival was significantly better in the nTMS group. The authors concluded that with the limitations of this study in mind, the data show that HGG patients might benefit from preoperative nTMS mapping. The lack of randomization was regarded by the authors as the major limitation of this study.

Frey et al. (2014) evaluated whether the use of navigated transcranial magnetic stimulation (nTMS) had an impact on treatment and outcome in patients with brain tumors in motor eloquent locations. The study included 250 consecutive patients and compared their functional and oncological outcomes to a matched pre-nTMS control group (n = 115). Navigated transcranial magnetic stimulation mapping results disproved suspected involvement of primary motor cortex in 25.1% of cases, expanded surgical indication in 14.8%, and led to planning of more extensive resection in 35.2% of cases and more restrictive resection in 3.5%. In comparison with the control group, the rate of gross total resections increased significantly from 42% to 59%. Progression-free-survival for low grade glioma was significantly better in the nTMS group at 22.4 months than in control group at 15.4 months. Integration of nTMS led to a nonsignificant change of postoperative deficits from 8.5% in the control group to 6.1% in the nTMS group. The authors concluded that TMS provides crucial data for preoperative planning and surgical resection of tumors involving essential motor areas. According to the authors, expanding surgical indications and extent of resection based on nTMS enables more patients to undergo surgery and might lead to better neurological outcomes and higher survival rates in brain tumor patients. The findings of this study need to be validated with a randomized trial comparing navigated transcranial magnetic stimulation with the gold standard of direct cortical stimulation intraoperative mapping.

In a prospective trial, Krieg et al. (2014) compared patients with motor eloquently located supratentorial lesions investigated with or without preoperative nTMS in terms of clinical outcome parameters. The trial included 100 patients with supratentorial lesions located in motor eloquent areas that was investigated by preoperative nTMS (2010-2013) and matched with a control of 100 patients who were operated on without nTMS data (2006-2010) by a matched pair analysis. Patients in the nTMS group showed a significantly lower rate of residual tumor on postoperative MRI. Twelve percent of patients in the nTMS and 1% of patients in the non-nTMS group improved while 75% and 81% of the nTMS and non-nTMS groups, respectively, remained unchanged and 13% and 18% of patients in the nTMS and non-nTMS groups, respectively, deteriorated in postoperative motor function on long-term follow-up. Moreover, the nTMS group showed smaller craniotomies. The authors concluded that this study increases the level of evidence for preoperative motor mapping by nTMS for rolandic lesions. The authors identify a need for a randomized trial comparing the gold standard of intraoperative mapping with navigated transcranial magnetic brain stimulation.

Picht et al. (2013) conducted a cohort study that compared the safety and effectiveness of preoperative nTMS with direct cortical stimulation (DCS) mapping during awake surgery for the identification of language areas in patients with left-sided cerebral lesions. Twenty patients with tumors in or close to left-sided language eloquent regions were examined by repetitive nTMS before surgery. During awake surgery, language-eloquent cortex was identified by DCS. nTMS results were compared for accuracy and reliability with regard to DCS by projecting both results into the cortical parcellation system. Presurgical nTMS maps showed an overall sensitivity of 90.2%, specificity of 23.8%, positive predictive value of 35.6%, and negative predictive value of 83.9% compared with DCS. For the anatomic Broca's area, the corresponding values were a sensitivity of 100%, specificity of 13.0%, positive predictive value of 56.5%, and negative predictive value of 100%, respectively. The authors concluded that good overall correlation between repetitive nTMS and DCS was observed. According to the authors, noninvasive inhibition mapping with nTMS is evolving as a valuable tool for preoperative mapping of language areas. The low specificity in posterior language areas in the current study necessitates further research to refine the methodology.



Tarapore et al. (2016) examined the safety and tolerability of nTMS in a large, multi-center cohort of neurosurgical patients. Functional mapping with monopulse and repetitive nTMS was performed in 733 patients. In this cohort, 57% of patients had left-sided tumors, 50% had frontal tumors, and 50% had seizures secondary to the lesion. Side effects and pain intensity related to the procedure were documented. Patients undergoing monopulse stimulation underwent an average of 490 pulses while those undergoing repetitive stimulation received an average of 2268 pulses. During monopulse stimulation, 5.1% reported discomfort, and 0.4% reported pain. During repetitive stimulation, 23.4% reported discomfort and 69.5% reported pain. No seizures or other adverse events were observed. The authors concluded that nTMS is safe and well-tolerated in neurosurgical patients. Clinicians should consider expanding nTMS to patients with frequent seizures, but more evaluation is necessary to evaluate this risk fully. Additional studies are needed to determine if nTMS improves patient outcomes.

There is limited information from the peer-reviewed published medical literature to conclude that navigated transcranial magnetic stimulation is an effective clinical diagnostic test. Randomized controlled studies with large populations are needed to evaluate how this test can reduce clinical diagnostic uncertainty or impact treatment planning.

## U.S. FOOD AND DRUG ADMINISTRATION (FDA)

On December 13, 2013, the Cerena™ Transcranial Magnetic Stimulator (TMS) (eNeura Therapeutics®) received FDA approval thru the de novo premarket review pathway, a regulatory pathway for low- to moderate-risk medical devices that are not substantially equivalent to an already legally marketed device. According to the FDA documents, the Cerena Transcranial Magnetic Stimulator is indicated for the acute treatment of pain associated with migraine headache with aura. See the following Websites for more information:

- [http://www.accessdata.fda.gov/cdrh\\_docs/pdf13/K130556.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf13/K130556.pdf). (Accessed November 13, 2017)
- [http://www.accessdata.fda.gov/cdrh\\_docs/reviews/K130556.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/K130556.pdf). (Accessed November 13, 2017)

For a complete list of approved products for transcranial magnetic stimulator for headache, see the following websites (use product code OKP):

- <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed November 13, 2017)
- <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm>. (Accessed November 13, 2017)

In 2009, the FDA approved the eXimia Navigated Brain Stimulation System (NBS) System (Nexstim) for use in pre-surgical planning for patients undergoing brain surgery. The NBS uses transcranial magnetic stimulation (TMS) guided by standard MR-image data, a non-invasive direct technique for functional mapping of the motor cortex. See the following Web Site for more information: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf9/K091457.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf9/K091457.pdf). (Accessed November 13, 2017)

The Navigated Brain Stimulation (NBS) System (Nexstim) received 510(k) clearance on May 22, 2012. See the following website for more information: [https://www.accessdata.fda.gov/cdrh\\_docs/pdf11/K112881.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf11/K112881.pdf). (Accessed November 13, 2017)

### **Additional Products**

Neuralie TMS device

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2018T0536K]

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#### POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
04/01/2018	<ul style="list-style-type: none"> <li>• Revised coverage rationale:               <ul style="list-style-type: none"> <li>○ Added language to indicate transcranial magnetic stimulation is unproven and/or not medically necessary for treating Alzheimer’s disease</li> <li>○ Replaced language indicating:                   <ul style="list-style-type: none"> <li>▪ “Transcranial magnetic stimulation is unproven <i>and</i> not medically necessary for treating all conditions including [those listed in the policy]” with “transcranial magnetic stimulation is unproven <i>and/or</i> not medically necessary for treating all <i>medical (i.e., non-behavioral)</i> conditions including <i>but not limited to</i> [those listed in the policy]”</li> <li>▪ “Navigated transcranial magnetic stimulation (nTMS) is unproven <i>and</i> not medically necessary for treatment planning or for diagnosing motor neuron diseases or neurological disorders” with “navigated transcranial magnetic stimulation (nTMS) is unproven <i>and/or</i> not medically necessary for treatment planning or for diagnosing motor neuron diseases or neurological disorders”</li> </ul> </li> </ul> </li> <li>• Updated list of applicable CPT codes:               <ul style="list-style-type: none"> <li>○ Added 64999</li> <li>○ Removed 95999</li> </ul> </li> <li>• Updated supporting information to reflect the most current clinical evidence, FDA information, and references</li> <li>• Archived previous policy version BEHAVIORAL 025.10 T2</li> </ul>