Molina Clinical Policy
Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for Essential Tremor: Policy No. 312

Last Approval: 2/9/2022
Next Review Due By: February 2023

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Essential tremor (ET) is the most prevalent adult-onset movement disorder and has been defined by the Tremor Task Force of the International Parkinson's and Movement Disorders Society (IPMDS) as an isolated tremor syndrome involving both upper limbs during action for a minimum time frame of 3 years, with or without tremor in other body segments (IPMDS, 2018). The underlying etiology of ET is unclear, but the disorder is considered to have a strong genetic component (Clark et al., 2018). While ET does not shorten life expectancy, it may affect quality of life, functional activities, mood, and socialization. Diagnosis is currently based on the clinical finding and family history. Laboratory and imaging studies are usually not required and there is no biomarker for ET. There is no known definitive cure for ET and goals of treatment include reduction in tremor severity and disability while improving quality of life (AANI, 2017). Pharmacotherapy is usually the first-line treatment and patients who do not respond to medications may be considered for surgical treatment (radiofrequency identification, stereotactic radiosurgery, gamma knife thalamotomy or deep brain stimulation). Pharmacological intervention for symptomatic and functional improvement of ET may include beta blockers (propranolol), anticonvulsants (primidone), benzodiazepines, gabapentin, and topiramate (AANI, 2017). Surgery or other invasive procedures are considered for patients with substantial disability who do not benefit from medication therapy (either due to inadequate response or if unable to tolerate adverse events). Surgical treatments options include thalamotomy with radiofrequency ablation and deep-brain stimulation (DBS); both effectively suppress tremor but require intracranial surgery. The current gold standard surgical treatment for medication-resistant ET is DBS.

Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive treatment for ET that combines a high intensity focused ultrasound beam that heats and destroys targeted tissue non-invasively and magnetic resonance imaging (MRI) which visualizes anatomy, and continuously monitors the tissue effect. The ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis while sparing the surrounding normal structures. MRgFUS has also been applied to uterine fibroids (leiomyomata), metastatic bone cancer, breast tumors, liver tumors and other tumor types.

Regulatory Status

In July 2016, the FDA granted premarket approval (PMA) of the ExAblate Neuro System for the treatment of ET in patients who have not responded to medication (β-blockers or anticonvulsant drugs). This PMA outlined required pending studies for the device, including investigational treatment with the ExAblate Neuro in 75 patients to be evaluated at 2-, 3-, 4- and 5-years post-operative. The best available published evidence to date on ExAblate Neuro for transcranial thalamotomy in patients with medically refractory ET includes the pivotal randomized, sham-controlled trial (Elias et al., 2016) and the feasibility trial (Elias et al., 2013).

FDA approval for MRgFUS treatment of ET was based on its pivotal study, a prospective, double-blind, randomized, sham-controlled trial (RCT) of MRgFUS to create a unilateral thalamic ablation for the treatment of ET. Elias et al. 2016 conducted a prospective, double-blind, randomized sham-controlled trial that evaluated MRgFUS for the treatment of ET. Seventy-six patients were randomized into 2 groups, MRgFUS thalamotomy (n=56) or sham treatment (n=20), and the criteria included moderate-to-severe ET which had not responded to at least 2 trials of medical therapies.

Mean score for hand tremor improved significantly from baseline in the treatment group (47%) compared with the sham group (0.1%) at 3 months. Change in mean functional improvement score from baseline differed significantly in the MRgFUS group (62%) compared with the sham group (3%) at 3 months. The Quality of Life in Essential Tremor Questionnaire (QUEST) scores also differed significantly in the treatment group compared with the sham group, with the largest improvements experienced in the psychosocial domain. The improvements in hand tremor score, functional improvement, and quality of life (QOL) were maintained at 12 months in the MRgFUS group. Side effects included sensory and gait disturbances. In conclusion, MRgFUS thalamotomy reduced hand tremor in patients with ET.

In an open-label pilot study, Elias et al. (2013) examined the use of transcranial MRI-guided focused ultrasound thalamotomy for the treatment of ET. Investigators used transcranial MRI-guided focused ultrasound to target the unilateral ventral intermediate nucleus of the thalamus in 15 patients with severe, medication-refractory ET. Safety data and the effectiveness of tremor suppression were measured using the Clinical Rating Scale for Tremor (CRST) to calculate the total score (ranging from 0 to 160), hand sub-score (primary outcome, ranging from 0 to 32), and disability sub-score (ranging from 0 to 32), with higher scores indicating worse tremor. Patients' perceptions of treatment effectiveness with the QUEST (ranging from 0 to 100 %, with higher scores indicating greater perceived disability) were recorded. Thermal ablation of the thalamic target occurred in all patients. Adverse effects of the procedure included transient sensory, cerebellar, motor, and speech abnormalities, with persistent paresthesias in 4 patients. Scores for hand tremor improved from 20.4 at baseline to 5.2 at 12 months. Total tremor scores improved from 54.9 to 24.3. Disability scores improved from 18.2 to 2.8. QOL scores improved from 37% to 11%. The authors concluded that ET improved in 15 patients treated with MRI-guided focused ultrasound thalamotomy; however, large RCTs are needed to evaluate the procedure's safety and effectiveness. Drawbacks of this study included: lack of a control group, comprehensive cognitive assessments were not performed; and it is possible that focused ultrasound thalamotomy resulted in cognitive impairment, and patients and researchers were all aware of treatments that were performed, which may have introduced bias in favor of reporting improvements in symptoms and QOL.

Informational, not addressed in this policy: The FDA approved the use of the ExAblate Model 4000 (Neuro) for the treatment of tremor-dominant Parkinson's disease with medication-refractory tremor through the PMA process On December 16, 2018. Patients must be at least age 30.

COVERAGE POLICY

MRgFUS **is considered experimental, investigational, and unproven** for the treatment of ET due to insufficient evidence in the peer-reviewed medical literature and the lack of evidence from well-designed RCTs establishing long-term safety, efficacy and effect on net health outcomes.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The available clinical data is primarily limited to case series and prospective and retrospective reviews and studies with small patient population, lack of controls and conflicting outcomes (Haray, et al., 2019; Ferreira, et al., 2019; Langford, at al., 2019). There is a lack of studies RCTs and meta-analyses in the published, peer-reviewed scientific literature to determine safety and effectiveness of this therapy compared to standard treatment (e.g., deep brain stimulation).

Agrawal et al. (2021) published a systematic review of 29 studies (N = 617) to analyze the efficacy and the safety profile of MRgFUS for ET. Studies that reported outcomes in patients with tremors secondary to any other causes, such as drug-induced tremor, trauma, psychogenic tremor, or co-morbid Parkinson disease and dystonia were excluded. Of the 29 studies, only one (Elias et al., 2016) was an RCT, the remaining were observational studies. Pre- and post- procedure changes in the CRST score, hand score, disability and quality of life scores were evaluated. A significant difference was observed in the pooled standard mean difference between pre- and post-operative total CRST score, hand score, and disability at 12 months. Ataxia was the most common postoperative complication. All

complications showed a decreasing trend over time. More than one third of patients developed sonication related complications, amongst which head pain and dizziness were the most common. No hemorrhage, seizure or trajectory related complications were reported. The authors noted that the limitation of this study is noted observational studies formed the majority basis for the analysis as there is only one clinical trial on the subject. The systematic review concluded that currently the MRgFUS procedure appears to be the procedure of choice for patients unable to tolerate an invasive procedure; however, for it to replace established surgical options like DBS, further research will be required to prove long-term clinical efficacy in both unilateral and bilateral procedures.

Chang et al. (2018) reported on the two-year results from 67 patients who participated in the open-label extension conducted by Elias et al. (2016). Because 9 patients from the original trial received additional treatment during the 2-year follow-up, they were excluded from the analysis. Follow-ups were conducted at 6, 12 and 24 months. Seventy patients were included in the analysis at the one-year follow-up, and 67 patients were analyzed at the two-year follow-up. Improvements in tremor and disability scores were maintained at the 2-year follow-up. Mean hand tremor score at baseline improved by 55% at 6 months, 53% at 12 months and 56% at 2 years. Similarly, the disability score at baseline improved by 64% at 6 months and the improvement was sustained at 1 year. At two years, mean score was 60%. Paresthesias and gait disturbances were the most common adverse effects at one year with no new complications at 2 years. The authors noted limitations included differences and discrepancies between these findings and the previous report specifically, the number of reported patients was different; 56 subjects in the previous report were compared to the 20 sham-treated patients, but here all 76 patients were analyzed. Latent or delayed complications do not develop after treatment. Tremor suppression after MRgFUS thalamotomy for ET is stably maintained at two years. Additional follow-up is needed to determine the incidence of recurrence and the efficacy of MRgFUS over the long-term.

Mohammed et al. (2018) conducted a systematic review and meta-analysis to analyze the overall outcomes and complications of MRgFUS in the treatment of ET. Patients with the diagnosis of ET who were treated with MRgFUS were included in the study. The change in the CRST score after treatment was analyzed. The improvement in disability was assessed with the QUEST score. Nine studies with 160 patients who had ET were included in the meta-analysis. Dizziness was the most common in-procedure complication, occurring in 45.5%, followed by nausea and vomiting in 26.85%. The review concluded thatthat MRgFUS improved CRST scores and QOL with a relatively low rate of complications. However, the review also noted that there was a high probability of bias due to study design, limited follow-up, small sample size, and a lack of comparative evidence evaluating MRgFUS and DBS.

Hayes published a Technology Assessment (HTA) that assessed the use of unilateral MRgFUS thalamotomy for the treatment of moderate-to-severe treatment-resistant ET (Hayes, 2019; updated 2021). The authors identified 5 eligible studies with patients who had moderate to severe medication-refractory ET. These studies compared MRgFUS to DBS, radiofrequency thalamotomy and sham treatment with follow-up ranging from 3 months to 4 years: DBS was compared in 2 studies (Huss et al., 2015; Kim et al., 2017), radiofrequency thalamotomy in 1 study (Kim et al., 2017), and sham treatment in 1 study (Elias et al., 2016). Follow-up periods ranged from 3 months to 4 years. Results suggest that unilateral MRgFUS thalamotomy may result in a statistically significant improvement in contralateral hand tremor; however, the clinical significance of this improvement has not been established. Additionally, MRgFUS did not result in improvements in axial tremors of the head, trunk, voice, or ipsilateral tremors. Substantial uncertainty arises from the individual study quality, inconsistency in the evidence, and lack of comparative evidence. The review concluded that a very-low-quality body of evidence is insufficient to draw conclusions regarding benefit (of the 5 eligible studies, 1 was fair quality, 1 was poor quality, and 3 were very poor quality). This quality rating is primarily due to the individual study quality, inconsistency in the evidence, and lack of comparative evidence.

National and Specialty Organizations

The **American Academy of Neurology** guideline for treatment of ET states that thalamotomy is possibly effective; there are no recommendations regarding MRgFUS for treatment of ET (AAN, 2017).

The **National Institute for Health and Care Excellence (NICE)** issued guidance on unilateral MRgFUS thalamotomy in treatment-resistant ET raises no major safety concerns but current evidence of efficacy was limited in quantity. The guideline recommends that this procedure should not be used unless there are special arrangements for clinical governance, consent, and audit or research. NICE suggests that future research include the identification of patient selection criteria and long-term follow-up data (NICE, 2018).

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

CPT Code

CPT	Description
0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed

HCPCS Codes – N/A

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

2/9/2022	Policy reviewed and updated, no changes in coverage position, updated references.
2/8/2021	Policy reviewed, no changes to criteria. Two new guidelines found at reference #5-6: American Society for Stereotactic and Functional Neurosurgeons (ASSFN) & Health Quality Ontario (HQO).
4/23/2020	Policy reviewed, no changes.
9/18/2019	Policy reviewed, no changes.
7/10/2018	New policy. IRO Peer Review 4/23/2018. Reviewed by practicing physician board-certified in Neurology.

REFERENCES

Government Agencies

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3. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). ExAblate 4000 Type 1.0 Neuro approval order. Available from FDA. Published July 2016.

Peer Reviewed Publications

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National and Specialty Organizations

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Evidence Based Reviews and Publications

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APPENDIX

Reserved for State specific information *(to be provided by the individual States, not Corporate). Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

Centers for Medicare & Medicaid (CMS)

According to LCD L37421 (effective 4/1/2018): MRgFUS is a promising new treatment approach that has attributes, positive and negative, distinct from both traditional thalamotomy and DBS. However, long-term effectiveness and safety remain uncertain and warrant a direct comparison with DBS, the current surgical standard. Widespread non-coverage

by both Medicare and commercial payers supports this interpretation. However, given the support for traditional thalamotomy, generally, as an alternative "if DBS is not available or practical", and the support for MRgFUS thalamotomy, specifically, as an alternative in patients "who are not a candidate for DBS" by the American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS) and the American Association of Stereotactic and Functional Neurosurgery (ASSFN), NGS considers MRgFUS reasonable and necessary in that context. Patient selection criteria will largely mirror those used in the pivotal study.

No CMS National Coverage Determination (NCD) was identified for MRgFUS thalamotomy for the treatment of essential tremor on April 2, 2019 (search National Coverage Documents by *magnetic resonance guided focused ultrasound*, *thalamotomy*, or *essential tremor* in all documents at: CMS Advanced Search Database). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carrier