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**SUBJECT: Support for Coverage for Magnetic Resonance Image Guided High Intensity
Focused Ultrasound (MRgFUS) for Essential Tremor (ET)**

Dear Drs. Patterson and Whites:

On behalf of the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS) and the American Society for Stereotactic and Functional Neurosurgery (ASSFN), we appreciate the opportunity to express our support for the recent formal reconsideration of the Novitas Local Coverage Decision (LCD) L35094 for Magnetic Resonance Image Guided High Intensity Focused Ultrasound (MRgFUS) for Essential Tremor (ET) submitted by the University of Pennsylvania Health System. We urge Novitas to reconsider its policy regarding this procedure and to begin the process of issuing a positive coverage policy for MRgFUS for the treatment of essential tremor (ET) patients with medication-refractory tremor.

As you will recall, on November 20, 2018, representatives of the AANS, the CNS and the ASSFN held a conference call with Dr. Whites, Vicki Kurkland and neurosurgeons from the University of Pennsylvania to discuss coverage by Novitas for MRgFUS for ET, reported with CPT Category III Code 0398T. Following that call, leaders of the ASSFN performed a thorough review of published literature on MRgFUS for ET and developed the attached position paper.

Novitas continues to be an outlier among other Medicare payors regarding coverage for this important procedure. Currently, five Medicare Administrative Contractors (MACs) provide coverage for MRgFUS. Neurosurgery has actively participated with several MACs to support coverage for MRgFUS for appropriately selected patients and provided guidance regarding details of their policies. We welcome the opportunity to share our expertise on this subject.

The AANS, the CNS and the ASSFN appreciate the opportunity to comment on this issue and to give our support for the University of Pennsylvania's request for reconsideration. We strongly recommend that

Novitas review the ASSFN position paper and remove MRgFUS from the non-coverage list.

Thank you for considering our comments.

Sincerely,



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Ganesh Rao, MD, President
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Robert Gross, MD, President
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Enclosure

- American Society for Stereotactic and Functional Neurosurgery
Position Paper: MR-guided Focused Ultrasound for the Management of Essential Tremor

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ASSFN Position Statement on

MR-guided Focused Ultrasound for the Management of Essential Tremor

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Executive Summary

Purpose of the Statement

1. To provide an evidence-based best practices summary to guide health care providers in the use of MR-guided Focused Ultrasound (MRgFUS) in the management of essential tremor (ET).
2. To establish expert consensus opinion and areas requiring additional investigation.

Importance of the ASSFN Statement

1. Stereotactic and functional neurosurgeons are involved in the care of patients with advanced, medically refractory essential tremor.
2. Stereotactic and functional neurosurgeons are domain-specific experts in the specialty literature and the practical use of stereotactic procedures for the management of essential tremor and other neuropsychiatric disorders.
3. Stereotactic and functional neurosurgeons are domain-specific experts in comparative assessment of benefits, risks, and alternatives of stereotactic procedures for the management of patients with essential tremor and other neuropsychiatric diagnoses.

Indications for the use of MRgFUS as a treatment option for patients with essential tremor include all of the following criteria:

1. Confirmed diagnosis of ET.
2. Failure to respond to, intolerance of, or medical contraindication to use of at least two medications for ET, one of which must be a first line medication.
3. Appendicular tremor that interferes with quality of life based on clinical history.
4. Unilateral treatment.

Contraindication to use of MRgFUS:

1. Bilateral MRgFUS thalamotomy.
2. Contralateral to a previous thalamotomy.
3. Cannot undergo MRI due to medical reasons.
4. Skull density ratio (ratio of cortical to cancellous bone) is <0.40 .

Recommendations are based on:

1. Safety and efficacy demonstrated in a single randomized, sham-surgery controlled double-blind clinical trial (RCT) and several uncontrolled clinical trials.
2. Dearth of direct comparative studies between different surgical treatment modalities and the unlikelihood that such comparative studies will be performed due to differences in indications, patient preference, and follow-up requirements.

Background and Supporting Literature

Prevalence and Impact of ET

Essential tremor (ET) is the most common movement disorder apart from restless leg syndrome.^{13,14,16} The prevalence of ET in the United States has been estimated to be between 0.3% and 5.55%. Although ET does not shorten life expectancy, it is progressive and disabling in the home and workplace, interfering significantly with quality of life (QoL), functional activities, mood, and socialization. ET can result in greater impairment than even Parkinson disease with respect to writing, eating, drinking, reading, social embarrassment, alcohol use, and concentration.¹⁵

Medical and Surgical Management of Essential Tremor

Management of ET is symptomatic rather than curative in intent. Treatment is only initiated when symptoms interfere with function or quality of life. First line treatment is pharmacotherapy,²¹ including propranolol and primidone, which are effective in up to 70% of patients.¹¹ Second line medical therapies (e.g., gabapentin, carbamazepine) are not as effective as first line medical therapies.²¹ Pharmacologic therapy can be limited by lack of efficacy, dose-limiting side effects, contraindication due to medical comorbidities (such as use of beta blockers in patients with chronic obstructive pulmonary disease), and occupational limitations.⁶ Surgical therapies are considered in the context of these limitations.

Prior to the advent of MRgFUS, surgical options included radiofrequency (i.e. open) thalamotomy, radiosurgical thalamotomy, and deep brain stimulation (DBS), all directed towards the ventral intermediate nucleus of the thalamus (VIM). Per the American Academy of Neurology Evidence Based Guideline on the treatment of essential tremor, while there was insufficient literature at the time of publication to support radiosurgical thalamotomy as a treatment option, open thalamotomy and DBS are both therapeutic options supported by the literature, but the decision to use either procedure should depend on “each patient’s circumstances and risk for intraoperative complications compared to feasibility of stimulator monitoring and adjustments.”²⁰

Efficacy of Magnetic Resonance-guided Focused Ultrasound (MRgFUS) Thalamotomy

MRgFUS combines high intensity focused ultrasound, which heats and destroys targeted tissue at the focal point of hundreds of ultrasound beams, with real-time MRI, which allows visualization of the ablation process using thermographic imaging superimposed on patient-specific anatomy.⁷ The combination of the focused ablative technology with real-time image guidance allows control by continuously monitoring the tissue temperature.² MRgFUS is an incisionless thermal ablation technique comparable to radiofrequency ablation, but avoiding the need for open brain surgery, i.e. a skin incision, a bone craniostomy (i.e. a twist drill hole), and physically traversing brain tissue on the trajectory towards the VIM with a radiofrequency probe (typically 1 – 2 mm in diameter).

The efficacy of MRgFUS is supported by several open label^{3,5,10,12,19} and a prospective double-blind sham-controlled randomized controlled trial (RCT). The RCT involved 3:1 randomization such that the MRgFUS group of 56 subjects was compared to 20 sham-operated subjects at three months following the intervention. Mean hand tremor scores improved by 47%, from a baseline of 18.1 ± 4.8 to 9.6 ± 5.1 , in the thalamotomy group, and by 0.1% in the sham-procedure group (from 16.0 ± 4.4 to 15.8 ± 4.9). As reported, the between-group difference in the mean change at three

months, which was the pre-specified primary efficacy end point, was 8.3 points (95% confidence interval [CI], 5.9 to 10.7; $P < 0.001$). Furthermore, in the open-label extension period, improvements were sustained at one year. Measuring solely the amplitude of the postural tremor, treated patients showed a 69% improvement. In addition, the overall Clinical Rating Scale for Tremor score (CRST) improved significantly ($p < 0.001$) in the thalamotomy group (41%) as compared to the sham group (2%) at three months, and was sustained in the open label 12 month time point (35%), despite the procedure having only been performed unilaterally. Importantly, disability scores (from the CRST) significantly improved in every category (including drinking and eating), as well as quality of life measures. The authors concluded that, compared to the sham control, MRgFUS thalamotomy significantly reduced hand tremor and disability in ET patients that had failed medical therapy.

Longevity of MRgFUS Thalamotomy Benefits

Chang et al. published two year open label follow up of 67 of the 76 subjects treated in the RCT of MRgFUS thalamotomy for tremor. Tremor scores improved by 53% at one year and by 56% at two years with similar sustained improvements in disability scores at one and two years.⁴ The authors concluded that tremor suppression after MRgFUS thalamotomy for ET is stably maintained at two years and that latent or delayed complications do not develop after treatment. Chang and colleagues subsequently published four year follow-up in 12 of 15 patients who were treated at their center as part of the MRgFUS thalamotomy RCT.¹⁷ At four years, the authors reported hand tremor improvement of 56% (similar to that reported at two years) and sustained improvement in disability (63%), postural tremor (70%), and action tremor scores (63%). All improvements were statistically significant compared to baseline scores.

Safety of MRgFUS Thalamotomy

In the RCT, early adverse effects, particularly gait disturbance and paresthesias, were not uncommon (36% and 38%, respectively). By one year after treatment, these were reduced to 9 and 14%, respectively. While these side effects were assumed to be permanent at one year, most were mild or moderate in severity and only one was classified as a serious adverse event (SAE). Fishman and colleagues performed a comprehensive review of complications across five studies using MRgFUS thalamotomy for tremor, concluding that SAEs were rare (1.6%). SAEs were deemed treatment-related in some cases (paresthesias, peri-procedural myocardial infarction) and unrelated in several other cases (e.g., remote embolic stroke). The vast majority of adverse events related to the procedure were mild or moderate (98.4%), with more than 50% resolved by one year. No incidents of hemorrhage or infection were noted (as may be seen with open surgical procedures). As expected there were none of the significant events associated with more invasive treatments (e.g. hemorrhage, infection, etc.). Based on this safety profile, the authors concluded that MRgFUS should be a treatment option for patients with ET.

On two year follow-up of the RCT reported by Chang and colleagues, of the 10 patients with gait disturbance or paresthesias and an additional five patients with neurological adverse events (out of a total of 76 patients), two had symptoms of adverse events resolve by two years after treatment,⁴ and there were no incidents of worsening. On four year follow-up, Chang and colleagues reported resolution of all adverse effects seen in the 12 patients in whom they had sufficient follow-up (out of 15 total patients treated).¹⁷

Given differences in ablative margins and techniques,⁸ it is important to note that the adverse event profile of open radiofrequency thalamotomy cannot be extrapolated to MRgFUS, as complications are inherently related to the technique employed. This difference is highlighted by a comparative effectiveness analysis reported by Kim and colleagues,¹⁰ in which the complication rate of MRgFUS thalamotomy at one year (4.4%) was significantly lower than that observed after radiofrequency open thalamotomy (11.8%) as well as DBS (21.1%).

Indications for MRgFUS Thalamotomy for Tremor

Treatment for tremor, whether pharmacologic or surgical, should be utilized when tremor interferes with quality of life and daily function.²¹ Surgical therapies should be considered when medical therapies are limited by lack of efficacy at maximum doses, dose-limited side effects, or contraindications due to medical comorbidities or occupational restrictions.

In the MRgFUS thalamotomy RCT, disability was defined as a score of two or above in any of the disability subsections of the Clinical Rating Scale for Tremor (CRST) assessment. This is similar to the criteria delineated for DBS coverage.¹ In contrast, the practice parameters published by the American Academy of Neurology do not identify a specific disability threshold for initiating therapy. Likewise, in regular practice, the decision to initiate therapy is based on patient-specific history and assessment of resulting disability.¹⁸ The assessment of disability captured in eight questions of the CRST may not reflect real-world contemporary needs and sources of disability (e.g., questions about writing). Patient endorsement of interference with other ADLs or functions in a moderate to severe manner is considered acceptable for consideration of treatment when documented adequately in the medical record. Of note, disability may arise for significant tremor in either the dominant or non-dominant hand, therefore treatment need not be limited to the dominant hand. Therefore, in practice, indication for treatment should be based on clinical history confirming appendicular tremor that interferes with quality of life.

Considerations of Relative Effectiveness of MRgFUS Thalamotomy

The current literature supports the efficacy, safety, and longevity of MRgFUS. However, there are no studies to support the superiority or inferiority of MRgFUS with respect to other surgical therapies, as there have been no comparative trials. As with other fields of medicine, when there is clinical equipoise, medical and social/demographic considerations as well as, importantly, patient preference should be considered to honor health care autonomy.

- With respect to DBS, there are various reasons why patients may have indications for surgical treatment but not be appropriate candidates to undergo DBS, including: not being a good candidate to have a permanent implant (e.g. history of infection(s)) with DBS; scalp lesions or thin scalp increasing risk of erosion); not being able to travel to a center for usual and frequent programming visits; occupational limitations precluding having a metallic implants; and not willing to undergo either frequent surgery to replace the neurostimulator or frequent recharging of rechargeable devices. All of these factors may limit access to deep brain stimulation therapy for many patients.
- There are reasons why patients may not wish to undergo radiofrequency thalamotomy, including potentially increased risk of hemorrhagic complications, and not wishing to undergo open surgery including twist drill craniostomy (which is often done awake).

Accordingly, it has been concluded that - even in patients who are eligible for open surgical procedures - MRgFUS could also be considered one of several surgical options.⁹ This is consistent with the design of the RCT which did not require prior treatment (or consideration of treatment) with DBS prior to participation.

Patients who should not be considered for MRgFUS thalamotomy include those in whom MRI is contraindicated or in whom the skull density ratio (ratio of cortical to cancellous bone) is <0.40. In addition, MRgFUS is not presently indicated for bilateral treatment or contralateral to a previous thalamotomy done by any technique. Finally, at this time there is insufficient data to support the use of MRgFUS thalamotomy for a primary indication of head, voice, and neck tremor.

Future investigations

The following areas are identified as areas for further investigation to further refine use of MRgFUS thalamotomy and counseling of patients regarding risks, benefits, and alternatives. Long term follow-up studies should continue to be pursued in larger cohorts of subjects. Investigations into precise targeting and dosing as well as temperature limits and correlations with outcomes should be evaluated. We specifically acknowledge that head-to-head comparisons of MRgFUS thalamotomy and DBS are unlikely given patient preferences for each modality and the differences with respect to surgical invasiveness which will make it impossible to enroll sufficiently to compare these modalities. Such comparative trials are unprecedented in the approval process or coverage decisions for other surgical treatments to treat tremor.

Conclusion

MRgFUS is an effective and safe treatment option for medically refractory ET. Indications and preferences for this treatment modality are distinct from that for DBS. Accordingly, prospective comparative analyses are unlikely to support superiority of one therapy vs another. Rather, MRgFUS should be considered a treatment option for those who can provide informed consent, who understand the benefits, risks, and alternatives, in whom tremor results in significant functional impairments based on clinical history, and in whom treatment of unilateral tremor (whether dominant or non-dominant hand) is anticipated to result in significant functional improvement. Such therapies should be managed by physicians with expertise in functional and stereotactic neurosurgery, who are specifically experienced in working with and qualified to surgically manage patients with medically refractory essential tremor. Practitioners should also have received specific training in MRgFUS before performing the procedure. This procedure is an important addition to the treatment armamentarium of patients with essential tremor in the treatment of essential tremor.

This document reflects current expert consensus opinion from the ASSFN based on literature and input of key opinion leaders at the time of manuscript preparation. Publication and accumulation of additional experience may change these positions.

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