Medical Policy

Subject:	MRI Guided High Intensity Focused Ultrasound Ablation for Non-Oncologic Indications		
Document #:	MED.00057	**Publish Date:**	04/13/2022
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Description/Scope

This document addresses magnetic resonance imaging (MRI) guided high intensity focused ultrasound (HIFU) ablation, also known as magnetic resonance guided focused ultrasound (MRgFUS), when used to treat any non-oncologic indications, including but not limited to uterine fibroids, essential tremor (ET), or benign prostatic hyperplasia (BPH). The ultrasound beam penetrates through the soft tissues and can be focused to targeted sites, using MR for guidance and monitoring.

Note: Please see the following related documents for additional information:

- CG-MED-81 Ultrasound Ablation for Oncologic Indications
- CG-SURG-28 Transcatheter Uterine Artery Embolization
- CG-SURG-91 Minimally Invasive Ablative Procedures for Epilepsy
- SURG.00026 Deep Brain, Cortical, and Cerebellar Stimulation

Position Statement

Investigational and Not Medically Necessary:

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B. Include a list of other state Medicaid agencies and private insurers who cover the service
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D. Include known risks of the service and health outcomes of others who have received it
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G. Include the recipient's health history
H. Include the disease information necessitating the requested service
I. Include a rationale for the immediacy of the review

Additional required information

A. Submit the rationale used to preliminarily indicate the service is experimental/investigational
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MRI guided high intensity focused ultrasound ablation is considered **investigational and not medically necessary** for all non-oncologic indications, including but not limited to benign prostatic hyperplasia, essential tremor, and uterine fibroids.

Rationale

BPH

HIFU ablation is a minimally invasive procedure using a transrectal ultrasound probe to image the prostate and deliver timed bursts of heat to create coagulation necrosis in a targeted area without harming adjacent healthy tissue (Leslie, 2006). Schatzl and colleagues (2000) compared the efficacy of transurethral resection of the prostate (TURP) to four less invasive treatment options including HIFU in a small clinical trial. Randomization was attempted but could not be carried out because treatment options for each participant were limited based on specific characteristics such as prostate size, prostatic calcifications and middle lobes. The individuals who received HIFU tended to have smaller prostates and less severe symptoms than those who received TURP. A second study reported by Madersbacher and colleagues (2000) attempted to determine the long-term outcome after HIFU therapy for individuals with lower urinary tract symptoms (LUTS) due to BPH. The data collected between June 1992 and March 1995 indicated that HIFU therapy for BPH, at least in its present form, did not "stand the test of time," as 43.8% of individuals had to undergo TURP within 4 years after initial therapy. Additional long-term studies are warranted to reliably assess the role of HIFU as an established alternative to standard treatments for BPH. In recent years, few trials evaluating the use of HIFU in BPH have been published.

Essential Tremor (ET)

In July 2016, the U.S. Food and Drug Administration (FDA) approved the ExAblate Neuro® system (InSightec, Inc., Dallas, TX) as a treatment of idiopathic ET in individuals whose tremor has failed pharmacological

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treatment. ExAblate Neuro is used as a unilateral thalamotomy procedure, when the ventralis intermedius has been identified and is accessible for ablation by the device. The intent of treatment is to reduce an individual's ET and increase motor function.

Elias and colleagues (2013) reported on the results of a feasibility trial for the ExAblate Neuro unilateral transcranial MRI-guided focused ultrasound thalamotomy to treat medication-refractory ET. In this uncontrolled pilot study, 15 individuals with severe medication-refractory ET underwent a single treatment session using the ExAblate Neuro system. Assessments were performed at baseline, 1 day, 1 week, 1 month, 3 months and 12 months following treatment, with the change in hand tremor score at 3 months being the primary clinical outcome. Hand tremor was scored using a summation of eight items which graded hand tremor and ability to perform tasks. Higher scores denoted more severe tremor, and the maximum score was 32. There was significant improvement in contralateral hand tremor from baseline (20.4 ± 5.2 to 4.3 ± 3.5 and 5.2 ± 4.8; p=0.001) at 3 months and 12 months respectively. However, no significant difference in ipsilateral hand tremor scores from baseline to 12 months was reported (13.4 ± 5.2 to 13.5 ± 6.3, p=0.90). Paresthesias of the face or fingers were the most common reported side effects, with 4 individuals reporting persistent paresthesias. While this prospective, unblinded study reported positive findings, this study was small and did not include a comparison group. In addition, the authors noted that the possibility of the treatment causing cognitive impairment was not addressed and subsequent trials should include comprehensive cognitive assessments.

Subsequent to the above pilot study, Elias and colleagues (2016) published the results of a prospective, sham-controlled, double-blind, randomized trial of 76 participants, which evaluated MRI-guided focused ultrasound thalamotomy treatment of moderate to severe medication-refractory ET. Participants were assigned in a 3:1 ratio to undergo either the active treatment, MRI-guided focused ultrasound thalamotomy, or sham treatment. Following evaluation of the primary endpoint at 3 months, the individuals in the sham group could cross over to the active treatment group. The change in hand tremor scores from baseline to 3 months was defined as the primary efficacy outcome measure. The hand tremor score was based upon components of the Clinical Rating Scale for Tremor (CRST) related to hand tremor, with higher scores indicating more severe tremor. At 3 months,

the mean score in the contralateral hand in the active treatment group improved by 47% compared to the sham group mean score improvement of 0.1% (18.1 ± 4.8 to 9.6 ± 5.1 versus 16.0 ± 4.4 to 15.8 ± 4.9; between group change 8.3 points; 95% confidence interval [CI], 5.9-10.7; p=0.001). At 12 months, the significant improvement over baseline persisted. There was no significant change in the tremor score in the ipsilateral hand compared to baseline. The results were similar in the sham crossover group; 19 participants who crossed over to active treatment reported a significant improvement in contralateral hand tremor at 3 and 6 months respectively (16.5 ± 4.2 to 7.4 ± 3.9; p<0.001 and 16.5 ± 4.2 to 8.0 ± 3.9, p<0.001). There were several limitations associated with this study. While the study was blinded, 95% of individuals in the active treatment group and 80% of individuals in the sham group correctly identified their assignment immediately following the procedure. There was no comparison of this treatment to the standard surgical therapy, deep brain stimulation (DBS). Participants were only followed for 12 months following treatment. The authors note that while this study supports that MRI-guided focused ultrasound thalamotomy can reduce tremor and improve quality of life when performed in a controlled clinical trial, results may differ when practiced in the clinical setting. Lastly, 74 neurological adverse events occurred in 56 individuals who underwent active treatment, including 38% with sensory alteration and 36% with cerebellar deficits such as dysmetria and ataxia and other gait disturbance, which persisted to 12 months at 14% and 9%, respectively. The authors noted that although this is a non-invasive procedure, it does induce a thalamic lesion and permanent neurological deficits can result.

Louis (2016) noted several concerns about the Elias pivotal study. In the active treatment group, the hand tremor group score increased at 1, 3, 6 and 12 months (8.84, 9.55, 10.13, and 10.89 respectively) resulting in an overall increase of 23% from 1 to 12 months. Secondary outcomes reported similar or greater increases. The author noted that it is not clear if this is due to a disease progression or tolerance. While a loss of efficacy is also reported in the current standard surgical intervention, DBS, DBS allows for adjustments and can be removed while MRI-guided focused ultrasound thalamotomy creates a fixed brain lesion. The author also notes that large improvements were not seen in all participants, 16% (9/56) showed less than a 20% change in tremor. Further studies should be focused on examining which individuals are likely to benefit from MRgFUS.

In an initial pilot investigation, Bond and associates (2017) evaluated the safety and efficacy of focused ultrasound thalamotomy for the treatment of medically refractory, tremor-dominant Parkinson disease (TDPD). Like ET, medically refractory TDPD can be treated with DBS or thalamic lesioning. In a double-blind, sham-controlled, pilot randomized controlled trial (RCT), 27 individuals were treated with focused ultrasound (FUS) thalamotomy (n=20) or sham procedure (n=7). After 3 months, individuals in the sham procedure group were offered open-label treatment and 6 individuals underwent FUS thalamotomy. The primary outcome was the change from baseline to 3 months in the treated upper limb tremor subscore. Hand tremor improved 62% (interquartile range [IQR] 22%-79%) from a baseline of 17 points (IQR 10.5-27.5) following FUS thalamotomy and 22% (IQR −11% to 29%) from a baseline of 23 points (IQR 14-27) after sham procedures (p=0.04). Adverse events occurred in approximately 35% of all individuals treated and included finger paresthesia, ataxia, and orofacial paresthesia. At 1 year, in those individuals in the initial treatment group that were available for evaluation (14/30), 13 individuals reported a positive outcome. While this initial pilot study reported positive results, this was a small study which did not reach its planned enrollment size and lost a significant portion of the treatment group at 1-year follow-up. In addition, the authors noted a potential confounder in allowing medication dose changes during the trial. Larger trials comparing FUS thalamotomy to standard treatment with longer follow-up are needed.

Several follow-up studies have evaluated durability of MRI-guided focused ultrasound thalamotomy 2 to 3 years following treatment. Chang and colleagues (2018) reported on the 2-year follow-up outcomes of the Elias 2016 RCT. The mean hand tremor score initially improved by 55% (from 19.8 ± 4.9 at baseline to 8.6 ± 4.5) at 6 months post procedure. At 2 years, the mean hand tremor motor score was improved by 56% over baseline (8.8 ± 5.0; change in the score from baseline to 2 years, 11 points). At 3 years post-procedure, Halpern and colleagues (2019) evaluated outcomes of this same group. The median hand tremor motor score was stable at 56% improvement over baseline (median score of 8). In a retrospective review, Meng and associates (2018) assessed the 2-year outcomes of 37 individuals who underwent unilateral MRgFUS thalamotomy to treat moderate to severe medically refractory ET. A 42.4% (95% CI, 32.0%-52.9%) improvement in the baseline dominant tremor score (20.3 ± 5.0) was maintained at 2 years (43.4%: 95% CI: 27.8%-59.0%). At 1 year post-treatment, 45.7% of the individuals had significant tremor improvement; this had decreased to 35.3% at 2 years (Halpern (2019).

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These follow-up studies report substantial drop-out rates, introducing an element of potential bias into the results. Additional studies with follow-up from 3 to 5 years post-procedure report sustained improvement from baseline, but are limited by the small number of participants and a substantial drop-out rate (Halpern, 2019; Park, 2019; Sinai, 2019)

In an industry sponsored, prospective feasibility study (Krishna, 2019), 10 individuals with medically refractory ET were treated using focused unilateral ultrasound thalamotomy. The purpose of the study was to investigate whether tractography-based targeting of the ventral intermediate nucleus (VIM) could improve the accuracy of lesion localization and minimize side effects. The study does not describe selection criteria for the 10 participants who were followed for 3 months. At 3 months, there was a 56% improvement in hand tremor scores on the treated side, and 45% in total tremor score. At 6 months, total tremor score improvement was maintained in 9 individuals. The authors did not report on the 6-month hand tremor score. This study was limited by its small size, short duration, failure to identify selection criteria, and lack of comparison to more established surgical ET treatments.

The International Parkinson and Movement Disorder Society published an evidence-based review of ET treatments (Ferreira 2019). The task force noted that unilateral MRgFUS thalamotomy is "likely efficacious*"* (evidence suggests, but is not sufficient to show, that the intervention has a positive effect on studied outcomes). The task force concluded that unilateral MRgFUS thalamotomy is "possibly useful" for clinical practice. The society's recommendation is based on the Elias (2016) RCT.

Altinel and colleagues (2019) conducted a systematic review and meta-analysis comparing lesion surgery to DBS to treat tremor related to Parkinson Disease, ET or multiple sclerosis. While the analysis included 15 randomized studies, only 2 studies used MRgFUS to create the lesion. The duration of follow-up in both studies was limited to 3 months. A separate analysis found no difference in tremor severity improvement between MRgFUS, DBS and other types of lesion surgery. Over the short-term 3-month follow-up period, MRgFUS was associated with higher QOL scores than DBS. This analysis was limited by heterogeneity (tremor etiology, type of lesion surgery), limited follow-up times and lack of direct comparison groups.

In 2018, Schreglmann and associates evaluated efficacy and the prevalence of persistent side effects of different lesioning techniques in the treatment of ET, Parkinson's disease, dystonic tremor, multiple sclerosis or lesions to the midbrain or cerebellar structures. ET was treated with MRgFUS, Gamma Knife or radiofrequency in 6 retrospective and 7 prospective studies. The primary outcome was the change in upper limb tremor severity from baseline to follow-up, with the selected follow-up time-point as the point with the largest number of individuals retained. As the follow-up times varied, the authors controlled for an effect on follow-up duration on the effect size. The authors reported that the duration of follow-up did not have a significant influence on treatment effect size. There were no significant differences over the studied time periods with regard to the mean effect on tremor severity or the rate of persistent side effects. The authors concluded that head-to-head comparisons between DBS and MRgFUS are needed to further evaluate tremor treatment and noted:

> Nevertheless, this systematic review also shows how limited the evidence base is in particular for MRIgFUS ablation so far. It therefore highlights the need for adequately designed prospective trials to support the existing data on safety and efficacy for established targets such as V.im. and of recently rediscovered targets within the PSA. Before that, the indiscriminate application of incisionless interventions to novel indications could potentially harm the further development of this fascinating technique.

In 2020, Giordano and associates published a systematic review comparing unilateral MRgFUS thalamotomy to unilateral and bilateral DBS. Studies reporting on the treatment of drug-refractory ET using DBS (n=37) or MRgFUS (n=7) were included. The authors found no prospective randomized studies comparing MRgFUS to DBS. A total of 1202 individuals were included in this study's DBS group and 477 individuals were included in the MRgFUS group. At 14.4-16.6 months follow-up, the improvement in quality of life was significantly greater in the MRgFUS group (61.9%) compared to the DBS group (52.5%). During that follow-up period, there was a significantly higher improvement in tremor severity in the DBS group (60.1%) compared to the MRgFUS group (55.6%). While a subgroup analysis showed no differences in tremor severity between unilateral DBS therapy and

MRgFUS therapy, bilateral DBS therapy was superior to both unilateral treatments. The authors asserted that bilateral DBS is the current gold standard treatment for medication-resistant ET. Bilateral staged MRgFUS thalamotomy is currently undergoing feasibility testing. MRgFUS and DBS have different complication patterns. MRgFUS is associated with a higher prevalence of gait disturbances/muscle problems, nausea and paresthesias. DBS is associated with a higher prevalence of speech disturbances and local adverse symptoms. Persistent complications are more frequent with MRgFUS than with DBS therapy. This may be due to permanent tissue destruction induced by MRgFUS compared to DBS which can be reprogrammed or turned off. This analysis was limited by heterogeneity within the studies and a lack of prospective, randomized studies directly comparing the techniques. The authors conclude that "further randomised prospective clinical trials are needed on this topic to reach definitive conclusions."

Miller and colleagues (2022) reported on the prevalence of worsening tremor over time following MRgFUS treatment of ET. This is the phenomenon noted above in Louis's analysis of the pivotal trial published by Elliot et al. Miller's meta-analysis included 17 prospective studies, 3 retrospective studies and 1 RCT. Tremor was evaluated using hand tremor scores (HTS), CRST scores, or Quality of Life in Essential Tremor Questionnaire (QUEST) using pool reported effects. The analysis showed ongoing treatment benefit but decreasing treatment effect from 3 to12 months and 24 months following treatment. The authors noted that this diminishing effect might be due to heterogeneity within the studies, disease progression, or a true waning effect over time. No studies described head-to-head comparisons of DBS and MRgFUS. This type of direct comparison is needed to fully understand how their effects may differ. Limitations with this meta-analysis include data heterogeneity, potential overlapping participant cohorts and the limited length of follow-up.

Individuals who are not candidates for surgery

Bilateral DBS may be contraindicated in some individuals due to poor health status or surgical contraindications such as anticoagulation treatment that cannot be temporarily withdrawn (Health Quality Ontario, 2018; Miller, 2022; Yuen, 2017; Welton, 2021). Evidence evaluating clinical outcomes of MRgFUS thalamotomy in these

individuals is lacking. Studies evaluating MRgFUS treatment for ET have excluded individuals with compromising conditions such as unstable cardiac conditions, coagulopathy, the presence of or risk factors for deep-vein thrombosis, or a neurodegenerative condition (Elias, 2013; Elias, 2016; Iacopino, 2018; Lipsman, 2013). Contraindications for DBS or stereotactic radiosurgery may also be contraindications for MRgFUS. The label for the ExAblate Neuro MRgFUS device includes the following contraindications for use:

- Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, allergies to MR contrast agent etc.
- Women who are pregnant.
- Patients with advanced kidney disease or on dialysis.
- Subjects with unstable cardiac status or severe hypertension.
- Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse.
- History of abnormal bleeding, hemorrhage, and/or coagulopathy.
- Subjects receiving anticoagulants or drugs known to increase risk or hemorrhage within one month of focused ultrasound procedure.
- Subjects with cerebrovascular disease.
- Subjects with brain tumors.
- Individuals who are not able or unwilling to tolerate the required prolonged stationary position during treatment (approximately 2 hours).
- Subjects who have an Overall Skull Density Ratio of 0.45 (± 0.05) or less as calculated from the screening CT.

There is currently insufficient evidence to guide surgical treatment choices for individuals with medically refractory ET who are not candidates for DBS or stereotactic radiosurgery.

Summary

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Radiofrequency or stereotactic radiosurgery thalamotomy (Gamma Knife) or DBS remain the standard treatments for medically refractory ET. While the initial results are encouraging, there is a need for further research directly comparing MRgFUS with the standard therapies for the treatment of ET. Future studies should be designed to overcome the current shortcomings of small sample sizes, short-term follow-up and use of non-validated clinical scales (Ferreira, 2019; Harary, 2019). Studies with long-term follow-up are needed to compare QOL for DBS and for MRgFUS beyond the surgical recovery period. Further evidence is also needed to determine appropriate treatment choices for individuals who cannot undergo standard surgical procedures for medically refractory ET.

Uterine Fibroids

Stewart and colleagues (2003) studied the safety and feasibility of MR-guided HIFU (referred to as focused ultrasound surgery [FUS] in this study) in a case series of 55 women with symptomatic uterine fibroids who underwent HIFU treatment and, in some cases, a planned hysterectomy within 1 month after the ultrasound treatment (n=28). In the latter group, hysterectomy specimens provided pathologic evidence of accurate levels of thermal energy delivered and revealed 3 times the volume of necrotic fibroid tissue than was targeted for treatment. Reported side effects related to HIFU were minimal. Authors concluded that "…correlation of both treatment and patient parameters with the surrogate endpoint of post-FUS MRI and, ultimately, symptom reduction will be necessary in future studies to optimize therapy for individual women."

In the study designed for FDA approval of the ExAblate® 2000 (InSightec, Ltd, Dallas, TX), Stewart and colleagues studied 109 women treated with MR-guided HIFU and 83 women treated with abdominal hysterectomy. The initial article published in 2004 and the follow-up article published in 2006, only reported the outcomes for the group treated with HIFU. The study's primary outcome was change in the symptom severity score (SSS) that is part of the validated Uterine Fibroid Symptom Quality of Life Questionnaire (UFS-QOL). Symptom severity was measured on a 0 (less severe) to 100 (most severe) scale with eight questions relevant to bulk and bleeding symptoms. At the 6-month follow-up, 71% of the HIFU group achieved a 10-point or greater reduction in SSS which decreased to 51% at 12 months. It was unclear what value represented a clinically

meaningful change in SSS. Furthermore, 21% of those treated by HIFU needed additional surgical treatment, and 4% underwent a repeat MRI guided HIFU within 12 months of the first treatment.

Stewart and colleagues (2007) published results from three phase III trials and one post-marketing study. A total of 416 women were enrolled who received HIFU. Quality of life outcomes, measured again by the SSS of the UFS-QOL, were assessed for 359 women who were available at the 24-month follow-up. Clinical endpoints of the trials included uterine shrinkage, the need for additional fibroid treatment and the time to additional fibroid treatment. The study found a relationship between the non-perfused volume ratio and the probability of undergoing additional fibroid treatment. There was significantly greater improvement in women who had a more complete ablation; however, for women with minimal ablation, the need for additional treatment/procedures was high.

Fennessy and colleagues (2007) evaluated MR-guided HIFU using different treatment protocols. Results from nonrandomized, consecutive participants treated with the original protocol (33% of fibroid volume with a maximum treatment time of 120 minutes, n=96) were compared to a modified protocol (50% treatment volume, 180-minute maximum treatment time, and a second treatment if within a 14-day period, n=64). In the original protocol group, the non-perfused (effectively treated) area was calculated at 17% of fibroid volume compared with 26% of fibroid volume with the modified protocol group. Overall, symptom severity was reported to have decreased from a score of 62 at baseline to 33 at 12 months, with fewer participants in the modified group choosing alternative treatment (28% versus 37%). Out of the 160 participants initially treated, 55 from the original treatment protocol and 21 from the modified protocol group were evaluated at the 12-month follow-up.

In 2009, Taran and colleagues reported outcomes for the hysterectomy group in the 2006 Stewart study. The Taran article did not use the original primary outcome measure (SSS scores) and instead reported findings using the SF-36 quality of life measure as well as safety data. A significantly higher proportion of women in the hysterectomy group (82 of 83, 99%) reported at least one adverse event compared to women in the MR-guided HIFU group (88 of 109, 81%). Pain or discomfort, adverse events associated with the gastrointestinal tract,

dermatological system, nervous system, and cardiovascular system were significantly more common in the hysterectomy group. However, a similar proportion reported a serious adverse event, 9 of 109 (8%) in the HIFU group and 8 of 83 (10%) in the hysterectomy group. The authors concluded that the results of their study showed that HIFU treatment of uterine fibroids leads to clinical improvement with fewer significant clinical complications and adverse events compared to hysterectomy during the 6-month follow-up period. The authors did acknowledge important limitations of the study--factors that were consistent with more severe disease. The women undergoing hysterectomy had increased body mass index (BMI), were less likely to be Caucasian, had higher symptom severity scores and had an increased use of medication for fibroid-related symptoms. They also pointed out the possibility of potential data collection bias between the novel-treatment group and the control group. Although this study proposes HIFU as a treatment alternative to hysterectomy for symptomatic fibroids, it did not demonstrate clinical efficacy when compared to the current accepted treatments of uterine fibroids.

Kim and colleagues (2011) reported a 3-year follow-up on a prospective study of 40 women with symptomatic fibroids. A total of 51 fibroids were treated with MR-guided HIFU. Clinical assessments were obtained at 3 months, 6 months, and 1, 2, and 3 years after HIFU treatment, as well as the SSS from the UFS-QOL. An MRI was performed at each follow-up to assess the efficacy of the treatment at 6 months, 1 year, 2 years, and 3 years. The mean baseline volume of treated fibroids was 336.9 cm^3. The mean improvement scores for transformed SSS was 47.8 ($p<0.001$) and for transformed UFS-QOL was 39.8 ($p<0.001$) at 3 years. The mean volume decrease in treated fibroids was 32.0% ($p<0.001$) and in the uterus, the volume decrease was 27.7% ($p<0.001$) at 3 years. There were no complications. The authors noted that although these results are preliminary, MR-guided HIFU for the treatment of uterine fibroids may be an acceptable treatment option.

Ikink (2013) conducted a nonrandomized uncontrolled study to assess the clinical efficacy of MR-guided ultrasound techniques for the treatment of symptomatic uterine fibroids (n=46 premenopausal women). Clinical outcomes were measured using the SSS of the UFS-QOL questionnaire. Results showed that HIFU treatment resulted in a significant reduction in fibroid volume compared with baseline measurements ($p<0.001$), corresponding to a volume reduction of about 29%. In addition, 25 of 46 women (54%) reported a significant

improvement in mean transformed SSS compared with baseline values ($p<0.001$). This study was also characterized by significant limitations, including lack of randomization and lack of a control arm.

Clark and colleagues (2014) conducted a systematic review of the efficacy of MRgFUS, specifically on its performance preserving fertility in women. A total of 10 studies, representing 589 women, were chosen for inclusion in the meta-analysis. Study inclusion criteria included a report of mean SSS at baseline and 6-month follow-up. The overall mean improvement in SSS 6 months after MRgFUS was estimated at 31.0% (95% CI, 23.9-38.2%). Authors concluded that, "Given the minimally invasive approach, MRgFUS could become the treatment of choice for patients desiring future fertility; however, further investigation is needed."

Another 2014 systematic review completed by Gizzo and colleagues evaluated the safety, feasibility, indications, complications, impact on UFS-QOL and fertility associated with myomectomy performed by MRgFUS. This review included 38 studies and a total of approximately 2500 women. While the authors concluded that MRgFUS was a safe and efficient technique, it was noted that comparisons with other traditional techniques have not yet been performed.

Pron (2015) reviewed the published evidence related to MRgHIFU to treat uterine fibroids. The evidence used in the review included two systematic reviews, two RCTs, 45 cohort study reports, and 19 case reports. This evaluation did not include any randomized trials comparing MRgFUS to other guidance methods, other minimally invasive treatments, or surgeries for symptomatic uterine fibroids. The author concluded MRgHIFU can be a safe and effective non-invasive, uterine preserving treatment alternative to hysterectomy for individuals failing medical therapy. However, the author also noted there is limited information regarding treatment durability. In addition, there is a lack of existing evidence comparing MRgHIFU to the current standard treatment.

Well-designed clinical studies evaluating the safety and efficacy of MRgFUS using relevant outcome measures are lacking. Studies have generally lacked comparison to the current accepted treatments of uterine fibroids. Additionally, based on the prevalence of uterine fibroids, a relatively small number of women have been studied

in clinical trials. The published evidence regarding MRgFUS does not adequately address the potential for regrowth of treated uterine fibroids over time, particularly beyond 3 to 5 years. In order to demonstrate MRgFUS as a safe and effective treatment option for uterine fibroids, well-designed RCTs with sufficient follow-up periods and appropriate clinical outcome measures are needed to compare therapy with alternative treatments.

The American College of Radiology (ACR) Appropriateness Criteria® Treatment of Uterine Leiomyomas (2017) states that:

> To date, there is little long-term information on the efficacy of this technology. It has been reported that myomas treated with HIFU have nearly 50% volume reduction at 1 year, but viable cells are present at biopsy in nearly 26% of specimens. Funaki et al. report a 24-month volume reduction of 40% with significant symptomatic improvement at 6 months that remained stable at 24-month follow-up. In a multicenter trial, Stewart et al. demonstrated significant reduction in fibroid-related symptoms in 70% of patients at 6 months and 51% of patients at 12 months.

The American College of Obstetricians and Gynecologists (ACOG) stated in their practice bulletin, Management of Symptomatic Uterine Leiomyomas (2021):

> Limited, low-quality data suggest that magnetic resonance-guided focused ultrasound and high-intensity focused ultrasound are associated with a reduction in leiomyoma and uterine size. However, small randomized comparative trial data suggest that compared with UAE, magnetic resonance-guided focused ultrasound is associated with less improvement in symptoms and quality-of-life measures and a higher risk of reintervention.

Other Conditions

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MRgFUS is being studied for a variety of conditions, including but not limited to benign thyroid nodules, chronic neuropathic pain, desmoid tumors, epilepsy, obsessive compulsive disorder or primary hyperparathyroidism (Chung, 2020; Jeanmonod, 2012; Jung, 2015; Kovatcheva, 2014; Martin, 2009; Monteith, 2016). These preliminary studies are in the early stages of evaluating the feasibility, efficacy and safety of the use of MRgFUS for the treatment of these conditions. Larger, well-designed studies are needed validate the use of MRgFUS for any non-oncologic conditions.

Background/Overview

BPH

BPH, the nonmalignant growth of the smooth muscle and epithelial cells within the prostate, is a common age-related manifestation. While almost all men will develop histologic BPH, this condition will not require treatment unless it is associated with subjective symptoms, such as LUTS. LUTS symptoms can be divided into two categories. Obstructive symptoms include hesitancy, straining, weak flow, prolonged voiding, partial or complete urinary retention or overflow incontinence. Irritative symptoms include frequency, urgency with urge incontinence, nocturia, and painful urination or voiding small amount (Roehrborn, 2005). The primary goal of treatment is to alter disease progression and prevent complications (AUA, 2014). If BPH has advanced to the point of causing obstruction, interventions may be aimed at removing excessive tissue and relieving the obstruction. HIFU has been proposed as a means of removing excessive prostate tissue.

ET

ET is considered the most common movement disorder, affecting as much as 4% of the population (Elias, 2013). While there does appear to be a familial component, the cause of this disorder is not known. Although medication is the first line of treatment, as many as 50% of those treated cannot tolerate or fail medication therapy. Surgical

treatments include radiofrequency thalamotomy, surgical resection and deep brain stimulation. MRgFUS is proposed as a noninvasive treatment. Similar to radiofrequency thalamotomy and surgical resection, MRgFUS creates a thalamic lesion which can reduce tremor, but can also result in permanent neurologic deficits (Elias, 2016). While creation of a lesion does reduce tremor and larger lesions can result in more enduring efficacy, larger lesions have a higher incidence of side effects (Elias, 2016).

Uterine Fibroids

The cause of fibroid tumors, also known as leiomyomas, of the uterus is unknown. However, it is suggested that fibroids may enlarge with estrogen therapy (such as oral contraceptives) or with pregnancy. Fibroid growth seems to depend on regular estrogen stimulation, and rarely affects women younger than 20 years of age or postmenopausal women. As long as a woman with fibroids is menstruating, the fibroids will probably continue to grow, although growth is usually quite slow.

Hysterectomy and various myomectomy procedures are considered the gold standard of treatment. However, there has been a longstanding research interest in developing minimally invasive alternatives. There has been interest in using HIFU treatment as a noninvasive approach to ablation of uterine fibroids. Treatment involves the use of focused high-intensity convergent ultrasound beam which increases the temperature within the targeted area to 60-95°C to destroy tissue without causing damage to adjacent tissue. During the procedure, individuals are typically placed under conscious sedation with or without epidural anesthesia, although general anesthesia may be used. Proposed advantages of HIFU include the noninvasive nature of the procedure that spares surrounding tissue, reducing postoperative morbidity, and hastening recovery.

The U.S. Food and Drug Administration (FDA) approved, via the Premarket Application (PMA) process, the ExAblate 2000 System for ablation of uterine fibroid tissue in pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure. The 2004 FDA approval letter stated that women must have a uterine gestational size of less than 24 weeks and must have completed childbearing (FDA, 2004).

Definitions

Benign prostate hyperplasia (BPH): A condition that causes an increase in the size of the prostate gland in men, commonly causing difficulty in urination; also referred to as benign prostatic hypertrophy.

Desmoid tumor: A type of benign, locally invasive fibrous tumor capable of growing anywhere in the body.

Essential tremor (ET): A chronic, incurable condition with unknown cause characterized by involuntary, rhythmic tremor of a body part, most typically the hands and arms.

High intensity focused ultrasound (HIFU): A surgical noninvasive procedure that uses focused high energy sound waves to destroy target tissues in the body.

Leiomyoma: A benign tumor that can be found in the uterus, commonly called a fibroid.

Menorrhagia: Excessive uterine bleeding occurring at the expected intervals of the menstrual periods.

MRI (magnetic resonance imaging): The use of a nuclear magnetic resonance spectrometer to produce electronic images of specific atoms and molecular structures in solids, especially human cells, tissues, and organs.

Myomectomy: A surgical procedure to remove only fibroids; is frequently the chosen treatment for premenopausal women who want to bear more children, because it usually can preserve fertility.

Uterine Fibroids: Benign fibrous tissue collected in the uterine wall.

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Ventralis intermediate nucleus of the thalamus (Vim): A part of the brain involved with movement.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

CPT

0071T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume less than 200 cc of tissue
0072T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume greater or equal to 200 cc of tissue
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

ICD-10 Diagnosis

All diagnoses

When services are also Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

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CPT

55899	Unlisted procedure, male genital system [when specified as image-guided focused ultrasound ablation of prostate tissue for non-oncologic indications, such as benign prostatic hyperplasia]
60699	Unlisted procedure, endocrine system [when specified as image-guided focused ultrasound ablation for non-oncologic indications]

HCPCS

C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance

ICD-10 Diagnosis

All non-oncologic diagnoses

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3. U.S. National Library of Medicine. Uterine fibroids. Review Date January 27, 2020. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000914.htm. Accessed on January 15, 2022.

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Below is a list of the materials the plans are required to submit when they deny coverage as experimental/investigational:

A. Include the CPT or HCPCS code(s)
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H. Include the disease information necessitating the requested service
I. Include a rationale for the immediacy of the review

Additional required information

A. Submit the rationale used to preliminarily indicate the service is experimental/investigational
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ExAblate 2000 System
ExAblate Neuro
Fibroids
Myomectomy
Thalamotomy

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/17/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Description, Rationale and References sections.
Reviewed	02/11/2021	MPTAC review. Updated Rationale and References sections. Updated Coding section, added NOC 60699.
	12/16/2020	Updated Coding section with 01/01/2021 HCPCS changes; code C9747 deleted 12/31/2020.
Reviewed	02/20/2020	MPTAC review. Updated Rationale, References and Websites sections.
Reviewed	03/21/2019	MPTAC review. Updated Description and References sections.
Reviewed	09/13/2018	MPTAC review. Updated Rationale, References and Websites sections.
Reviewed	11/02/2017	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date."
	07/01/2017	Updated Coding section with 07/01/2017 HCPCS changes.

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Revised	02/02/2017	MPTAC review. Revised investigational and not medically necessary position statement indications to include essential tremor. Updated Description, Rationale, Background, Definitions, References and Websites sections.
Revised	11/03/2016	MPTAC review. Title changed from *MRI Guided High Intensity Focused Ultrasound Ablation of Uterine Fibroids* to *MRI Guided High Intensity Focused Ultrasound Ablation for Non-Oncologic Indications.* Revised investigational and not medically necessary position statement to include all non-oncologic indications. Updated Description, Rationale, Background, Definitions, Coding, References and Websites sections.
Reviewed	05/05/2016	MPTAC review. Updated Description, Rationale, Background and References sections. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review. Updated Rationale and References sections.
Reviewed	05/15/2014	MPTAC review. Updated Rationale and References sections.
Reviewed	05/09/2013	MPTAC review.
Reviewed	05/10/2012	MPTAC review. Rationale and References sections updated.
Reviewed	05/19/2011	MPTAC review. Rationale and References sections updated.
Reviewed	05/13/2010	MPTAC review. Rationale and References sections updated.
Reviewed	05/21/2009	MPTAC review. Rationale and References sections updated.
Reviewed	05/15/2008	MPTAC review. Rationale, Background and References sections updated.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review. References updated.
Reviewed	06/08/2006	MPTAC review. Rationale, Background, Definitions and References sections updated. Removed CMS NCD which was added November 2005 in error. Position statement unchanged.

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	11/21/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.		No prior document	
WellPoint Health Networks, Inc.	06/24/2004	2.09.18	MRI Guided High Intensity Focused Ultrasound Ablation of Uterine Fibroids

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