7.01.109	Magnetic Resonance-Guided Focused Ultrasound		
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Section:	7.0 Surgery	**Page:**	Page 1 of 24

Policy Statement

I. Magnetic resonance-guided high-intensity ultrasound ablation may be considered **medically necessary** for pain palliation in adults with metastatic bone cancer who have failed or are not candidates for radiotherapy.

II. Magnetic resonance-guided high-intensity ultrasound ablation may be considered **medically necessary** for the treatment of medicine-refractory essential tremors.

III. Magnetic resonance-guided high-intensity ultrasound ablation is considered **investigational** in all other situations including but not limited to:
   A. Treatment of uterine fibroids
   B. Treatment of other tumors (e.g., brain cancer, prostate cancer, breast cancer, desmoid)
   C. Treatment of medication-refractory tremor dominant Parkinson disease

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding
See the Codes table for details.

Description

An integrated system providing magnetic resonance-guided focused ultrasound (MRgFUS) treatment is proposed as a noninvasive therapy for uterine fibroids and pain palliation of bone metastases. MRgFUS is also being investigated as a treatment of other benign and malignant tumors as well as essential tremors.

Related Policies

- Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In October 2004, the ExAblate 2000 System (InSightec) was approved by the FDA through the premarket approval process for "ablation of uterine fibroid tissue in pre- or perimenopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure." Treatment is indicated for women with a uterine gestational size of fewer than 24 weeks who have completed childbearing.
In October 2012, the ExAblate System, Model 2000/2100/2100 VI, was approved by the FDA through the premarket approval process for pain palliation in adults with metastatic bone cancer who have failed or are not candidates for radiotherapy. The device was evaluated through an expedited review process. The FDA required a postapproval study with 70 patients to evaluate the effectiveness of the system under actual clinical conditions.

In July 2016, the FDA approved the use of the ExAblate Neuro System for the treatment of ET in patients who have not responded to medication (beta-blockers or anticonvulsant drugs) through the premarket approval process. In December 2018, the FDA approved the use of the ExAblate Model 4000 (Neuro) for the treatment of tremor-dominant PD with medication-refractory tremor through the premarket approval process.

In November 2021, the FDA approved the use of the Exablate Prostate System for prostate tissue ablation through the premarket approval process.
FDA product codes: NRZ, POH, PLP.

Rationale

Background

Uterine Fibroids

Uterine fibroids are 1 of the most common conditions affecting women in the reproductive years. African American women have a greater lifetime incidence of uterine fibroids compared to other racial groups.[1,]Symptoms of uterine fibroids include menorrhagia, pelvic pressure, or pain.

Treatment

Approaches currently available to treat symptomatic uterine fibroids include hysterectomy, abdominal myomectomy, laparoscopic and hysteroscopic myomectomy, hormone therapy, uterine artery embolization, and watchful waiting. Hysterectomy and various myomectomy procedures are considered the criterion standard treatments.

Metastatic Bone Disease

Metastatic bone disease is 1 of the most common causes of cancer pain.

Treatment

Existing treatments include conservative measures (e.g., massage, exercise) and pharmacologic agents (e.g., analgesics, bisphosphonates, corticosteroids). For patients who do not respond to these treatments, standard care is external-beam radiotherapy. However, a substantial proportion of patients have residual pain after radiotherapy, and there is a need for alternative treatments for these patients. (One option, radiofrequency ablation, is addressed in Blue Shield of California Medical Policy: Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors).

Essential Tremors

Essential tremor (ET) is the most common movement disorder, with an estimated prevalence of 5% worldwide. Essential tremor most often affects the hands and arms, may affect head and voice, and rarely includes the face, legs, and trunk. Essential tremor is heterogeneous among patients, varying in frequency, amplitude, causes of exacerbation, and association with other neurologic deficits.

Treatment

The neuropathology of ET is uncertain, with some evidence suggesting that ET is localized in the brainstem and cerebellum. If patients with ET experience intermittent or persistent disability due to the tremors, initial therapy is with drugs (beta-blockers or anticonvulsants). For medicine-refractory patients, surgery (deep brain stimulation or thalamotomy) may be offered, though high rates of adverse events have been observed.

Tremor-Dominant Parkinson Disease

The 3 cardinal features of Parkinson disease (PD) are tremor, bradykinesia, and rigidity. The tremor in PD is a resting tremor that occurs when the body part is not engaged in purposeful activities. Major subtypes of PD include tremor-dominant, akinetic-rigid, and postural instability and gait difficulty. The progression of PD is highly variable and patients can change subtypes as the disease progresses.

Treatment

Dopaminergic therapy (i.e., levodopa or a dopamine agonist) is the first-line treatment for PD, which improves tremor. Amantadine and anticholinergics (e.g., trihexyphenidyl) can also be considered as initial treatment for tremor-dominant PD or as add-on therapy in patients who have persistent tremor despite dopaminergic therapy. For medication-refractory patients, surgery (deep brain stimulation or lesioning procedures) may be offered. Lesioning procedures include conventional unilateral thalamotomy and focused ultrasound thalamotomy. Deep brain stimulation is the most frequently performed surgical procedure for the treatment of PD.

Magnetic Resonance-Guided Focused Ultrasound

Magnetic resonance-guided focused ultrasound (MRgFUS) is a noninvasive treatment that combines 2 technologies: focused ultrasound and magnetic resonance imaging (MRI). The ultrasound beam penetrates through the soft tissues and, using MRI for guidance and monitoring, the beam can be focused on targeted sites. Ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis while sparing the surrounding normal structures. Ultrasound waves from each sonication are directed at a focal point that has a maximum focal volume of 20 nm in diameter and 15 nm in height/length. This causes a rapid rise in temperature (i.e., to 65°C to 85°C), which is sufficient to ablate tissue at the focal point. In addition to providing guidance, the associated MRI can provide online thermometric imaging, a temperature "map", to confirm the therapeutic effect of the ablation treatment and allow for real-time adjustment of the treatment parameters.

The U.S. Food and Drug Administration (FDA) approved the ExAblate® MRgFUS system (InSightec) for 4 indications: treatment of uterine fibroids (leiomyomata), palliation of pain associated with tumors metastatic to bone, medication refractory ET, and tremor-dominant PD. The ultrasound equipment is specifically designed to be compatible with magnetic resonance magnets, and it is integrated into standard clinical MRI units; it also includes a patient table, which has a cradle that houses the focused ultrasound transducer in water or a light oil bath. Some models have a detachable cradle; only certain cradle types can be used for palliation of pain associated with metastatic bone cancer. For treating pain associated with bone metastases, the aim of MRgFUS is to destroy nerves in the bone surface surrounding the tumor.

MRgFUS is also being investigated for the treatment of other tumors, including breast, prostate, brain, and desmoid tumors as well as nonspinal osteoid osteoma.

Literature Review

This review was informed by a TEC Assessment (2005) on magnetic resonance-guided focused ultrasound (MRgFUS) for symptomatic uterine leiomyomata, which found the evidence of efficacy insufficient compared with conventional therapies.[2,]

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and

ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Magnetic Resonance-guided Focused Ultrasound for Uterine Fibroids

Clinical Context and Therapy Purpose

The purpose of MRgFUS in individuals with uterine fibroids is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with uterine fibroids

Interventions

The therapy being considered is MRgFUS, which is a thermoablative procedure to heat targeted tissue in small volume increments, under constant magnetic resonance imaging guidance.

Comparators

The comparators of interest are alternative nonsurgical treatments or surgery.

Outcomes

For uterine fibroids, the goal is to reduce or eliminate fibroid-related symptoms by reducing fibroid size. Measures to assess the effect of treatment include quality of life, change in uterine and fibroid volume, pain levels, and pain medication use. Outcome measures can be assessed at several months to several years postprocedure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;

- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Evidence for the use of MRgFUS for the treatment of uterine fibroids consists of RCTs, systematic reviews, and many observational studies. RCTs and relevant non-randomized trials not included in the systematic reviews are summarized.

Randomized Controlled Trials

Barnard et al (2017) published preliminary results from Fibroid Interventions: Reducing Symptoms Today and Tomorrow trial, a parallel RCT and cohort study comparing MRgFUS with fibroid embolization to treat uterine fibroids.[3,] For the RCT, patients were randomized to uterine artery embolization (UAE; n=22) or to MRgFUS (n=27). Patients and investigators were not blinded. Women who did not want to be randomized were enrolled in the cohort study; 16 underwent UAE and 16 underwent MRgFUS. Patients were instructed to keep diaries with the following information: medication use, return to normal activities, and symptoms. After 6 weeks of follow-up for the RCT patients, there were no differences between groups in symptoms such as fatigue, hot flashes, discomfort urinating, vaginal discharge, or constipation. Recovery was significantly faster in the MRgFUS group, as measured by the first day back to work and the first day back to normal.

Medication use (i.e., opioids, nonsteroidal anti-inflammatory drugs, acetaminophen or aspirin, nausea medication, bowel medication) was also significantly lower in the MRgFUS group. Analyses combining the RCT and cohort patients showed similar results. The MRgFUS procedure took significantly longer than the UAE procedure. A trial limitation was the inability to recruit more patients. Long-term follow-up results were reported by Laughlin-Tommaso et al (2019)[4,]. Patients in both the RCT and cohort studies had follow-up for up to 3 years. The primary outcome assessed was reintervention for uterine fibroids within 3 years; secondary outcomes included change in anti-Mullerian hormone levels and standardized measures of quality of life, pain, sexual function, and fibroid symptoms. Among the women in the MRgFUS arm (n=43), 13 (30%) had a second fibroid procedure compared to 5 (13%) women in the UAE arm (hazard ratio [HR], 2.81; 95% confidence interval [CI], 1.01 to 7.79). There was a significantly greater absolute decrease in anti-Mullerian hormone levels at 24 months in the UAE arm compared to the MRgFUS arm.

A pilot sham-controlled randomized trial evaluating MRgFUS for the treatment of uterine fibroids was published by Jacoby et al (2016).[5,] The trial included 20 premenopausal women with symptomatic uterine fibroids. Patients were randomized to MRgFUS with the ExAblate 2000 System (n=13) or to a sham treatment not using thermal energy (n=7). The sample size was calculated to assess the feasibility of a larger trial, not to provide sufficient statistical power. All patients who were assigned to the MRgFUS group and 6 of 7 in the placebo group received their allocated treatment; patients were unblinded at 3 months. The trialists concluded that a larger sham-controlled randomized trial of MRgFUS was feasible.

Systematic Reviews

A systematic review, published by Gizzo et al (2014), conducted a literature search through February 2013 and identified 38 uncontrolled studies with a total of 2500 patients who underwent MRgFUS for the treatment of uterine fibroids.[6,] All published studies included women 18 years or older with symptomatic uterine fibroids, and most excluded patients who desired future pregnancies. Reviewers did not pool study findings due to the heterogeneity of outcomes but concluded that, overall, MRgFUS appeared to be a safe, noninvasive option for treating uterine fibroids. Future research, particularly RCTs, were recommended to compare MRgFUS with other noninvasive procedures and to explore the fertility-sparing potential further. A meta-analysis by Xu et al (2021) compared the reintervention rates of UAE, myomectomy, and MRgFUS in patients with uterine fibroids.[7,] There were 31 studies (N=42,103) that were included in the analysis, with 6 being RCTs and the other 25 being

cohort studies. The 12-month, 24-month, 36-month and 60-month re-intervention rates were assessed as the primary outcome. Myomectomy has the lowest re-intervention rate of the 3 regimens in all time points assessed while the MRgFUS had the highest re-intervention rate. The estimations of the pooled rates of reintervention of MRgFUS also increased rapidly in the sixtieth month after treatment compared to myomectomy and UAE.

Non-randomized Trials

Chen et al (2016) evaluated 107 women undergoing MRgFUS for the treatment of uterine fibroids.[8,] Efficacy was defined as the proportion of patients with at least 10% fibroid shrinkage from baseline, as measured by magnetic resonance imaging. At the 6-month follow-up, 93% efficacy was reported.

Fertility Following Magnetic Resonance-guided Focused Ultrasound for Treatment of Uterine Fibroids

A prospective registry of pregnancies after MRgFUS had been maintained by the manufacturer of the ExAblate device. Rabinovici et al (2010) reported on 54 known pregnancies a mean of 8 months after treatment.[9,] They included 8 pregnancies from clinical trials designed for women who did not desire pregnancy, 26 pregnancies after commercial treatment, and 20 pregnancies in 17 patients from an ongoing study of MRgFUS in women trying to conceive. Twenty-two (42%) of the 54 pregnancies resulted in deliveries and 11 were ongoing beyond 20 weeks at the time the article was written. There were 14 (26%) miscarriages and 7 (13%) elective terminations. Among the 22 live births, the mean live birth weight was 3.3 kg, and the vaginal delivery rate was 64%. The article provided initial information on the impact of MRgFUS on uterine fibroids in pregnancy; findings suggested that fertility may be maintained but that the number of cases was too small to draw definitive conclusions. The study also did not address the possible impact of MRgFUS treatment on the future ability to become pregnant.

A prospective cohort study by Otonkoski et al (2023) evaluated if there was any adverse impact of MRgFUS treatment on ovarian reserve. [10,] Seventy-four premenopausal women were included who had either symptomatic uterine fibroids or adenomyosis. Ovarian reserve was estimated using serum Anti-Mullerian hormone (AMH) levels before and 3 months after treatment. The median baseline AMH level prior to treatment was 1.20 (range, 0.1 to 7.75 mcg/L) and 1.23 (range, 0.1 to 8.51 mcg/L) after treatment, and no statistically significant change was detected (p=.90). Also, none of the patients reported any symptoms that would indicate a loss of ovarian function.

Section Summary: Uterine Fibroids

For the treatment of uterine fibroids, there are 2 RCTs, 1 with 49 women that compared MRgFUS with UAE and the other a feasibility trial assessing 20 women that had a sham control. Several nonrandomized studies have also compared MRgFUS with different treatments. The sham-controlled randomized trial concluded that a larger trial would be feasible. The trial reported significantly lower fibroid volumes in the active treatment group; however, there were no statistically significant differences in quality of life between the groups. The other RCT reported no significant differences in medication use or symptoms between the MRgFUS and UAE groups. Recovery was significantly faster in the MRgFUS group than in the UAE group, however long-term follow-up results reported that there was lower reintervention rate and greater improvement in symptoms after UAE compared to MRgFUS. A 2014 systematic review, which identified only noncomparative studies, did not pool results due to heterogeneity in outcomes among the studies. While reviewers concluded that MRgFUS may be a safe and effective minimally invasive option for the treatment of fibroids, they noted that RCTs comparing MRgFUS with other noninvasive procedures would be informative. A 2021 meta-analysis reported that, comparatively, myomectomy had the lowest re-intervention rate of the 3 regimens (myomectomy vs UAE vs MRgFUS) in all time points assessed, while the MRgFUS had the highest re-intervention rate. There is insufficient evidence on the long-term treatment effects, recurrence rates, and impact on future fertility and pregnancy of this therapy.

Magnetic Resonance-guided Focused Ultrasound for Palliative Treatment of Bone Metastases

Clinical Context and Therapy Purpose

The purpose of MRgFUS in individuals with metastatic bone cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with metastatic bone cancer who have failed radiotherapy or who are not candidates for radiotherapy.

Interventions

The therapy being considered is MRgFUS, which is a thermoablative procedure to heat targeted tissue in small volume increments, under constant magnetic resonance imaging guidance.

Comparators

The comparator of interest for metastatic bone cancer is supportive care.

Outcomes

For metastatic bone cancer, the goal is to alleviate pain. Measures to assess the effect of treatment include pain levels and pain medication use. Outcome measures can be assessed at several months to several years post procedure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Evidence for the use of MRgFUS for the treatment of painful bone metastases consists of a large RCT and a systematic review of RCTs and observational studies. Observational studies with longer-term follow-up or not included in the systematic review are summarized.

Systematic Reviews

Baal et al (2021) conducted a systematic review of studies published between 2007 and 2019 evaluating MRgFUS treatment for painful bone metastases.[11,] A total of 33 studies were identified, comprised of 3 RCTs, 6 retrospective studies, and 24 prospective studies, representing 1082 patients. Thirteen studies were available in abstract form only. The median study sample size was 21 patients (range, 5 to 140) with a median follow-up period of 3 months (range, 1 to 12 months). Efficacy was assessed by treatment response (complete response or partial response [≥2-point improvement in pain score]) and the mean difference in pain scores (10-point VAS [visual analog scale] or NRS [numeric rating scale]) from baseline to month 1/month 3. The pooled proportion of patients with a treatment response to MRgFUS was 79% (95% CI, 73% to 83%; based on 20 studies [n=636]). The pooled 1-month and 3-month mean difference from baseline in pain score were -3.8 (95% CI, -4.3 to -3.3) and -4.4 (95% CI, -5.0 to - 3.7), respectively (based on 20 studies [n=543]). Across 26 studies (n=799), 7 high-grade adverse events were observed (1 deep vein thrombosis, 2 cases of grade 3 skin burn, and 4 fractures). Approximately 11.8% of patients experienced sonication-related pain during MRgFUS treatment. The analysis was limited by a lack of a pooled comparator. Additionally, there

was substantial heterogeneity of the included studies due to variable study populations (e.g., type of primary cancer), reported data, and treatment details. The majority of the included studies had follow-up periods that were limited to 3 months.

Randomized Controlled Trials

In an RCT evaluating the ExAblate System for the treatment of painful bone metastases, Hurwitz et al (2014) evaluated patients with 3 or more months of life expectancy who had painful bone metastases despite radiotherapy, or who were unsuitable for or declined radiotherapy.[12,] Patients rated tumor pain on a 10-point scale NRS at 4 or greater. While they could have up to 5 painful lesions, only 1 lesion was treated, and it had to cause pain at least 2 points greater on the NRS than any other lesion. Also targeted tumors needed to be device-accessible. Study participants were randomized 3:1 to active (n=122) or sham (n=39) MRgFUS treatment. Ten patients in the treatment group and 4 in the sham group did not receive the allocated treatment. An additional 26 patients in the treatment group and 23 in the sham group did not complete the 3-month follow-up. A larger proportion of the placebo group dropped out: 17 (49%) of 35 who were treated decided to have rescue MRgFUS treatment after a lack of response to placebo. A modified intention-to-treat analysis was used that included patients who had at least 1 MRgFUS or placebo sonication. Missing values were imputed using the last observation carried forward method. The primary efficacy endpoint, assessed at 3 months, was a composite outcome comprised of the change in baseline in worst NRS score and morphine equivalent daily dose (MEDD) intake. Patients were considered responders if their worst NRS score decreased by at least 2 points and if their MEDD intake did not increase more than 25% from baseline to 3 months. NRS scores and MEDD intake were reported separately as secondary outcomes.

Seventy-two (64%) of 112 patients in the MRgFUS group and 7 (20%) of 35 patients in the control group were considered responders, as previously defined. The difference was statistically significant (p=.01), favoring active treatment. When the 2 measures comprising the primary endpoint were analyzed separately, there was a statistically significant difference between groups in change in worst NRS score and a nonsignificant difference in change from baseline in pain medication. The NRS score decreased by a mean (standard deviation [SD]) of 3.6 (3.1) points in the MRgFUS group and by a mean of 0.7 (2.4) in the placebo group (p<.01). Change in MEDD from baseline was 3.7 in the MRgFUS group and 15.3 in the placebo group. Fifty-one (46%) patients in the MRgFUS group and 1 (3%) in the placebo group experienced at least 1 adverse event. Most adverse events were transient, with the most common being sonication pain, experienced by 36 (32%) patients in the MRgFUS group. In 17 (15%) patients, sonication pain was severe; 3 patients did not complete treatment due to pain. The most clinically significant adverse events that lasted more than a week were third-degree skin burns in 1 patient (associated with noncompliance with the treatment protocol) and fracture in 2 patients (1 of which was outside the treatment location). Potential trial limitations included a nonconventional primary outcome measure and the small initial size of the sham group. Moreover, a large number of sham patients (66%) did not complete the 3-month follow-up; the trialists indicated that this low completion rate was due to a lack of response to placebo treatment.

Observational Studies

Arrigoni et al (2017) evaluated the use of MRgFUS in a case series of 14 patients with intra-articular benign bone lesions who were followed for 12 months.[13,] Pain was measured by a VAS and all patients underwent computed tomography and magnetic resonance imaging. Mean pain scores significantly decreased from 7.8 pretreatments to 2.0 at 6-month follow-up to 0.6 at 12-month follow-up (p<.001). No patients reported worse symptoms and none reported the procedure unsuccessful. Diagnostic imaging supported the clinical findings and showed calcification of the lesion, lack of contrast enhancement, and resolution of bone edema.

Section Summary: Palliative Treatment of Bone Metastases

The evidence consists of a systematic review of RCTs and observational studies, a single industry-sponsored RCT, and case series. The RCT found significant improvement after MRgFUS in a

composite outcome comprised of a reduction in pain and morphine use, and in pain reduction as a stand-alone outcome. This trial was appropriately sham-controlled. A substantial proportion of patients in the treatment group experienced adverse events but most adverse events were transient and not severe. Pooled efficacy data from a systematic review reported a treatment response to MRgFUS of 79%.

Magnetic Resonance-guided Focused Ultrasound for Other Tumors

Clinical Context and Therapy Purpose

The purpose of MRgFUS in individuals with other tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with other tumors (e.g., breast cancer, brain cancer, prostate cancer, desmoid, nonspinal osteoid osteoma).

Interventions

The therapy being considered is MRgFUS, which is a thermoablative procedure to heat targeted tissue in small volume increments, under constant magnetic resonance imaging guidance.

Comparators

The comparator of interest for other tumors is standard of care.

Outcomes

For other tumors, the goal is tumor ablation. Outcomes include reductions in tumor size. Outcome measures can be assessed at several months to several years postprocedure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Nonrandomized trials

Ghai et al (2021) conducted a phase II trial to evaluate the safety and efficacy of transrectal MRgFUS treatment for intermediate-risk prostate cancer.[14,] The primary efficacy endpoint was the presence of residual disease at the treatment site at 5 months after the procedure. Ninety-three percent of patients were free of clinically significant prostate cancer at the 5-month biopsy. No major treatment-related adverse events occurred. Ghai et al (2024) recently published the 24-month follow-up results.[15,] Treatment was successfully completed for 43 patients through month 24, although 1 participant refused biopsy at 24 months. After 2 years, 39/42 participants (93%) had no clinically significant prostate cancer at the treatment site and 36/42 (86%) had no cancer in the entire prostate gland. Additionally, there was no significant decline in quality of life per the validated questionnaires at 24 months and no major adverse events were recorded.

Ehdaie et al (2022) conducted a phase II trial to evaluate whether MRgFUS could safely reduced treatment burden for patients with intermediate-risk prostate cancer. [16,] The co-primary efficacy endpoints were oncological efficacy (defined as absence of cancer that was grade group 2 or higher

in the treated area on prostate biopsy) and safety (measured by adverse event reporting). At 24 months, 88% (78 out of 89) of patients had no evidence of grade group 2 or higher prostate cancer in the treated area; there was 1 grade 3 adverse event that was reported and no grade 4 or 5 adverse events.

Study characteristics and results are presented in Tables 1 and 2.

Table 1. Summary of Key Nonrandomized Trials Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Comparator	Follow-Up
Ghai et al (2021)[14]; Ghai et al (2024)[15]	Prospective phase II trial	Canada	2016-2019	44 men with unifocal, intermediate-risk prostate cancer with <20 mm of MRI-visible GG2 or GG3 disease (not previously treated); 2 participants did not undergo biopsy at 2-year follow-up	Transrectal MRgFUS	None	24 months
Ehdaie et al (2022)[16]	Prospective phase II trial	USA	2017-2022	101 men ≥50 years old, with intermediate risk prostate adenocarcinoma with no previous treatment for prostate cancer	Transrectal MRgFUS	None	24 months

GG: grade group; MRgFUS: magnetic resonance-guided focused ultrasound; MRI: magnetic resonance imaging.

Table 2. Summary of Key Nonrandomized Trials Results

Study	Residual Disease	Recurrence/response	PSA	Adverse Events
Ghai et al (2021)[14]; Ghai et al (2024)[15]	7% (95% CI, 2.4 to 18.2) had residual disease at 5 months after ablation	Of the 42 other participants at 2 years, 36 (86%) were free of clinically significant disease, 3 (7%) had clinically significant disease at the treatment site, and 3 (7%) had clinically significant disease outside of the treatment zone.	Median PSA was 2.4 ng/mL (IQR, 1.1 to 5.4) at 5 months (baseline PSA was 6.4 ng/mL [IQR, 1.1 to 5.4]) and 2.7 ng/mL (IQR, 1.2 to 6.7) at 24 months.	5 months: 16 patients reported dysuria; 5 patients required antispasmodics for bladder spasm in the first week; 2 patients had urinary retention; 1 patient had severe pelvic pain 24 months: no major adverse events reported
Ehdaie et al (2022) [16]	NR	96 out of 101 patients (95%; 95% CI, 89 to 98) had no evidence of grade group 2 or higher prostate cancer on 6-month biopsy in the treated area; 78 out of 89 patients (88%; 95% CI, 79 to 94) had no evidence of grade group 2 or higher cancer on 24-month biopsy in the treated area	Mean decrease in PSA after treatment was -3.0 ng/mL (95% CI, -3.6 to -2.4) at 6 months and -2.6 ng/mL (95% CI, -3.3 to -2.0) at 24 months.	No serious TRAEs were reported during the study period. There was 1 grade 3 AE (UTI) that was reported. Common AEs that were reported (grade 2 or lower) included hematuria and urinary retention.

AE, adverse event; CI: confidence interval; IQR: interquartile range; MRgFUS: magnetic resonance-guided focused ultrasound; NR, not reported; PSA: prostate specific antigen; TRAE, treatment-related adverse event; UTI, urinary tract infection

Observational Studies

Only case series have assessed the safety and/or efficacy of MRgFUS for treating tumors related to breast cancer[17,18,19,20,21,] and brain cancer.[22,] The most recent case series on the use of MRgFUS for breast cancer ablation was published by Merckel et al (2016).[21,] Ten patients with early-stage invasive breast cancer underwent MRgFUS prior to surgical resection. Ablation was confirmed histopathologically in 6 of these patients. The investigators concluded that MRgFUS is safe and feasible. A noted limitation is the long procedure time (average, 145 minutes), due to waiting time after contrast injection and time to find a proper magnetic resonance navigator signal.
Several case series have investigated the use of MRgFUS for nonspinal osteoid osteoma.[23,24,25,] Arrigoni et al (2021) conducted a propensity score-matched retrospective study to compare treatment with radiofrequency ablation and MRgFUS.[23,] A total of 116 patients were treated (61 with radiofrequency ablation and 55 with MRgFUS). After propensity score matching, both radiofrequency ablation and MRgFUS treatment resulted in a significant reduction in pain from baseline as measured by VAS (8.9 to 0.02 and 8.8 to 0.54, respectively). There was no statistically significant difference between the mean values of both groups after the treatment. Four cases of relapse (1 with radiofrequency ablation and 3 with MRgFUS) were observed. Arrigoni et al (2019) prospectively enrolled children into a study to evaluate MRgFUS treatment for osteoid osteoma.[24,] The primary clinical endpoint was defined as the absence of pain (evaluated on the Faces Pain Scale-Revised) at the first follow-up study 1 week after the procedure. A total of 33 children were included in the study and treated with MRgFUS. The mean pain score at baseline was 7.6; the score at week 1 after the procedure significantly improved in all children (mean score, 0.21). Complete absence of pain was reported in 32 of 33 (97%; 95% CI, 84 to 100) patients at week 1. At the 24-month follow-up visit, imaging results confirmed the complete disappearance of bone edema around all lesions. Geiger et al (2014) prospectively enrolled patients into a study to evaluate MRgFUS treatment for osteoid osteoma.[25,] Clinical success was evaluated based on pain reduction (evaluated on a VAS) through 12 months. At the 12-month follow-up, complete clinical success was achieved in 90% of the 29 patients enrolled (mean VAS, 0±0 points); partial success was achieved in the remaining patients (mean VAS, 5±0 points).

In addition, several case series have investigated the use of MRgFUS for desmoid tumors.[26,27,28,] Avedian et al (2016) used MRgFUS to treat 9 patients with desmoid tumors.[26,] Five patients were available for follow-up for at least 12 months. Mean decrease in tumor size was 36% (95% CI, 7% to 66%). Bucknor et al (2017) described the use of MRgFUS to treat 3 patients with large aggressive desmoid tumors within the posterior thigh.[27,] Each patient received multiple MRgFUS treatments. In this case series, the use of MRgFUS for desmoid tumors required different treatment parameters than those used for fibroids or bone lesions, due to differences in vascularity of the target tissue and the need for effective skin protection when using MRgFUS on extremities. Ghanouni et al (2017) used MRgFUS to treat 15 patients with extra-abdominal desmoid tumors.[28,] Treatment times ranged from 0.8 to 8 hours. Results were presented on 9 patients (3 were lost to follow-up before 6 months, 3 received additional treatments). Seven of 9 patients experienced durable clinical benefits, with a median reduction in tumor volume of 98%. Treatment-related adverse events included skin burns, nerve injury, and off-target heating.

Section Summary: Treatment of Other Tumors

Evidence on the use of MRgFUS for the treatment of prostate cancer consists of 2 nonrandomized, uncontrolled phase II trials. Evidence on the use of MRgFUS for the treatment of nonspinal osteoid osteoma consists of several case series, including a propensity score-matched retrospective study that reported similar reductions in pain with radiofrequency ablation and MRgFUS. Currently, evidence on the use of MRgFUS for the treatment of other tumors consists of small case series, which

is insufficiently robust to draw conclusions about efficacy. RCTs comparing MRgFUS with other noninvasive procedures would be informative.

Magnetic Resonance-guided Focused Ultrasound for Essential Tremors

Clinical Context and Therapy Purpose

The purpose of MRgFUS in individuals with essential tremors (ET) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with medication-refractory ET.

Interventions

The therapy being considered is MRgFUS, which is a thermoablative procedure to heat targeted tissue in small volume increments, under constant magnetic resonance imaging guidance.

Comparators

The comparators of interest for ET are neurosurgery or standard of care. Surgical procedures include deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus and stereotactic thalamotomy.

Outcomes

For ET, the goal is to decrease the frequency of tremors and improve the quality of life. Outcome measures can be assessed at several months to several years postprocedure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Evidence for the use of MRgFUS to treat medication-refractory ET consists of a technology assessment, meta-analyses, and a double-blind, sham-controlled randomized trial.

Systematic Reviews

Miller et al (2021) published a meta-analysis that evaluated the efficacy of MRgFUS for treating medication-refractory ET with a focus on long-term trends and the durability of the response.[29,] Twenty-one studies (N=395) were included; 17 were prospective studies, 3 were retrospective, and only 1 was an RCT.[30,] Hand tremor scores decreased from a weighted mean pre-operative value of 19.2±5.0 to 7.4±5.0 after 3 months. Over time, the hand tremor score values gradually increased: 8.3±5.3 after 12 months and 9.1±5.4 after 36 months. The pooled standardized mean difference of hand tremor scores compared to pre-treatment values was 2.68 (95% CI, 1.94 to 3.41) at 3 months (5 studies), 2.44 (95% CI, 1.97 to 2.91) at the 12-month time point (7 studies), and 2.18 (95% CI, 1.50 to 2.86) at the 24-month time point (3 studies). Clinical Rating Scale for Tremor scores were only reported through 12 months. The pooled standardized mean difference in Clinical Rating Scale for Tremor scores compared to pre-treatment values was 1.86 (95% CI, 1.51 to 1.21) at the 3-month time point (8 studies) and 2.24 (95% CI, 1.55 to 2.94) at the 12-month time point (6 studies). Six studies reported Quality of Life in Essential Tremor Questionnaire (QUEST) scores as a quality of life

measure. The pooled pre-treatment QUEST score was 48.2±22.4, which improved to 24.9±18.2 at 3 months. Additionally, a single study detailed a mean 23.8±19.6 QUEST score at 36 months follow-up, an increase of 2.2 over 30 months.

Giordano et al (2020) conducted a meta-analysis to compare unilateral MRgFUS to unilateral and bilateral DBS for medication-refractory ET.[31,] Forty-five studies published between 1996 and 2019 were identified. Thirty-seven studies (n=1202) evaluated DBS and 8 studies (n=477) evaluated MRgFUS. Fifteen studies had a retrospective study design, while 30 were prospectively designed. Means and standard deviations were calculated for each intervention and differences between groups were compared where appropriate. The average percentage improvement in tremor severity was significantly improved in the pooled DBS group (60.1%±9.7%) as compared to the MRgFUS group (55.6%±8.2%, p<.001). Subgroup analyses demonstrated that the improvement in tremor severity was significantly greater with the bilateral DBS (61.2%±5.2%) as compared to both unilateral DBS (56.4%±9.7%) and MRgFUS; there was no significant difference between unilateral DBS and MRgFUS. For average percentage improvement in quality of life, MRgFUS was associated with significantly improved measures as compared to DBS (61.9%±7.9% vs 52.5%±16.2%, p<.001). There were 517 complications reported in the DBS group and 484 complications reported in the MRgFUS group. The most common adverse events reported with DBS were lead-related complications (11.4%) and speech disturbances (11.1%). For MRgFUS, adverse events of sensory nature (36.7%) and gait disturbances/muscle problems (34.4%) were most common. Limitations of the review included the different scales used in studies to measure tremor severity and quality of life. There was only 1 retrospective study that directly compared DBS and MRgFUS.

The technology assessment was published by Health Quality Ontario (2018).[32,] The literature search, conducted through April 2017, identified 9 studies for inclusion: 4 single cohort studies, 2 retrospective chart reviews, 2 uncontrolled prospective studies, and an RCT. The RCT compared MRgFUS with sham treatment, and the chart reviews compared MRgFUS with DBS and radiofrequency thalamotomy.[30,] Study quality was evaluated using the GRADE system. The RCT was rated high-quality, the uncontrolled comparative studies were rated very low-quality, and the remaining studies were rated low-quality. All studies reported tremor severity as an outcome. Pooling of results was not conducted due to heterogeneity in study designs, analyses, and outcomes across the studies. Reviewers determined that, overall, MRgFUS decreased tremor severity and improved quality of life.

Randomized Controlled Trials

A single high-quality study, a double-blind, sham-controlled randomized trial by Elias et al (2016)[30,] was identified by the 2 systematic reviews. Trial selection criteria included patients with moderate or severe postural or intention tremor of the hand (≥2 on the Clinical Rating Scale for Tremor) and refractory to at least 2 medical therapies. Patients were randomized to MRgFUS thalamotomy (n=56) or sham treatment (n=20). Outcomes were tremor severity, improvement, and quality of life, measured at 3 months postprocedure. Patients in the treatment group were followed for an additional 12 months. The mean score for hand tremors 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. Change in Quality of Life in Essential Tremor Questionnaire 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 were maintained at 12 months in the MRgFUS group.

Chang et al (2018) published results from 67 patients who participated in the open-label extension of the RCT.[33,] Because 9 patients from the original trial received additional treatment during the 2-year follow-up, they were excluded from the analysis. Improvements in tremor and disability scores were maintained at the 2-year follow-up (tremor, 19.8±4.9 [baseline] to 8.8±5.0 [at 2 years]; disability, 16.4±4.5 [baseline] to 6.5±5.0 [at 2 years]).

Section Summary: Essential Tremors

Evidence for the use of MRgFUS in the treatment of medication-refractory ET consists of a technology assessment, meta-analyses, and a double-blind, sham-controlled randomized trial. The assessment did not pool results from the studies but concluded, overall, that MRgFUS decreased tremor severity and improved quality of life. One meta-analysis reported significant improvements in hand tremor scores from baseline up to 24 months post-treatment, with evidence of a diminishing treatment benefit over time. Another meta-analysis found similar improvements in tremor severity with MRgFUS to unilateral DBS, but improvements in both were inferior to bilateral DBS. The sham-controlled randomized trial which was considered high-quality found significant improvements in the treatment group in tremor severity, functional improvement, and quality of life after 3 months of follow-up, and these results were maintained through 2 years of follow-up.

Magnetic Resonance-guided Focused Ultrasound for Tremor-Dominant Parkinson Disease

Clinical Context and Therapy Purpose

The purpose of MRgFUS in individuals with tremor-dominant Parkinson disease (PD) is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with medication refractory tremor-dominant PD.

Interventions

The therapy being considered is MRgFUS, which is a thermoablative procedure to heat targeted tissue in small volume increments, under constant magnetic resonance imaging guidance.

Comparators

The comparators of interest for tremor-dominant PD are neurosurgery or standard of care. Surgical procedures include DBS and conventional unilateral thalamotomy.

Outcomes

For refractory tremor associated with tremor-dominant PD, the goal is to decrease the frequency of tremors and improve quality of life. Outcome measures can be assessed at several months to several years post procedure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Review

Evidence for the use of MRgFUS to treat medication-refractory tremor-dominant PD consists of a double-blind, sham-controlled randomized trial.

Randomized Controlled Trial

A double-blind, sham-controlled, pilot randomized trial by Bond et al (2017) assessed the safety and efficacy of unilateral MRgFUS thalamotomy in patients with tremor-dominant PD.[34,] The primary efficacy outcome evaluated was the change from baseline (on-medication state) to 3 months after the procedure in the hand tremor subscore in the Clinical Rating Scale for Tremor. Trial

characteristics and results are summarized in Tables 3 and 4. After unblinding at 3 months, 6 of the 7 patients who received sham procedures crossed over to undergo open-label treatment with MRgFUS. The most common thalamotomy-related adverse events reported for all 26 patients treated were finger paresthesia (39%), ataxia (35%), and orofacial paresthesia (27%). Paresthesia and ataxia persisted to 1 year in 19% and 4% of patients, respectively. Eight severe adverse events were reported in 4 patients, and 3 were thalamotomy-related (2 patients with persistent mild hemiparesis and 1 patient had an associated persistent mild ataxia).

Table 3. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Bond et al (2017)[34,]	US	2	2012 to 2015	27 patients with medication-refractory, severe, and disabling tremor-dominant PD	MRgFUS thalamotomy (n=20)	Sham treatment (n=7)

MRgFUS: magnetic resonance-guided ultrasound; PD: Parkinson disease; RCT: randomized controlled trial.

Table 4. Summary of Key RCT Results

Study	Hand Tremor Subscore	CRST
Bond et al (2017)[34,]	Percent change from baseline to month 3 (IQR)	Percent change from baseline to month 3 (IQR)
MRgFUS thalamotomy	62% (22.0 to 79.0)	44% (23.0 to 78.0)
Sham treatment	22% (−11.0 to 29.0)	12% (−8.0 to 37.0)
Difference (p-value)	.04	

CRST: Clinical Rating Scale for Tremor; IQR: interquartile range; MRgFUS: magnetic resonance-guided ultrasound; RCT: randomized controlled trial.

Tables 5 and 6 summarize the relevance and conduct limitations of the RCT.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Bond et al (2017)[34,]			2. Comparison to a sham treatment instead of an alterative surgical procedure		1. Efficacy evaluated through 3 months, limiting interpretation for long-term effects

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Bond et al (2017)[34,]			1. 3 of 20 patients who underwent the intervention received deep brain stimulation after 3 months in the		4. Study planned to enroll 30 patients, slow enrollment	3. p-values not reported for efficacy outcomes other than

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
				open-label phase (additional detail not provided for these patients) 3. 6 of 7 patients receiving sham treatment crossed over after 3 months in the open-label phase	limited the study to 27 randomized patients	hand tremor subscores

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Tremor-Dominant Parkinson Disease

Evidence for the use of MRgFUS in the treatment of medication-refractory tremor-dominant PD consists of a double-blind, sham-controlled randomized trial (N=27). The sham-controlled randomized trial found significant improvements in the treatment group in tremor severity after 3 months of follow-up. Authors of the study noted that a larger study is needed to prove efficacy
.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology

In 2018, the American College of Radiology published appropriateness criteria for the radiological management of uterine leiomyomas (fibroids).[35,] The clinical guidance states that "MR [magnetic resonance]-guided high-intensity focused US [ultrasound] (MRgFUS) is another uterine-sparing option to treat focal leiomyomas. It is noninvasive, though each treatment may take several hours to complete. Its use currently is restricted to patients with fewer than six leiomyomas or leiomyoma volume < 900 cm^3," and "although a reasonable alternative for patients unable or unwilling to tolerate sedation or anesthesia, long-term data and viability results are still lacking."

These appropriateness criteria were most recently updated in 2023, with evidence summaries provided for each reviewed clinical scenario.[36,] Table 7 summarizes the appropriateness category for specific populations with uterine fibroids.

Table 7. ACR Appropriateness Criteria: Management of Uterine Fibroids

Clinical situation	MRgFUS Appropriateness Category[a]
Reproductive age patient with uterine fibroids, symptomatic with heavy uterine bleeding or bulk symptoms (eg, pressure, pain, fullness, bladder, or bowel symptoms), and a desire to preserve fertility. Initial therapy.	Usually appropriate
Reproductive age patient with uterine fibroids, symptomatic with heavy uterine bleeding or bulk symptoms (eg, pressure, pain, fullness, bowel, or bladder symptoms), and no desire for future fertility. Initial therapy.	Usually appropriate
Reproductive age patient with uterine fibroids and concurrent adenomyosis, symptomatic with heavy uterine bleeding or bulk symptoms (eg, pressure, pain, fullness, bladder, or bowel symptoms), and no desire for future fertility. Initial therapy.	Usually not appropriate
Reproductive age patient with pedunculated submucosal uterine fibroids, symptomatic with heavy uterine bleeding. Initial therapy.	May be appropriate
Postmenopausal patient with uterine fibroids, symptomatic with heavy uterine bleeding or bulk symptoms (e.g., pressure, pain, fullness, bladder, or bowel symptoms). Negative endometrial biopsy. Next step.	Usually not appropriate
Reproductive age patient with uterine fibroids desiring pregnancy and experiencing reproductive dysfunction. Initial therapy.	May be appropriate

ACR: American College of Radiology; MRgFUS: magnetic resonance-guided focused ultrasound.
[a]Usually appropriate: the imaging procedure or treatment is indicated in teh specified clinical scenarios at a favorable risk-benefit ratio for patients; May be appropriate: The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal; Usually not appropriate: The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

American Society for Radiation Oncology et al

In 2017, the American Society for Radiation Oncology (ASTRO) published guidelines on palliative radiotherapy for bone metastases, which stated that external-beam radiotherapy continues to be the primary therapy for treating painful uncomplicated bone metastases.[37,] The guidelines did not mention magnetic resonance-guided focused ultrasound. If patients experience persistent or recurrent pain more than 1 month after initial treatment, the guidelines recommended retreatment with external-beam radiotherapy. As for advanced radiotherapy such as stereotactic body radiotherapy for retreatment of recurrent pain in spine bone lesions, these "may be feasible, effective, and safe, but the panel recommends that this approach should be limited to clinical trial participation or on a registry given limited data supporting routine use."

In 2022, the American Urological Association (AUA)/ASTRO published guidance on the management of clinically localized prostate cancer.[38,] The guidance states that "there is a lack of data to date to support the use of whole gland or focal ablation for the treatment of clinically localized prostate cancer."

National Comprehensive Cancer Network

Guidelines from the National Comprehensive Cancer Network (NCCN) on bone cancer (v.2.2024),[39,] breast cancer (v.2.2024),[40,] and brain cancer (v.1.2023),[41,] do not mention magnetic resonance-guided ultrasound as a treatment option. The NCCN guideline for prostate cancer (v.3.2024) states that "Cryotherapy or other local therapies are not recommended as routine primary therapy for localized prostate cancer due to lack of long-term data comparing these treatments to radiation. At this time, the panel recommends only cryosurgery and high-intensity focused ultrasound (HIFU; category 2B) as local therapy options for RT [radiotherapy] recurrence in the absence of metastatic disease". [42,]

National Institute for Health and Care Excellence

Guidance from NICE (2018) on unilateral magnetic resonance-guided ultrasound for treatment-resistant essential tremor states "the evidence on the safety of unilateral MRI [magnetic resonance imaging]-guided focused ultrasound thalamotomy for treatment-resistant essential tremor raises no major safety concerns. However, current evidence on its efficacy is limited in quantity. Therefore, this procedure should not be used unless there are special arrangements for clinical governance, consent, and audit or research."[43,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01473485[a]	A Study to Evaluate the Safety and Feasibility of Transcranial MRI-Guided Focused Ultrasound Surgery in the Treatment of Brain Tumors	10	Dec 2022
NCT03998657[a]	A Continued Access Study to Evaluate Focal MR-Guided Focused Ultrasound Treatment of Localized Intermediate Risk Prostate Lesions	14	Dec 2022
NCT02923011	Phase III Study to Compare the Effectiveness of Magnetic Resonance Guided Focused Ultrasound With Computed Tomography Guided Radiofrequency Ablation for Treatment of Osteoid Osteomas	56	Dec 2024
NCT03948789	Multicenter, Randomized Phase III Study of MR-Guided Focused Ultrasound Surgery for the Treatment of Uterine Fibroids (MRgFUS TUF) Compared to Myomectomy in Symptomatic Medication and Not Sufficiently Treatable Uterine Fibroids	127	Jun 2025
NCT03100474[a]	Global Registry: ExAblate 4000 Transcranial MR Guided Focused Ultrasound (TcMRgFUS) of Neurological Disorders	500	Jan 2024
NCT02252380[a]	A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-Refractory Movement Disorders	10	Dec 2023
Unpublished			
NCT02260752	Comparing Options for Management: Patient-Centered Results for Uterine Fibroids	3094	Apr 2020
NCT01833806[a]	A Phase IV Post Approval Clinical Study of ExAblate Treatment of Metastatic Bone Tumors for the Palliation of Pain	32	Jan 2022
NCT01285960[a]	A Clinical Study to Evaluate Safety of the ExAblate Model 2100 Type 1.1 System in the Treatment of Symptomatic Uterine Fibroids	108	Apr 2016 (completed)
NCT01620359[a]	Study of ExAblate Focused Ultrasound Ablation of Breast Cancer under MR Guidance and MRI Evaluation of Ablation	14	Jul 2016 (completed)
NCT02794558[a]	A Clinical Study to Evaluate the Safety and Effectiveness of MR Guided Focused Ultrasound Surgery in the Treatment of Early Breast Carcinomas	100	Mar 2019

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for magnetic resonance imaging (MRI)-guided focused ultrasound ablation
  - Documentation of prior treatments and response

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
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

Type	Code	Description
		disorder including stereotactic navigation and frame placement when performed
HCPCS	C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/07/2006	BCBSA Medical Policy adoption
04/02/2010	Policy Revision with title change from MRI: Magnetic Resonance Imaging Guided Focused Ultrasound Therapy for Symptomatic Uterine Fibroids
01/11/2012	Policy title change from MRI-Guided Focused Ultrasound for the Treatment of Uterine Fibroids with position change
01/11/2013	Policy title change from MRI-Guided Focused Ultrasound for the Treatment of Uterine Fibroids with position change
03/29/2013	Coding Update
05/29/2015	Policy title change from MRI-Guided Focused Ultrasound for the Treatment of Uterine Fibroids and Other Tumors Policy revision with position change
02/01/2016	Coding update
04/01/2016	Policy title change from Magnetic Resonance Imaging-Guided Focused Ultrasound Policy revision without position change
09/01/2017	Policy revision without position change
11/01/2018	Policy revision without position change
09/01/2019	Policy revision without position change
09/01/2020	Annual review. No change to policy statement. Literature review updated.
09/01/2021	Annual review. Policy statement and literature review updated.
09/01/2022	Annual review. No change to policy statement. Literature review updated.
09/01/2023	Annual review. No change to policy statement. Literature review updated.
09/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Magnetic Resonance-Guided Focused Ultrasound 7.01.109 **Policy Statement:** I. Magnetic resonance-guided high-intensity ultrasound ablation may be considered **medically necessary** for pain palliation in adults with metastatic bone cancer who have failed or are not candidates for radiotherapy. II. Magnetic resonance-guided high-intensity ultrasound ablation may be considered **medically necessary** for the treatment of medicine-refractory essential tremors. III. Magnetic resonance-guided high-intensity ultrasound ablation is considered **investigational** in all other situations including but not limited to: A. Treatment of uterine fibroids B. Treatment of other tumors (e.g., brain cancer, prostate cancer, breast cancer, desmoid) C. Treatment of medication-refractory tremor dominant Parkinson disease	**Magnetic Resonance-Guided Focused Ultrasound 7.01.109** **Policy Statement:** I. Magnetic resonance-guided high-intensity ultrasound ablation may be considered **medically necessary** for pain palliation in adults with metastatic bone cancer who have failed or are not candidates for radiotherapy. II. Magnetic resonance-guided high-intensity ultrasound ablation may be considered **medically necessary** for the treatment of medicine-refractory essential tremors. III. Magnetic resonance-guided high-intensity ultrasound ablation is considered **investigational** in all other situations including but not limited to: A. Treatment of uterine fibroids B. Treatment of other tumors (e.g., brain cancer, prostate cancer, breast cancer, desmoid) C. Treatment of medication-refractory tremor dominant Parkinson disease