Magnetic Resonance–Guided Focused Ultrasound

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for MRI-guided high-intensity ultrasound ablation when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Magnetic resonance guided high-intensity ultrasound ablation may be considered medically necessary for pain palliation in adult patients with metastatic bone cancer who failed or are not candidates for radiotherapy.

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

When Policy Topic is not covered
Magnetic resonance guided high-intensity ultrasound ablation is considered investigational. This includes, but is not limited to, its use in the following situations:

- Treatment of uterine fibroids; and
- Treatment of other tumors eg, brain cancer, prostate cancer, breast cancer, desmoid.

Considerations
The procedure may be performed in an MRI suite with an open MRI scanner, which may not be available at many institutions. The procedure is performed in an outpatient setting, with the patient under conscious sedation.

Description of Procedure or Service

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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.

For individuals who have uterine fibroids who receive MRgFUS, the evidence includes 2 small randomized controlled trials (RCTs), nonrandomized comparative studies, and case series. Relevant outcomes are symptoms, quality of life, resource utilization, and treatment-related morbidity. One RCT (N=20) has reported some health outcomes, but its primary purpose was to determine the feasibility of a larger trial. It did not find statistically significant differences in quality of life outcomes between active and sham treatment groups, but it did find lower fibroid volumes after active treatment. This trial did not have an active comparator, the clinical significance of the primary outcome was unclear, and there were no follow-up data beyond 1 year. The second RCT (N=49) is ongoing; preliminary results at 6 weeks posttreatment, comparing MRgFUS with uterine artery embolization have shown that the 2 groups are comparable in medication use and symptom improvement following treatments. Patients in the MRgFUS group reported recovering significantly faster than patients in the uterine artery embolization group, as measured by time to return to work and time to normal activities. In a separate 2013 comparative study, outcomes appeared to be better with uterine artery embolization than with MRgFUS. Long-term data on the treatment effects, recurrence rates, and impact on future fertility and pregnancy are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals with metastatic bone cancer who have failed or are not candidates for radiotherapy who receive MRgFUS, the evidence includes a sham-controlled randomized trial and several case series. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The RCT found statistically significant improvements after MRgFUS in a composite outcome comprised of a reduction in pain and morphine use, and in pain reduction as a stand-alone outcome. A substantial proportion of patients in the treatment group experienced adverse events, but most events were transient and not severe. The case series reported reductions in pain following MRgFUS treatment, consistent with the RCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with other tumors (eg, breast cancer, brain cancer, prostate cancer, desmoid, nonspinal osteoid osteoma) who receive MRgFUS, the evidence includes small case series. Relevant outcomes are symptoms, health status measures, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with medicine-refractory essential tremors who receive MRgFUS, the evidence includes 2 systematic reviews that identified an RCT and several observational studies. Relevant outcomes include symptoms, functional outcomes, quality of life, and treatment-related morbidity. The assessment did not pool study results but concluded that, overall, MRgFUS decreased tremor severity and improved quality of life. The sham-controlled randomized trial found significant improvements in the treatment group in tremor severity, functional improvement, and quality of life after 3 months of follow-up. The improvements in hand tremor score, function, and quality of life were maintained at the 2-year follow-up. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Background**

**Uterine Fibroids**

Uterine fibroids are one of the most common conditions affecting women in the reproductive years. Symptoms of uterine fibroids include menorrhagia, pelvic pressure, or pain.

**Treatment**

Several 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 one of the most common causes of cancer pain.
**Treatment**
Existing treatments include conservative measures (eg, massage, exercise) and pharmacologic agents (eg, 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.

**Essential Tremors**
Essential tremor (ET) is the most common movement disorder, with an estimated prevalence of 5% worldwide. ET most often affects the hands and arms, may affect head and voice, and rarely includes the face, legs, and trunk. ET 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 (β-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.

**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 (ie, to 65°C-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 2 indications: treatment of uterine fibroids (leiomyomata) and palliation of pain associated with tumors metastatic to bone. 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.

**Regulatory Status**
In October 2004, the ExAblate® 2000 System (InSightec) was approved by 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 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. FDA required a postapproval study with 70 patients to evaluate the effectiveness of the system under actual clinical conditions.

In July 2016, FDA approved the use of the ExAblate® Neuro System for the treatment of essential tremors in patients who have not responded to medication (β-blockers or anticonvulsant drugs) through the premarket approval process.

**Rationale**
This evidence review was created in July 2004 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through May 13, 2019.

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.

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 (QOL), 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, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one 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.

**Magnetic Resonance-guided Focused Ultrasound**

**Clinical Context and Test Purpose**
The purpose of MRgFUS in patients with uterine fibroids, metastatic bone cancer, other tumors, or essential tremors (ET) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of MRgFUS to treat patients with uterine fibroids, metastatic bone cancer, other tumors, or ET improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant populations of interest are patients with:

- Uterine fibroids
- Metastatic bone cancer who have failed radiotherapy or who are not candidates for radiotherapy
- Other tumors
- ETs who are medication-refractory.

**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**
Comparators of interest, by indication, include:

- For uterine fibroids, alternatives nonsurgical treatment or surgery
- For metastatic bone cancer, supportive care
- For other tumors, the standard of care
- For ET, neurosurgery or standard of care.

**Outcomes**
The following therapies and practices are currently being used, by indication:

- 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 QOL, change in uterine and fibroid volume, pain levels, and pain medication use.

- For metastatic bone cancer, the goal is to alleviate pain. Measures to assess the effect of treatment include pain levels and pain medication use.
- For other tumors, the goal is tumor ablation. Outcomes include reductions in tumor size.
- For ET, the goal is to decrease the frequency of tremors and improve QOL.

**Timing**
Outcome measures can be assessed at several months to several years postprocedure.

**Setting**
The procedure, which can be performed on an outpatient basis, is performed in a specialized treatment center.

**Uterine Fibroids**
Evidence for the use of MRgFUS for the treatment of uterine fibroids consists of two small RCTs and many observational studies.

**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. 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 six 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 (ie, 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 will be forthcoming.

A pilot sham-controlled randomized trial evaluating MRgFUS for the treatment of uterine fibroids was published by Jacoby et al (2016). The trial included 20 premenopausal women with symptomatic uterine fibroids (women who were pregnant or had a desire for future children were excluded). Patients were randomized to MRgFUS with the ExAblate 2000 System (n=13) or to a sham treatment not using thermal energy (n=7). The investigators did not specify primary outcomes. 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 six of seven in the placebo group received their allocated treatment; all patients who were treated completed three months of follow-up. Patients were unblinded at three months, and those in the sham group were given the option of active treatment.

QOL outcomes included the Uterine Fibroid Symptom and Quality of Life Questionnaire, which has scales that include the symptom severity score and health-related QOL score. The 36-Item Short-Form Health Survey, which includes the Mental Component Summary and Physical Component Summary, was also used. At 4- and 12-week follow-ups, there were no statistically significant differences between the MRgFUS and the sham groups in the symptom severity score, the health-related QOL score, and the 36-Item Short-Form Health Survey Physical Component Summary or Mental Component Summary scores. Change in uterine and fibroid volume, however, differed significantly between groups at 12 weeks. Uterine volume decreased by 17% in the MRgFUS group and by 3% in the sham group (p=0.04). Total fibroid volume decreased by 18% in the MRgFUS group and did not change in the sham group (p=0.03). The trialists concluded that a larger sham-controlled randomized trial of MRgFUS was feasible.

**Systematic Reviews**
The remaining published studies are nonrandomized. 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. 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.

**Nonrandomized Studies**
The following studies were published after the Gizzo (2014) systematic review.

Chen et al (2016) evaluated 107 women undergoing MRgFUS for the treatment of uterine fibroids. 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.

Froeling et al (2013) reported on 121 women with symptomatic uterine fibroids who were eligible for treatment with MRgFUS and UAE. Forty-four (36%) women were lost to follow-up. Follow-up data at 60 months were available for 77 women, 41 in the UAE group, and 36 in the MRgFUS group. The primary outcome was the rate of reintervention (eg, repeat MRgFUS, myomectomy, hysterectomy, endometrial ablation). During follow-up, 5 (12%) women in the UAE group and 24 (67%) women in the MRgFUS group experienced a reintervention (statistical comparison not reported). Health-related QOL scores (secondary outcomes) were significantly better in the UAE group than in the MRgFUS group at follow-up.
Fertility Following MRgFUS 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. 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, 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.

Section Summary: Uterine Fibroids
For the treatment of uterine fibroids, there are 2 small 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 treatment. 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 QOL 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. 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. In a 2013 comparative study, outcomes appeared to be better with UAE than with MRgFUS. There is insufficient evidence on the long-term treatment effects, recurrence rates, and impact on future fertility and pregnancy of this therapy.

Palliative Treatment of Bone Metastases
Evidence for the use of MRgFUS for the treatment of painful bone metastases consists of a large RCT and many observational studies.

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. Patients rated tumor pain on a 10-point scale numeric rating scale (NRS) at four or greater. While they could have up to five painful lesions, only one lesion was treated, and it had to cause pain at
least two 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 four 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 one MRgFUS or placebo sonication. Missing values were imputed using the last observation carried forward method.

The primary efficacy endpoint, assessed at three 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=0.01), favoring active treatment. When the two 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) of 3.6 (3.1) points in the MRgFUS group and by a mean of 0.7 (2.4) in the placebo group (p<0.01). 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 one patient (associated with noncompliance with the treatment protocol) and fracture in two patients (one 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
Liberman et al (2009) conducted a multicenter prospective study in Canada, Israel, and Germany. The study included 31 patients with painful bone metastases who had failed or refused other treatment options; 25 (81%) patients were available for 3-month follow-up. Mean visual analog scale score decreased from 5.9 at baseline to 1.8 three months after treatment. Thirteen of 25 patients
who used nonopioid analgesics and 6 of 10 who used opioids decreased medication use after treatment. Neither group reported treatment-related adverse events.

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. Pain was measured by a visual analog scale 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<0.001). 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 single industry-sponsored RCT that 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. Several case series have also reported improvements in pain and patient satisfaction with MRgFUS.

Treatment of Other Tumors
Only small case series have assessed the safety and/or efficacy of MRgFUS for treating tumors related to breast cancer, brain cancer, prostate cancer, and nonspinal osteoid osteoma. The most recent case series on the use of MRgFUS for breast cancer ablation was published by Merckel et al (2016). Ten patients with early-stage invasive breast cancer underwent MRgFUS prior to surgical resection. Ablation was confirmed histopathologically in six 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.

In addition, several case series have investigated the use of MRgFUS for desmoid tumors. Avedian et al (2016) used MRgFUS to treat 9 patients with desmoid tumors. Five patients were available for follow-up for at least 12 months. Mean decrease in tumor size was 36% (95% confidence interval, 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. Each patient received multiple MRgFUS treatments. In this case series, 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. Treatment times ranged from 0.8 to 8 hours. Results were presented on nine patients (three were lost to follow-up before six months, three 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**
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. Several ongoing trials are evaluating the safety and efficacy of MRgFUS for other tumors, with completion dates in the coming years (see Table 1).

**Essential Tremors**
Evidence for the use of MRgFUS to treat medicine-refractory ET consists of a technology assessment, a meta-analysis, and a single-arm study published subsequent to the technology assessment.

**Systematic Reviews**
The technology assessment was published by Health Quality Ontario (2018). 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, the chart reviews compared MRgFUS with deep brain stimulation and radiofrequency thalamotomy. 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 QOL. The high-quality RCT by Elias et al (2016) is discussed below.

Mohammed et al (2018) conducted a meta-analysis evaluating the use of MRgFUS to treat medicine-refractory ET. The literature search, conducted through August 2017 identified 9 studies (total n=160 patients) for inclusion, 8 of which were also evaluated in the Ontario technology assessment. Pooled analyses found significant improvements in the mean percentage change in the Clinical Rating Scale for Tremor scores (62.2%) and Quality of Life in Essential Tremor scores (46.5%). Complications included nausea, vomiting, and ataxia, which decreased during the 12-month follow-up.

**Randomized Controlled Trials**
A single high-quality study, a double-blind, sham-controlled randomized trial by Elias et al (2016), 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 two medical therapies. Patients were randomized to MRgFUS thalamotomy (n=56) or sham treatment (n=20). Outcomes were tremor severity, improvement, and QOL, measured at three months postprocedure. Patients in the treatment group were followed for an additional 12 months. Mean score for hand tremor improved significantly from baseline in the treatment group (47%) compared with
the sham group (0.1%) at 3 months. Change in mean functional improvement score from baseline differed significantly in the MRgFUS group (62%) compared with the sham group (3%) at 3 months. 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 QOL 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.25 Because nine patients from the original trial received additional treatment during the two-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: ET
Evidence for the use of MRgFUS in the treatment of medicine-refractory ET consists of a technology assessment that included a high-quality RCT; a meta-analysis; and a noncomparative study published after the technology assessment. The assessment did not pool results from the studies but concluded, overall, MRgFUS decreased tremor severity and improved QOL. The meta-analysis, which included nine studies total (eight were also in the technology assessment), found that MRgFUS significantly improved Clinical Rating Scale for Tremor scores as well as QOL measures. The sham-controlled randomized trial which was considered high-quality found significant improvements in the treatment group in tremor severity, functional improvement, and QOL after three months of follow-up, and these results were maintained through two years of follow-up.

Summary of Evidence
For individuals who have uterine fibroids who receive MRgFUS, the evidence includes two small RCTs, nonrandomized comparative studies, and case series. The relevant outcomes are symptoms, QOL, resource utilization, and treatment-related morbidity. One RCT (n=20) has reported some health outcomes but its primary purpose was to determine the feasibility of a larger trial. It did not find statistically significant differences in QOL outcomes between active and sham treatment groups but it did find lower fibroid volumes after active treatment. This trial did not have an active comparator, the clinical significance of the primary outcome was unclear, and there were no follow-up data beyond one year. The second RCT (n=49) is ongoing; preliminary results at 6 weeks posttreatment, comparing MRgFUS with uterine artery embolization have shown that the 2 groups are comparable in medication use and symptom improvement following treatments. Patients in the MRgFUS group reported recovering significantly faster than patients in the uterine artery embolization group, as measured by time to return to work and time to normal activities. In a separate 2013 comparative study, outcomes appeared to be better with uterine artery embolization than with MRgFUS. Long-term data on the treatment effects, recurrence rates, and impact on future fertility and pregnancy are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals with metastatic bone cancer who have failed or are not candidates for radiotherapy who receive MRgFUS, the evidence includes a sham-controlled randomized trial and several case series. The relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The RCT found statistically significant improvements after MRgFUS in a composite outcome comprised of a reduction in pain and morphine use, and in pain reduction as a stand-alone outcome. A substantial proportion of patients in the treatment group experienced adverse events but most events were transient and not severe. The case series reported reductions in pain following MRgFUS treatment, consistent with the RCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with other tumors (eg, breast cancer, brain cancer, prostate cancer, desmoid, nonspinal osteoid osteoma) who receive MRgFUS, the evidence includes small case series. The relevant outcomes are symptoms, health status measures, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with medicine-refractory ET who receive MRgFUS, the evidence includes two systematic reviews that identified an RCT and several observational studies. The relevant outcomes include symptoms, functional outcomes, QOL, and treatment-related morbidity. The assessment did not pool study results but concluded that, overall, MRgFUS decreased tremor severity and improved QOL. The sham-controlled randomized trial found significant improvements in the treatment group in tremor severity, functional improvement, and QOL after three months of follow-up. The improvements in hand tremor score, function, and QOL were maintained at the two-year follow-up. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Society for Radiation Oncology
The American Society for Radiation Oncology (2017) 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. 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."
National Comprehensive Cancer Network

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 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00981578</td>
<td>A Feasibility Study to Evaluate the Safety and Initial Effectiveness of ExAblate MR Guided Focused Ultrasound Surgery in the Treatment of Pain Resulting from Metastatic Bone Tumors with the ExAblate 2100 Conformal Bone System</td>
<td>50</td>
<td>Jun 2019 (ongoing)</td>
</tr>
<tr>
<td>NCT01833806</td>
<td>A Phase IV Post Approval Clinical Study of ExAblate Treatment of Metastatic Bone Tumors for the Palliation of Pain</td>
<td>70</td>
<td>Oct 2020</td>
</tr>
<tr>
<td>NCT01473485</td>
<td>A Study to Evaluate the Safety and Feasibility of Transcranial MRI-Guided Focused Ultrasound Surgery in the Treatment of Brain Tumors</td>
<td>10</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>NCT00147056</td>
<td>A Study to Evaluate the Safety and Feasibility of Transcranial MRI-Guided Focused Ultrasound Surgery in the Treatment of Brain Tumors</td>
<td>10</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>NCT02252380</td>
<td>A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-Refractory Movement Disorders</td>
<td>10</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT02260752</td>
<td>Comparing Options for Management: Patient-Centered Results for Uterine Fibroids</td>
<td>10,000</td>
<td>Apr 2020</td>
</tr>
<tr>
<td>NCT01657942</td>
<td>Focal MR Guided Focused Ultrasound Treatment of Localized Low and Intermediate Risk Prostate Lesions</td>
<td>100</td>
<td>Oct 2020</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------</td>
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</tr>
<tr>
<td>NCT02794558^a</td>
<td>A Clinical Study to Evaluate the Safety and Effectiveness of MR Guided Focused Ultrasound Surgery in the Treatment of Early Breast Carcinomas</td>
<td>100</td>
<td>Apr 2021</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01285960^a</td>
<td>A Clinical Study to Evaluate Safety of the ExAblate Model 2100 Type 1.1 System in the Treatment of Symptomatic Uterine Fibroids</td>
<td>106</td>
<td>Apr 2016 (completed)</td>
</tr>
<tr>
<td>NCT01620359^a</td>
<td>Study of ExAblate Focused Ultrasound Ablation of Breast Cancer under MR Guidance and MRI Evaluation of Ablation</td>
<td>14</td>
<td>Jul 2016 (completed)</td>
</tr>
<tr>
<td>NCT01834937^a</td>
<td>A Post Approval Registry: ExAblate Treatment of Metastatic Bone Tumors for the Palliation of Pain</td>
<td>17</td>
<td>Apr 2017 (completed)</td>
</tr>
<tr>
<td>NCT01091883^a</td>
<td>Phase IIIA Study Comparing the Safety and Effectiveness of MR Guided Focused Ultrasound and External Beam Radiation for Treatment of Metastatic Bone Tumors and Multiple Myeloma</td>
<td>60</td>
<td>Mar 2018 (unknown)</td>
</tr>
<tr>
<td>NCT01226576^a</td>
<td>Focal MR Guided Focused Ultrasound Treatment of Localized Low-Intermediate Risk Prostate Cancer: Feasibility Study</td>
<td>8</td>
<td>Dec 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

REFERENCES

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

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

**ICD-10 Codes**

- **C50.01-C50.92**
  Malignant neoplasm of the breast code range

- **C61**
  Malignant neoplasm of the prostate

- **C71.0-C71.9**
  Malignant neoplasm of the brain code range

- **C79.51**
  Secondary malignant neoplasm of bone

- **D16.0-D16.9**
  Benign neoplasm of the bone code range (includes Osteoid Osteoma)

- **D25.0-D25.9**
  Leiomyoma of uterus code range

- **D48.1**
  Neoplasm of uncertain behavior of connective and other soft tissue (includes desmoid)

- **G25.0-G25.1**
  Familial and drug induced tremors. (includes essential benign)

**Policy Implementation/Update Information**

- **3/1/07**
  New policy; considered investigational.

- **9/1/07**
  Policy statement expanded to include the use of MRI-guided high-intensity ultrasound ablation of other tumors as investigational. Policy moved from Ob/Gyn/Reproduction section to Surgery section and assigned a new number (previous number was 4.01.20).

- **9/1/08**
  No policy statement changes.

- **9/1/09**
  No policy statement changes.

- **9/1/10**
  Palliative treatment of bone metastases added to the policy statement on treatment of conditions other than uterine fibroids.

- **9/1/11**
  No policy statement changes.

- **9/1/12**
  No policy statement changes.

- **9/1/13**
  No policy statement changes.

- **9/1/14**
  Reworded investigational statement does not change the intent of statement. Added HCPCS code C9734.

- **8/1/15**
  Statement added the MRgFUS may be considered medically necessary for pain palliation in adult patients with metastatic bone cancer who failed or are not candidates for radiotherapy. Bullet point on bone metastases removed from Investigational statement.

- **8/1/16**
  Policy statements unchanged. Global change to policy to remove
“imaging” (eg, title, policy statement) to standardize terminology to magnetic resonance-guided focused ultrasound (MRgFUS).

8/1/17 No policy statement changes.
8/1/18 No policy statement changes.
12/1/18 A policy statement added that MRgFUS ablation may be considered medically necessary for the treatment of medicine-refractory essential tremors. Added ICD-10 Code G25.0.
8/1/19 No policy statement changes.
8/1/20 No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.