BlueCross BlueShield of Alabama

Name of Policy:
Magnetic Resonance Guided Focused Ultrasound (MRgFUS)

Policy #: 178
Category: Obstetrics/Gynecology
Latest Review Date: August 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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 that patient's illness, injury or disease.*

Description of Procedure or Service:

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

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 treatment.

Metastatic Bone Disease

Metastatic bone disease is one 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, the standard care is to use 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 (□-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

MRgFUS is a noninvasive treatment that combines two technologies, focused ultrasound and MRI. The ultrasound beam penetrates through the soft tissues and, using MRI for guidance and monitoring, the beam can be focused on targeted sites. The ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis while sparing the surrounding normal structures. The ultrasound waves from each sonication are focused at a focal point which 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 approximately 65°C to 85°C), which is sufficient to achieve tissue ablation at the focal point. In addition to providing guidance, the associated MRI can provide on-line thermometric imaging that provides a temperature "map" that can further 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) have approved the ExAblate® MRgFUS system for two indications: treatment of uterine fibroids and for palliation of pain associated with tumors metastatic to bone. The ultrasound equipment is specially designed to be compatible with MR magnets and is integrated into standard clinical MRI units. It includes a patient table, which includes a cradle housing the focused ultrasound transducer in a water or light oil bath. Some models of the device 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 treatment of other tumors, including breast, prostate, and brain tumors.

For coverage information regarding radiofrequency ablation of bone tumors, refer to medical policy #119- *Radiofrequency Ablation of Solid Tumors Excluding Liver Tumors.

***For coverage information regarding cryosurgical ablation of bone tumors, refer to medical policy #429- *Cryosurgical Ablation of Miscellaneous Solid Tumors other than Liver, Prostate, or Dermatologic Tumors*.**

***For coverage information regarding focal treatments of the prostate, refer to medical policy 596- *Focal Treatments for Prostate Cancer*.**

Policy:

Effective for dates of service on and after August 17, 2018:
Magnetic resonance-guided high-intensity ultrasound ablation meets Blue cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of **medicine-refractory essential tremors.**

Magnetic resonance imaging (MRI)-guided high-intensity ultrasound ablation does not meet Blue Cross and Blue Shield's medical criteria for coverage and is considered **investigational for all other situations, including but not limited to:**

- Treatment of uterine fibroids;
- Pain palliation for patients with metastatic bone cancer;
- Treatment of other tumors e.g., brain cancer, prostate cancer and breast cancer

Effective for dates of service prior to August 17, 2018:

Magnetic resonance imaging (MRI)-guided high-intensity ultrasound ablation does not meet Blue Cross and Blue Shield's medical criteria for coverage and is considered **investigational.** This includes, but is not limited to, its use in the following situations:

- Treatment of uterine fibroids;
- Pain palliation for patients with metastatic bone cancer;
- Treatment of other tumors e.g., brain cancer, prostate cancer and breast cancer.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature search was performed through May 7, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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 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 essential tremors 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
- Essential tremors that 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, standard of care
- For essential tremors, 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 quality of life (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 essential tremors, 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.

Essential Tremors

Evidence for the use of MRgFUS to treat medicine-refractory essential tremors 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 essential tremors. 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 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 2 medical therapies. Patients were randomized to MRgFUS thalamotomy (n=56) or sham treatment (n=20). Outcomes were tremor severity, improvement, and QOL, measured at 3 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. 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 medicine-refractory essential tremors 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 9 studies total (8 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 3 months of follow-up, and these results were maintained through 2 years of follow-up.

Uterine Fibroids

Evidence for the use of MRgFUS for the treatment of uterine fibroids consists of 2 small RCTs and many observational studies.

Randomized Controlled Trials

In 2017, Barnard et al published preliminary results from Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT) study, a parallel RCT and cohort study comparing MRgFUS with fibroid embolization for the treatment of 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 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 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 limitation of the trial was the inability to recruit more patients. Long-term follow-up results will be forthcoming.

In 2016, a pilot sham-controlled RCT with 20 patients was published by Jacoby et al. The trial included 20 premenopausal women with symptomatic uterine fibroids. Women who were pregnant or had a desire for future fertility were excluded. Patients were randomized to MRgFUS with the ExAblate 2000 system (n=13) or a sham treatment in which no thermal energy was delivered (n=7). The investigators did not specify primary outcomes. The sample size was selected, not to have sufficient statistical power, but to assess the feasibility of a larger trial. All patients assigned to the MRgFUS group and six of seven in the placebo group received their allocated treatment and all treated patients completed three months of follow-up. Patients were unblinded at three months and the sham group was given the option of active treatment.

QOL outcomes included the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL), which has scales including the Symptom Severity Score (SSS) and Health Related Quality of Life (HRQL) score. The 36-Item Short-Form Health Survey, which includes the Mental Component Summary (MCS) and Physical Component Summary (PCS), was also used. At both the four and 12-week follow-ups, there were no statistically significant differences between the MRgFUS and sham groups in the SSS, HRQL, PCS, or MCS. 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 18% in the MRgFUS group and did not change in the sham group (p=0.03). The authors concluded that larger sham controlled trials are feasible.

Systematic Reviews

The remaining published studies are nonrandomized. A systematic review, published by Gizzo et al in 2013, identified 38 uncontrolled studies with a total of 2500 patients who underwent MRgFUS for treatment of uterine fibroids. All of the published studies included women older than age 18 years with symptomatic uterine fibroids, and most excluded patients who desired future pregnancies. Reviewers did not pool study findings but concluded that, overall, MRgFUS appeared to be a safe, noninvasive option for treating uterine fibroids. Future research was 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 systematic review:
In 2016, Chen et al 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 MRI. At the 6-month follow-up, 93% efficacy was reported.

In 2013, Froeling et al reported on 121 women with symptomatic uterine fibroids who were equally eligible for treatment with MRgFUS and uterine artery embolization (UAE). Forty-four (36%) women were lost to follow-up. Follow-up data at approximately 60 months were available on 77 women, 41 in the UAE group and 36 in the MRgFUS group. The primary study outcome was the rate of reintervention (e.g., repeat MRgFUS, myomectomy, hysterectomy, endometrial ablation). During follow-up, five (12%) women in the UAE group and 24 (67%) women in the MRgFUS group experienced a reintervention (statistical comparison not reported).Healthcare QOL scores, secondary outcomes, were significantly better in the UAE group compared with 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 eight months after treatment. They included eight 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 of the 54 pregnancies (42%) resulted in deliveries, 11 were ongoing beyond 20 weeks at the time the article was written. There were 14 miscarriages (26%) and seven elective

terminations (13%). Among the 22 live births, the mean birth weight of live births was 3.3 kg, and the vaginal delivery rate was 64%. The article provides initial information on the impact of MRgFUS for uterine fibroids on pregnancy; findings suggest that fertility may be maintained but that the number of cases is too small to draw definitive conclusions. Moreover, the study does not address the possible impact of MRgFUS treatment on the ability to become pregnant.

Section Summary: Uterine Fibroids

For the treatment of uterine fibroids, there are 2 small RCTs, one with 49 women that compared MRgFUS with UAE and one with 20 women that had a sham control. Several non-randomized studies have also compared MRgFUS with a different treatment. The sham controlled RCT determined that a larger trial is 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 the 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

An industry sponsored RCT evaluating the ExAblate System for the treatment of painful bone metastases was published by Hurwitz et al in 2014. The trial included patients with at least 3 months of life expectancy who had bone metastases that were painful, despite radiotherapy, or who were unsuitable for or declined radiotherapy. Patients rated tumor pain on a numeric rating scale (NRS) at 4 or higher on a 10-point scale. While they could have up to 5 painful lesions, only 1 lesion was treated, and it had to cause at least 2 points greater pain on the NRS than any other lesion. Also targeted tumors needed to be device-accessible.

Study participants were randomized in a 3:1 ratio 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 three month follow-up. A much larger proportion of the placebo group dropped out; 17 of 35 who were treated (49%) decided to have rescue MRgFUS treatment after 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 outpoint, assessed at three months, was a composite outcome comprised of 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 two points and if their MEDD intake did not increase more than 25% from baseline to three months. NRS score and MEDD intake separately were reported as secondary outcomes.

Seventy-two of 112 (64.3%) patients in the MRgFUS group and seven of 35 patients (20%) in the control group were considered responders, as previously defined. The difference between groups was statistically significant (p=0.01), favoring active treatment. When the two measures that made up the primary end point 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 of 3.6 points (SD=3.1) in the MRgFUS group and a mean of 0.7 (SD=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 patients (45.5%) in the MRgFUS group and one (2.9%) in the placebo group experienced at least one AE. Most AEs were transient, and the most common was sonication pain, experienced by 36 patients (32.1%) in the MRgFUS group. In 17 patients (15.2%), sonication pain was severe; three patients did not complete treatment due to pain. The most clinically significant AEs 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 limitations of the trial include 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 three month follow-up; however, the authors stated that this low completion rate was due to lack of response to placebo treatment.

Observational Studies

In 2009, Liberman et al published findings of a multicenter prospective study conducted in Canada, Israel, and Germany. The study included 31 patients with painful bone metastases who had failed or refused other treatment options; 25 patients (81%) were available for three-month follow-up. The mean visual analog scale score decreased from 5.9 before treatment to 1.8 three months after treatment. Thirteen of 25 patients who used nonopioid analgesics and six of ten who used opioids decreased medication use after treatment. Neither group reported any treatment-related adverse events.

In a 2017 recent case series, Arrigoni et al evaluated use of MRgFUS in 14 patients with intra-articular benign bone lesions who were followed for 12 months. Pain was measured by visual analog scale and all patients underwent computed tomography and magnetic resonance imaging. Mean pain scores decreased from 7.8 pretreatment 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 base consists of a single industry-sponsored RCT which found improvement after MRgFUS in a composite outcome comprised of 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 AEs, but most of these were nonsevere and transient. Although results are promising

for the palliation treatment of bone metastases, additional RCTs with appropriate sham controlled studies are needed.

Treatment of other Tumors
Only small case series have been published investigating the safety and/or efficacy of MRgFUS for treating other tumors, including 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 in 2016. 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.

In addition, several case series have investigated the use of MRgFUS for desmoid tumors. One by 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% 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. Each patient received multiple MRgFUS treatments. In this case series, the authors noted that 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. 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
Currently, evidence on the use of MRgFUS for the treatment of other tumors consists of small case series. There are several ongoing trials evaluating the safety and efficacy of MRgFUS for other tumors, with completion dates in the coming years.

Summary
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.

For individuals who have uterine fibroids who receive MRgFUS, the evidence includes 2 small 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 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 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. However, there is insufficient evidence from randomized controlled trials or nonrandomized controlled trials that MRgFUS improves the net health outcome for individuals with metastatic bone cancer. Additional well-designed studies with sufficient numbers of patients, high rates of follow-up and sufficient lengths of follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with other tumors (e.g., 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.

Practice Guidelines and Position Statements

Society of Obstetricians and Gynaecologists of Canada

In 2015, the Society of Obstetricians and Gynaecologists of Canada published a clinical practice guideline entitled "Management of Uterine Fibroids in Women with Otherwise Unexplained Infertility." The guideline states that there are no studies comparing MRgFUS with myomectomy or in women with fibroids who have infertility as their primary complaint, and thus additional data are needed before the treatment is offered to this patient population.

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
Guidelines from the National Comprehensive Cancer Network on bone cancer (v.2.2018), breast cancer (v.1.2018), brain cancer (v.1.2018), and prostate cancer (v.2.2018) do not mention MRgFUS as a treatment option.

U.S. Preventive Services Task Force Recommendations
Not applicable

Key Words:

Fibroids, ultrasound ablation, MRI-guidance, ultrasound ablation of uterine fibroids, ExAblate 2000, high intensity ultrasound ablation; uterine, leiomyoma; uterine; high intensity ultrasound ablation (HIFU), ExAblate, ultrasound ablation of breast tumors, ultrasound ablation of brain tumors, ultrasound ablation of prostate cancer, ultrasound ablation of bone metastasis, trans rectal high intensity focused ultrasound for prostate cancer, Ablatherm®, Sonablate 500®; MRgFUS, essential tremors

Approved by Governing Bodies:

In October 2004, the U.S. Food and Drug Administration (FDA) approved via the premarket application (PMA) process, the ExAblate® 2000 System (Insightec, Inc., Haifa, Israel) 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 less than 24 weeks who have completed childbearing.

In October 2012, the FDA approved the ExAblate® System, Model 2000/2100/2100 VI via the PMA process. The intended use of the device is for pain palliation in adult patients with metastatic bone cancer who failed or are not candidates for radiation therapy. The device was evaluated through an expedited review process. The FDA required a post-approval 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 (beta blockers or anticonvulsant drugs) through the premarket approval process.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT codes:

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
0071T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume of 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

There is no specific code for MRgFUS in reference to bone cancer. This code may come in on unlisted code **20999** along with the appropriate radiology guidance code.

These CPT codes should not be used in conjunction with **51702** (insertion of temporary indwelling bladder catheter, simple) or **77022** (magnetic resonance imaging guidance for, and monitoring of, visceral tissue ablation). Prior to the introduction of the above codes, the procedure may have been coded for using several codes describing the individual components of the procedure. CPT codes **0071T-0072T** describe the comprehensive service.

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Policy History:

Medical Policy Group, June 2004 **(3)**
Medical Policy Administration Committee, July 2004
Available for comment September 7-October 21, 2004
Medical Policy Group, June 2005 **(2)**
Medical Policy Group, June 2006 **(1)**
Medical Policy Group, August 2006 **(2)**
Medical Policy Administration Committee, August 2006
Available for comment August 30-October 13, 2006
Medical Policy Group, August 2007 **(1)**
Medical Policy Group, October 2007 **(3)**
Medical Policy Group, May 2009 **(1)**
MPRM Update, February 2010
Medical Policy Group, February 2010 **(2)**
Medical Policy Administration Committee, February 2010
Available for comment February 23-April 8, 2010
Medical Policy Group, March 2011; Reference added to Policy section
Medical Policy Administration Committee, Marcy 2011
Available for comment April 4 – May 18, 2011
Medical Policy Group March 2012 **(2):** 2012 Update: Key Points & References
Medical Policy Panel February 2013
Medical Policy Group, May 2013 (**4**): Update to Title (removed for the treatment of Uterine Fibroids and Other Tumors), Description, changed Policy verbiage, Key Points, Approved governing bodies and references.
Medical Policy Administration Committee, May 2013
Available for comment May 22 through July 5, 2013
Medical Policy Panel, February 2014
Medical Policy Group, February 2014 **(1):** Update to Key Points and References; no change to policy statement
Medical Policy Panel, February 2015
Medical Policy Group, February 2015 **(4):** Updates to Key Points, Coding, and References. No change to policy statement.
Medical Policy Group **(4):** Added statement under policy section to refer to MP# 596 for Focal Treatments for Prostate Cancer.
Medical Policy Group, November 2015: 2016 Annual Coding Update. Added CPT code 0398T to current coding.
Medical Policy Panel, February 2016
Medical Policy Group, February 2016 **(4):** Updates to Description, Key Points, and References. No change to policy statement. Title change to take out “Imaging”.
Medical Policy Panel, July 2017
Medical Policy Group, July 2017 **(4):** Updates to Description, Key Points, Coding and References. Removed CPT code 0398T from Current Coding. Code was added in error.

Medical Policy Panel, July 2018
Medical Policy Group, August 2018 **(4):** Updates to Description, Policy, Key Points, Key Words, Coding, and References. Added 0398T to Current Coding for essential tremors. Added Key Word essential tremors. Updated policy section to include coverage for medicine refractory essential tremors. Available for comment August 18 through October 1, 2018
