Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors

Policy # 00175
Original Effective Date: 08/24/2005
Current Effective Date: 07/11/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Stereotactic Radiosurgery and Stereotactic Body Radiotherapy is addressed separately in medical policy 00045.

Note: The use of Radiofrequency Ablation (RFA) of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00182.

Note: Cryosurgical Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00220.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Osteolytic Bone Metastases
Based on review of available data, the Company may consider radiofrequency ablation (RFA) to palliate pain in patients with osteolytic bone metastases who have failed or are poor candidates for standard treatments such as radiation or opioids to be **eligible for coverage**.

Osteoid Osteomas
Based on review of available data, the Company may consider RFA to treat osteoid osteomas that cannot be managed successfully with medical treatment to be **eligible for coverage.**

Localized Renal Cell Carcinoma
Based on review of available data, the Company may consider RFA to treat localized renal cell carcinoma (RCC) that is no more than 4 cm in size to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for RFA to treat localized renal cell carcinoma (RCC) that is no more than 4 cm in size will be considered when EITHER of the following is met:

- In order to preserve kidney function in patients with significantly impaired renal function (i.e., the patient has one kidney or renal insufficiency defined by a glomerular filtration rate [GFR] of less than 60 mL/min/m^2) when the standard surgical approach (i.e., resection of renal tissue) is likely to substantially worsen kidney function; or
- Patient is not considered a surgical candidate.

Isolated Peripheral Non-Small Cell Lung Cancer Lesion
Based on review of available data, the Company may consider RFA to treat an isolated peripheral non-small cell lung cancer (NSCLC) lesion that is no more than 3 cm in size to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for RFA to treat an isolated peripheral NSCLC lesion that is no more than 3 cm in size will be considered when ALL of the following criteria are met:

- Surgical resection or radiation treatment with curative intent is considered appropriate based on stage of disease, however, medical co-morbidity renders the individual unfit for those interventions; and
- Tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

Malignant Non-Pulmonary Tumor(s) Metastatic to the Lung
Based on review of available data, the Company may consider RFA to treat malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for RFA to treat malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size when ALL of the following criteria are met:

- In order to preserve lung function when surgical resection or radiation treatment is likely to substantially worsen pulmonary status or the patient is not considered a surgical candidate; and
- There is no evidence of extrapulmonary metastases; and the tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart; and
- No more than 3 tumors per lung should be ablated; and
- Tumors should be amenable to complete ablation; and
- Twelve months should elapse before a repeat ablation is considered.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers RFA to be **investigational*** as a technique for ablation of:

- Breast tumors;
- Lung cancer not meeting the criteria above;
- Renal cell cancer not meeting criteria above;
- Osteoid osteomas that can be managed with medical treatment;
- Painful bony metastases as initial treatment; and
- All other tumors outside the liver including, but not limited to, the head and neck, thyroid, adrenal gland, ovary, and pelvic/abdominal metastases of unspecified origin.

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Policy Guidelines

The following are additional criteria developed by clinical judgment or consensus and existing guidelines for the use of RFA to treat metastatic tumors to the lung:

- No more than 3 tumors per lung should be ablated;
- Tumors should be amenable to complete ablation; AND
- Twelve months should elapse before a repeat ablation is considered.

Background/Overview

RADIOFREQUENCY ABLATION

RFA was initially developed to treat inoperable tumors of the liver (see medical policy 00182). Recently, studies have reported on the use of RFA to treat other tumors. For some of these, RFA is being investigated as an alternative to surgery for operable tumors. Well-established local or systemic treatment alternatives are available for each of these malignancies. The hypothesized advantages of RFA for these cancers include improved local control and those common to any minimally invasive procedure (e.g., preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

Goals of RFA may include (1) controlling local tumor growth and preventing recurrence; (2) palliating symptoms; and (3) extending survival duration for patients with certain tumors. The effective volume of RFA depends on the frequency and duration of applied current, local tissue characteristics, and probe configuration (e.g., single vs multiple tips). RFA can be performed as an open surgical procedure, laparoscopically or percutaneously, with ultrasound or computed tomography (CT) guidance.

Potential complications associated with RFA include those caused by heat damage to normal tissue adjacent to the tumor (e.g., intestinal damage during RFA of kidney), structural damage along the probe track (e.g., pneumothorax as a consequence of procedures on the lung), and secondary tumors (if cells seed during probe removal).

OSTEOLYTIC BONE METASTASES

After lung and liver, bone is the third most common metastatic site and is relatively frequent among patients with primary malignancies of the breast, prostate, and lung. Bone metastases often cause osteolysis (bone breakdown), resulting in pain, fractures, decreased mobility, and reduced quality of life.

Treatment

External-beam radiotherapy often is the initial palliative therapy for osteolytic bone metastases. However, pain from bone metastases is refractory to radiotherapy in 20% to 30% of patients, while recurrent pain at previously irradiated sites may be ineligible for additional radiation due to risks of normal tissue damage. Other alternatives include hormonal therapy, radiopharmaceuticals (e.g., strontium 89), and bisphosphonates. Less often, surgery or chemotherapy may be used for palliation, and intractable pain may require opioid medications. RFA has been investigated as an alternative for palliation of bone metastases.

OSTEOID OSTEOMAS

Osteomas are the most common benign bone tumor, comprising 10% to 20% of benign and 2% to 3% of all bone tumors. They are typically seen in children and young adults, with most diagnosed in patients between 5 and 20 years of age. Osteomas are most common in the lower extremity (usually the long bones, mainly the femur) and less common in the spine. These tumors typically have a characteristic clinical presentation and radiologic appearance, with pain, usually continuous and worse at night, and usually relieved by aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). The natural history of the osteoid osteoma varies based on location, and although they rarely exceed 1.5 cm in diameter, may produce bone widening and deformation, limb length inequality, or angular deviations when near a growth plate. When located in the spine, these lesions may lead to painful scoliosis or torticollis. Sometimes, they heal spontaneously after 3 to 7 years.

Treatment

Treatment options include medical management with NSAIDs, surgical excision (wide/en bloc excision or curetting), or the use of CT- or magnetic resonance imaging (MRI)–guided minimally invasive procedures including core drill excision, laser photocoagulation, or RFA. For many years, complete surgical excision was the classic treatment of osteomas, usually performed in patients with pain, despite medical management. However, a substantial incision may be necessary, with the removal of a considerable amount of bone (especially in the neck of the femur). This increases the need for bone grafting plus internal fixation (which often necessitates a second procedure to remove the metal work). Other possible risks include avascular necrosis of the femoral head and postoperative pathologic fracture. In addition, surgical excision leads to a lengthier convalescence and postoperative immobilization. Anatomically inaccessible tumors may not be completely resectable and may recur. RFA of osteoid osteoma is done with a needle puncture, so no incision or sutures are needed; further, patients may immediately walk on the treated extremity and return to daily activities when the anesthetic effect wears off. The risk of recurrence with RFA of an osteoma is 5% to 10%, and recurrent tumors can be retreated with RFA. In general, RFA is not performed in many spinal osteomas because of possible thermal-related nerve damage.

LOCALIZED RENAL CELL CARCINOMA

Radical nephrectomy remains the principal treatment of RCC; however, partial nephrectomy or nephron-sparing surgery has been shown to be as effective as radical nephrectomy, with comparable long-term recurrence-free survival rates, in a select group of patients. Alternative therapy such as RFA is of interest in patients with small renal tumors when preservation of renal function is necessary (e.g., in patients with marginal renal function, a solitary kidney, bilateral tumors) and in patients with comorbidities that would render them unfit for surgery. Another consideration would be in patients at high risk of developing additional renal cancers (e.g., von Hippel-Lindau disease).

PRIMARY PULMONARY AND NONPULMONARY TUMORS

Surgery is the current treatment of choice in patients with stage I primary NSCLC (stage I includes Ia [T1N0M0] and 1b [T2N0M0]). Approximately 20% of patients present with stage I disease, although this number is expected to increase as a result of screening programs, advances in imaging modalities and widespread use of CT scans for other indications. Postsurgical recurrence rates of stage I NSCLC have

been reported as between 20% and 30%, with most occurring at distant sites; locoregional recurrences occur in approximately 12%. Large differences in survival outcome are observed after surgery in stage 1 patients, with 5-year overall survival rates ranging from 77% for small T1 tumors to 35% for large T2 tumors. Untreated, stage I NSCLC has a 5-year overall survival rate range from 6% to 14%.

Patients with early-stage NSCLC who are not surgical candidates may be candidates for radiotherapy with curative intent. In the 2 largest retrospective radiotherapy series, patients with inoperable disease treated with definitive radiotherapy achieved 5-year survival rates of 10% and 27%. In both studies, patients with T1N0 tumors had better 5-year survival rates of 60% and 32%, respectively.

Stereotactic body radiotherapy (SBRT) has gained more widespread use because it is a high-precision mode of therapy that delivers very high doses of radiation. Two- to 3-year local control rates of stage I NSCLC with SBRT have ranged from 80% to 95%. SBRT has been investigated in patients unfit to undergo surgery, with survival rates similar to surgical outcomes.

RFA also is being investigated in patients with small primary lung cancers or lung metastases who are deemed medically inoperable.

BREAST TUMORS
The treatment of small cancers of the breast has evolved from total mastectomy to more conservative treatment options such as lumpectomy, with more acceptable cosmetic outcomes and preservation of the breast. The selection of surgical approach balances the patient's desire for breast conservation and the need for tumor-free margins in resected tissue. Minimally invasive nonsurgical techniques such as RFA are appealing if they can produce local control and survival equivalent to breast-conserving surgical alternatives. Nonsurgical ablative techniques pose difficulties such as the inability to determine tumor size, complete tumor cell death, and local recurrence. Additionally, RFA can burn the skin and damage to muscle, possibly limiting use in patients with tumors near the skin or chest wall.

THYROID TUMORS
Surgical resection is the primary treatment choice for medically unresponsive, symptomatic benign thyroid tumors and thyroid carcinomas. However, techniques for ablation of thyroid tumors (e.g., RFA, microwave ablation) are being investigated.

MISCELLANEOUS TUMORS
RFA has been investigated for use in individuals with different lesions in different anatomic sites. These anatomic sites include, but are not limited to, breast and head and neck.

Head and Neck Cancer
In patients with head and neck cancer with recurrent disease, surgical salvage attempts are poor in terms of local control, survival, and quality of life; further, these recurrent tumors are often untreatable with standard salvage therapies. Palliative chemotherapy or comfort measures may be offered. The safety and efficacy of RFA has been investigated as an option for palliative treatment in these situations.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. FDA issued a statement in September 2008, concerning the regulatory status of RFA. FDA has cleared RFA devices for the general indication of soft tissue cutting, coagulation, and ablation by thermal coagulation necrosis. Under this general indication, RFA can be used to ablate tumors, including lung tumors. Some RFA devices have been cleared for additional specific treatment indications, including partial or complete ablation of nonresectable liver lesions and palliation of pain associated with metastatic lesions involving bone. FDA has not cleared any RFA devices for the specific treatment indication of partial or complete ablation of lung tumors, citing lack of sufficient clinical data to establish safety and effectiveness for this purpose. FDA has received reports of death and serious injuries associated with the use of RFA devices in the treatment of lung tumors.

Centers for Medicare and Medicaid Services (CMS)

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.

Rationale/Source

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

BONE TUMORS

Osteolytic Bone Metastases

Goetz et al (2004) reported on an international study (N=43) conducted at 9 centers in which patients with painful osteolytic bone metastases were treated palliatively with RFA. The study's primary outcome measure was the Brief Pain Inventory–Short Form, a validated scale from 0 (no pain) to 10 (worst pain imaginable). Patient eligibility required baseline values of 4 or more from 2 or fewer painful sites. Thirty-nine (91%) of the patients had previously received opioids to control pain from the lesion(s) treated with RFA, and 32 (74%) had prior radiotherapy to the same lesion. The mean pain score at baseline was 7.9 (range, 4-10). At 4, 12, and 24 weeks after RFA, average pain scores decreased to 4.5, 3.0, and 1.4, respectively (all $p<0.001$). Forty-one (95%) patients achieved a clinically significant improvement in pain scores, prospectively defined as a decrease of 2 units from baseline. Investigators also reported statistically significant ($p=0.01$) decreases in opioid use at weeks 8 (by 59%) and 12 (by 54%).

An earlier case series (2002) showed that palliative RFA provided significant pain relief in 9 (90%) of 10 patients with unresectable, osteolytic spine metastases who had no other treatment options. Pain was reduced by an average of 74%; back pain–related disability was reduced by an average of 27%. Neurologic

function was preserved in 9 patients and improved in the other. An additional small case series (2006) of 24 patients with painful metastatic bone tumors who experienced pain-alleviating effects with RFA is consistent with other evidence.

Section Summary: Osteolytic Bone Metastases
Case series have shown clinically significant pain relief and reduction in opioid use following treatment with RFA of osteolytic pain metastases in patients with no or limited treatment options.

Osteoid Osteomas
Systematic Reviews
Lanza et al reported on a systematic review of various ablative techniques for osteoid osteomas in 2014. Included in the review were 23 articles on RFA, 3 on interstitial laser ablation, and one with a combination of ablation techniques, totaling 27 articles (total N=1772 patients). The mean technical success was 100% and clinical success, defined as being pain-free, ranged from 94% to 98%, depending on length of follow-up. Complications occurred in 2% of patients and included skin or muscle burn in 9 patients, 4 infections, nerve lesions or tool breakage in 3 patients each, delayed skin healing, hematoma, and failure to reach target temperature in 2 patients each, and fracture, pulmonary aspiration, thrombophlebitis, and cardiac arrest in 1 patient each. Eighty-six patients had tumor recurrence.

Longer Term Follow-Up
An observational study published in 2015 evaluated long-term clinical outcomes after CT–guided RFA in patients diagnosed with osteoid osteoma located in the upper and lower extremities. The study population included 52 patients with a typical clinical history and radiologically confirmed osteoid osteoma who received CT-guided RFA treatment from 1998 to February 2014 at a Danish university hospital. The clinical outcome was evaluated based on patient-reported outcome measures and medical record review. The response rate was 52 (87%) of 60. After 1 RFA treatment, 46 (88%) of 52 patients experienced pain relief, and 51 (98%) of 52 patients had pain relief after repeat RFA. One patient underwent open resection after RFA. No major complications were reported; 4 patients reported minor complications including small skin burn, minor skin infection, and hypoesthesia at needle entry point. In all, 50 (96%) of 52 patients were reported to be "very satisfied" with the RFA treatment.

In 2012, Rimondi et al reported on a retrospective study of 557 patients treated with CT-guided RFA as primary treatment for nonspinal osteoid osteomas. All patients were followed for a mean of 3.5 years (range, 0.5-9 years). Pain relief occurred in all 557 patients within the first week after RFA and continued in 533 (96%) patients who remained asymptomatic through their last follow-up. Pain recurrence occurred in 24 (4%) patients. Complications occurred in 5 patients and included thrombophlebitis, skin burn, broken electrode, and 2 procedures in which the RFA generator failed to reach maximum temperature.

Rosenthal et al (2003) reported their experience over an 11-year period with 271 RFA procedures for osteoid osteomas in 263 patients. Short-term outcome was evaluated to detect procedure-related problems; by this definition, all procedures were considered technically successful. Long-term clinical success data (defined as being free of pain without the necessity of additional procedures) were available in 126 patients,

with a complete clinical success observed in 89%. For procedures performed as the initial treatment, the success rate was 91%.

Section Summary: Osteoid Osteomas
Numerous case series and a systematic review of case series have evaluated RFA for the treatment of painful osteoid osteomas. In a systematic review of thermal ablation techniques, clinical success (pain-free) was achieved in 94% to 98% of patients. Most patients (89%-96%) remained pain-free at longer term follow-up.

LOCALIZED RENAL CELL CARCINOMA
Systematic Reviews
In a 2014 systematic review and meta-analysis, Katsanos et al reviewed 1 RCT and 5 cohort studies (total N=587 patients) assessing thermal ablation (RFA or microwave) or nephrectomy for small renal tumors with a mean size of 2.5 cm. The local recurrence rate was 3.6% in both groups (relative risk [RR], 0.92; 95% confidence interval [CI], 0.4 to 2.14; p=0.79). Disease-free survival was also similar in both groups up to 5 years (hazard ratio, 1.04; 95% CI, 0.48 to 2.24; p=0.92). However, the overall complication rate was significantly lower in the patients undergoing ablation (7.4%) vs nephrectomy (11.1%; pooled RR=0.55; 95% CI, 0.31 to 0.97; p=0.04).

In another 2014 systematic review and meta-analysis, Wang et al reported on studies evaluating RFA and partial nephrectomy for stage I (no more than 7 cm across) renal tumors. Reviewers selected 166 studies (total N=9565 patients). The rate of local progression was greater with RFA than with laparoscopic/robotic or open partial nephrectomy (4.6%, 1.2%, 1.9%, respectively; p<0.001). RFA had more frequent minor complications than laparoscopic/robotic or open partial nephrectomy (13.8%, 7.5%, 9.5%, respectively; p<0.001). However, the rate of major complications was greater with open partial nephrectomy than laparoscopic/robotic partial nephrectomy or RFA (7.9%, 7.9%, 3.1%, respectively, p<0.001).

In 2012, El Dib et al conducted a meta-analysis evaluating RFA and cryoablation for small renal masses. Selected were 11 RFA case series (426 patients) and 20 cryoablation case series (457 patients) published through January 2011. The mean tumor size was 2.7 cm (range, 2-4.3 cm) in the RFA group and 2.5 cm (range, 2-4.2 cm) in the cryoablation group. Mean follow-up times for the RFA and cryoablation groups were 18.1 and 17.9 months, respectively. Clinical efficacy, defined as cancer-specific survival rate, radiographic success, no evidence of local tumor progression, or distant metastases, did not differ significantly between groups. The pooled proportion of clinical efficacy for RFA was 90% (95% CI, 86% to 93%) and 89% (95% CI, 83% to 94%) for cryoablation.

Kunkle and Uzzo (2008) conducted a comparative meta-analysis evaluating cryoablation and RFA as primary treatments for small renal masses. Forty-seven case series representing 1375 renal tumors were analyzed. Of 600 lesions treated with cryoablation, 494 underwent biopsy before treatment and 482 of 775 treated with RFA. The incidence of RCC with known pathology was 71.7% in the cryoablation group and 90% in the RFA group. The mean duration of follow-up after RFA was 15.8 months. Local tumor progression was reported in 31 of 600 lesions after cryoablation and in 100 of 775 lesions after RFA, a

difference that was statistically significant (p<0.001). Progression to metastatic disease was described in 6 (1%) of 600 lesions after cryoablation vs 19 (3%) of 775 after RFA (p=0.06).

Longer Term Follow-Up
Stern et al (2007) retrospectively compared patients with stage T1a renal tumors, confirmed by pathology to be RCC, treated with partial nephrectomy (n=34) or RFA (n=34). The mean follow-up for the partial nephrectomy group was 47 months (range, 24-93 months) and 30 months (range, 18-42 months) for the RFA group. The 3-year recurrence-free survival rate was 95.2% for partial nephrectomy and 91.4% for RFA (p=0.58). There were no disease-specific deaths in either group. In this small study, intermediate outcomes for patients with T1a RCCs were similar whether treated with partial nephrectomy or RFA.

A 2016 publication by Iannuccilli et al reported a mean 34.1-month follow-up (range, 1-131 months) of RFA with intent to cure in 203 patients with renal tumors. Patients who were referred for RFA were either high risk or had refused surgery. Smaller tumors were treated with a single electrode with a 2- or 3-cm active tip. Larger tumors were treated with a cluster electrode with 3 active tips. Patients were assessed annually for appearance of residual tumor at the treatment site, and 26 (13%) had residual disease. Treatment effectiveness was 87% during follow-up. The likelihood was increased for tumors 3.5 cm or larger, clear cell subtype, and treatment temperature of 70° or less. All-cause mortality increased with increasing tumor size. The median survival was 7 years for patients with tumors less than 4 cm, with 80% survival at 5 years. Major complications, including urinary stricture or urine leak, occurred in 8 (3.9%) treatments.

Section Summary: Localized Renal Cell Carcinoma
The evidence on RFA for renal tumors includes meta-analyses of an RCT, cohort studies, and case series that have compared RFA with nephrectomy or cryoablation. A 2014 meta-analysis that included 1 RCT and 5 cohort studies found that RFA was as effective as nephrectomy for small renal tumors, with a reduction in complications. Another 2014 meta-analysis, which included case series of stage I (no more than 7 cm across) renal tumors, found that the rate of local progression was greater with RFA than with nephrectomy, but the rate of major complications was lower with RFA. The conflicting results between these meta-analyses might be due to differences in tumor sizes in selected studies as well as selection bias when comparing case series. The correlation between tumor size and RFA efficacy has been reinforced by a large case series with a mean 34-month follow-up; it found that residual disease and mortality increased with tumors over 4 cm.

PRIMARY PULMONARY AND NONPULMONARY TUMORS
Systematic Reviews
In 2013, the Agency for Healthcare Research and Quality published a comparative effectiveness review on local nonsurgical therapies for stage I NSCLC. In this review, no comparative RFA studies were identified. The Agency report found that available evidence was insufficient to draw conclusions on the comparative effectiveness of local nonsurgical therapies for NSCLC, including RFA. In a 2014 systematic review of RFA, surgery, and SBRT for colorectal cancer lung metastases, no randomized trials were identified, and evidence was insufficient to draw conclusions on the comparative effectiveness of these therapies.

In a 2012 review of 16 studies, Bilal et al compared RFA with SBRT in patients with inoperable early-stage NSCLC. Reviewers found that overall survival (OS) rates for RFA and SBRT were similar in patients at 1 year (68.2%-95% vs 81%-85.7%) and 3 years (36%-87.5% vs 42.7%-56%), all respectively. However, survival rates at 5 years were lower with RFA (20.1%-27%) than with SBRT (47%). These findings were drawn from comparisons of results of uncontrolled case series and retrospective reviews.

In a 2011 evidence-based review, 46 studies on RFA for lung tumors were evaluated, which included 2905 ablations in 1584 patients with a mean tumor size of 2.8 cm. Twenty-four studies reported rates of local recurrence, which occurred in 282 (12.2%) cases at a mean follow-up time of 13 months (range, 3-45 months). Primary lung cancer rates of local recurrence did not differ significantly (22.2%) from metastases (18.1%). Twenty-one studies reported mean OS rates of 59.4% at a mean follow-up time of 17.7 months. The mean cancer-specific survival rate was 82.6%, at a mean follow-up of 17.4 months. The mean overall morbidity was 24.6% and most commonly included pneumothorax (28.3%), pleural effusion (14.8%), and pain (14.1%). Mortality related to the RFA procedure was 0.21%, overall.

Comparative Studies

In 2010, Zemlyak et al prospectively compared 3 treatments for medically inoperable patients with stage I NSCLC: RFA in 12 patients, sublobar resection in 25 patients, and percutaneous cryoablation in 27 patients. At 3-year follow-up, survival rates did not differ significantly between groups. OS and cancer-specific 3-year survival rates were 87.5%, 87.1%, and 77% and 87.5%, 90.6%, and 90.2%, respectively, in the 3 groups. The authors concluded that all 3 procedures were reasonable options for treatment of lung tumors in patients unfit for major surgery. The authors also noted that because surgeons chose the treatment option with patient input for this study, selection bias limited study interpretation. In 2011, Huang et al prospectively followed 329 consecutive patients treated with RFA for lung tumors (237 primary, 92 metastatic). Complications were experienced by 34.3% (113) of patients, most commonly pneumothorax (19.1%). OS rates at 2 and 5 years were 35.3% and 20.1%, respectively. The risk of local progression did not differ significantly for tumors less than 4 cm but were statistically significant for tumors greater than 4 cm.

Inoperable Lung Tumors

A prospective, single-arm, multicenter trial (2008) from 7 centers in Europe, the United States, and Australia reported the technical success, safety, response of tumors, and survival in 106 patients with 183 lung tumors. All patients were considered unsuitable for surgery and unfit for radiotherapy or chemotherapy. Tumors measured less than 3.5 cm (mean, 1.7 cm; SD=1.3) and included patients with NSCLC (n=22), colorectal metastases (n=41), and other metastases (n=16). Technical success rate was 99%. Patients were followed for 2 years, and a confirmed complete response lasting at least 1 year was observed in 88% of assessable patients, with no differences in response rate between patients with primary and metastatic tumors. OS rates in patients with NSCLC were 70% at 1 year (95% CI, 51% to 83%; cancer-specific survival, 92% [78% to 98%]), and 48% at 2 years (95% CI, 30% to 65%; cancer-specific survival, 73% [54% to 86%]). OS rates in patients with metastatic colorectal cancer were 89% at 1 year (95% CI, 76% to 95%; cancer-specific survival, 91% [78% to 96%]) and 66% at 2 years (95% CI, 53% to 79%; cancer-specific survival 68% [54% to 80%]). OS rates in patients with other metastases were 92% at 1 year (95% CI, 65%

to 99%; cancer-specific survival, 93% [67% to 99%]) and 64% at 2 years (95% CI, 43% to 82%; cancer-specific survival, 67% [48% to 84%]). Patients with stage I NSCLC (n=13) had an OS rate of 75% (95% CI, 45% to 92%) at 2 years (cancer-specific, 92%; 95% CI, 66% to 99%). No differences in response were seen between patients with NSCLC or lung metastases.

Zhu et al (2009) assessed the incidence and risk factors of various pulmonary neoplastic complications after RFA. They prospectively evaluated the clinical and treatment-related data for 129 consecutive percutaneous RFA treatment sessions for 100 patients with inoperable lung tumors. There was no postprocedural mortality. The overall morbidity rate was 43% (55/129). The most common adverse effect was pneumothorax, occurring in 32% (41/129) of treatment sessions. Other significant complications included pleuritic chest pain (18%), hemoptysis (7%), pleural effusions (12%), and chest drain insertion (20%). Both univariate and multivariate analyses identified more than 2 lesions ablated per session as a significant risk factor for overall morbidity, pneumothorax, and chest drain insertion. The length of the ablation probe trajectory greater than 3 cm was an additional independent risk factor for overall morbidity and pneumothorax.

In 2009, Pennathur et al reported on 100 patients with inoperable lung tumors. Forty-six patients had primary lung neoplasm, 25 had recurrent cancer, and 29 had pulmonary metastases. The mean follow-up was 17 months. Median OS for all patients was 23 months. The probability of 2-year OS for primary lung cancer patients, recurrent cancer patients, and metastatic cancer patients were 50% (95% CI, 33% to 65%), 55% (95% CI, 25% to 77%), and 41% (95% CI, 19% to 62%), respectively.

Section Summary: Primary Pulmonary and Nonpulmonary Tumors
The evidence on RFA for primary NSCLC and nonpulmonary tumor metastatic to the lung includes prospective and retrospective case series of patients with inoperable lung tumors with over 100 patients and systematic reviews of those studies. No RCTs identified compared treatment approaches. For inoperable lung tumors, a multicenter study found that RFA for tumors less than 3.5 cm can lead to a complete response in as many as 88% of patients for at least 1 year. Two-year survival has been reported to range from 41% to 75% in case series. Survival at 1 and 2 years appears to be similar, following treatment with RFA or stereotactic ablative radiotherapy in patients with inoperable lung tumors. Survival rates at 5 years were lower with RFA (20.1%-27%) than with stereotactic ablative radiotherapy (47%), but this finding was drawn from comparisons of uncontrolled case series and retrospective reviews. Prospective comparison in an RCT would permit greater certainty for this finding, but the studies are consistent with some effect of RFA on lung tumors.

BREAST TUMORS
Systematic Reviews
In 2010, Zhao and Wu conducted a systematic review of 38 studies on ablation techniques for breast cancer treatment published from 1994 to 2009. Nine studies focused on RFA. Reviewers included small breast tumors ranging in size from 0.5 to 7 cm. Tumor resection was performed immediately after ablation or up to 4 weeks after RFA. Complete coagulation necrosis rates of 76% to 100% were reported. The

results suggested RFA for breast cancer tumors is feasible, but further studies with longer follow-up on survival, tumor recurrence, and cosmetic outcomes are needed to establish clinical efficacy.

In another 2010 review, Soukup et al examined 17 studies on RFA for the treatment of breast tumors and found RFA is feasible and promising. Even though few adverse events and complications occurred with breast RFA, incomplete tumor ablation remains a concern.

Clinical Studies
In 2012, Wilson et al reported on 73 patients with invasive breast cancer who had a lumpectomy followed immediately by RFA to the lumpectomy bed. The average breast tumor size was 1.0 cm (range, 0.2-2.6 cm) and follow-up averaged 51 months. Disease-free survival was 100%, 92%, and 86% at 1, 3, and 5 years, respectively. One patient had tumor recurrence within 5 cm of the lumpectomy site, and 3 patients had ipsilateral breast recurrences.

In a 2011 phase 1/2 study, 49 patients were treated with RFA for breast tumors (mean size, 1.70 cm) followed immediately with surgical resection. Complete ablation was achieved in 30 (61%) patients as assessed by hematoxylin-eosin (H&E) staining and/or nicotinamide adenine dinucleotide (NADH) diaphorase staining. Complete ablation increased to 83% in 24 patients with tumor sizes of 2 cm or less in diameter. Adverse events related to the procedure included 3 muscle and 2 skin burns.

In 2009, Imoto et al reported on a series of 30 patients with T1N0 breast cancer who had sentinel node biopsy followed by RFA and breast-conserving surgery. Twenty-six patients showed pathologic degenerative changes in tumor specimens with H&E staining, and, in 24 of 26 cases, tumor cell viability was diagnosed as negative by NADH diaphorase staining. Two patients had skin burns, and seven had muscle burn related to RFA.

In a 2008 two-stage phase 2 clinical trial, patients with histologically confirmed noninflammatory and 3 cm or less ipsilateral breast tumor recurrence were treated with RFA followed by mastectomy. The study was ended early due to lack of efficacy of the technique tested.

Section Summary: Breast Tumors
Systematic reviews and observational studies have reported varied and incomplete ablation rates as well as concerns about postablation tumor cell viability. Long-term improvements in health outcomes have not been demonstrated. Additionally, available studies have not compared RFA with conventional breast-conserving procedures. For small breast tumors, further study, with long-term follow-up, is needed to determine whether RFA can provide local control and survival rates comparable with conventional breast-conserving treatment.

BENIGN THYROID NODULES
Systematic Reviews
In 2014 Fuller et al reported on a systematic review of studies on RFA for benign thyroid tumors. Selected were 9 studies (5 observational studies, 4 randomized studies), totaling 306 treatments. After RFA,

statistically significant improvements were reported in nodule size reduction (29.77 mL; 95% CI, -13.83 to -5.72 mL), combined symptom improvement and cosmetic scores on the 0 to 6 scale (mean, -2.96; 95% CI, -2.66 to -3.25), and withdrawal from methimazole (odds ratio, 40.34; 95% CI, 7.78 to 209.09). Twelve adverse events were reported, two of which were considered significant but did not require hospitalization. The interpretation of the meta-analysis is limited by the variability in the comparator arms (percutaneous ethanol injection, percutaneous laser ablation and, high-intensity focused ultrasound ablation. The only RCT included in the meta-analysis had a small sample size of 30.

In 2012, the Korean Society of Thyroid Radiology developed consensus recommendations for RFA of thyroid tumors after a review of the literature found few controlled studies. The recommendations indicated RFA might be appropriate for the treatment of benign thyroid nodules, inoperable thyroid nodules, and recurrent thyroid cancers in the operation bed and lymph nodes. The Society's recommendations also indicated RFA should not be used for primary thyroid cancers or follicular neoplasms, citing no evidence of treatment benefit.

Longer Term Outcomes and Adverse Events
In 2013, Lim et al reported on a case series of 111 patients treated with RFA for 126 benign nonfunctioning thyroid nodules. The mean duration of patient follow-up was 49.4 months. RFA significantly decreased the volume of the thyroid nodules from 9.8±8.5 mL to 0.9±3.3 mL ($p<0.001$), for a mean volume decrease of 93.4%. Tumors recurred in 7 (5.6%) patients. Complications occurred in 4 (3.6%) patients. There was also a significant improvement in thyroid symptom scores ($p<0.001$).

Baek et al (2012) retrospectively reviewed RFA for 1543 benign thyroid nodules in 1459 patients at 13 thyroid centers. Forty-eight (3.3%) complications occurred and included 20 major complications: voice changes (n=15), brachial plexus injury (n=1), tumor rupture (n=3), and permanent hypothyroidism (n=1). Twenty-eight minor complications included: hematoma (n=15), skin burn (n=4), and vomiting (n=9).

A 2009 case series of 94 elderly subjects with solid or mainly solid benign thyroid nodules was reported by an Italian center. Thyroid nodule volume, compressive symptoms, and thyroid function were evaluated at baseline and 12 to 24 months posttreatment. All thyroid nodules significantly decreased in size after RFA. Compressive symptoms improved in all patients, disappearing completely in 88% of patients. Hyperthyroidism resolved in most patients, permitting complete withdrawal of methimazole therapy in 79% of patients with pretoxic and toxic thyroid nodules (100% with pretoxic and 53% with toxic thyroid nodules).

Section Summary: Benign Thyroid Tumors
Evidence on the treatment of benign thyroid nodules includes randomized trials, case series, and systematic reviews of these studies. A systematic review that included 1 RCT, 3 randomized studies, and 5 observational studies found significant reductions in nodule size and withdrawal from methimazole following treatment with RFA. Reports of complications vary. The most frequent major complication from a large multicenter series was voice changes. However, the comparators were variable and nonconventional. The single RCT had a small sample size of 30.

MISCELLANEOUS SOLID TUMORS

Thyroid Cancer

In 2016, Kim et al reported on a comparative review of 73 patients with recurrent thyroid cancer smaller than 2 cm who had been treated with RFA (n=27) or repeat surgery (n=46). RFA was performed in cases of patient refusal to undergo surgery or poor medical condition. Data were weighted to minimize potential confounders. The 3-year recurrence-free survival rates were similar for RFA (92.6%) and surgery (92.2%, p=0.681). Posttreatment hoarseness rate did not differ between the RFA (7.3%) and surgery (9.0%) groups. Posttreatment hypocalcemia occurred only in the surgery group (11.6%).

Head and Neck Cancer

In 2011, Owen et al reported on RFA for 13 patients with recurrent and/or unresectable head and neck cancer who failed curative treatment. Median patient survival was 127 days. While stable disease was reported in 8 patients after RFA, and quality of life scores improved, 3 deaths occurred (1 carotid hemorrhage, 2 strokes).

A case series of RFA for 14 patients with recurrent advanced head and neck malignancies was reported by Brook et al (2008). Tumor targeting and electrode deployment was successful in all cases, and 4 of 6 patients who completed quality of life assessments showed improvement. Three major complications (in 27 [11%] applications) occurred 7 days to 2 weeks postprocedure. They included stroke, carotid artery rupture leading to death, and threatened carotid artery rupture with subsequent stroke. Retrospective analysis of intraprocedural CT scans revealed that the retractable electrodes were within 1 cm of the carotid artery during ablation in these cases.

A 2004 case series showed palliative CT-guided RFA provided subjective improvement with regard to pain, appearance, and function in 12 patients who had recurrent and advanced head and neck malignancies and were not candidates for radiotherapy or surgery. The procedure appeared reasonably safe and feasible for this indication.

Other Tumors

A large 2015 series evaluated the effectiveness and safety of RFA for uterine myomas in a 10-year retrospective cohort study. From 2001 to 2011, a total of 1216 patients treated for uterine myomas were divided into 2 groups. Group A consisted of 476 premenopausal patients (average age, 36 years) who had an average of 1.7 myomas with an average diameter of 4.5 cm. Group B consisted of 740 menopausal patients (average age, 48 years) with an average of 2.6 myomas with an average diameter of 5.0±2.5 cm. Patients were followed for a mean of 36 months. At 1, 3, 6, 12, and 24 months after RFA, the average diameters of myomas in group A were 3.8, 3.0, 2.7, 2.4, and 2.2 cm, respectively; 48% (227/476) of patients had residual tumor at 12 months. In group B, myoma diameters were 4.7, 3.7, 3.3, 2.3, and 2.3 cm, respectively; 59% (435/740) of patients had trace disease at 12 months. Three months after RFA treatment, myoma volumes were significantly reduced in both the groups ($p<0.01$), although group B had a higher rate of residual tumor 12 months after RFA than group A ($p<0.05$). Clinical symptoms and health-related quality of life were significantly improved after RFA in both groups. The postoperative recurrence rate of uterine myomas was significantly higher in group A at 10.7% (51/476) than in group B at 2.4% (18/740; $p<0.05$).

One 2004 case series of 13 patients with adrenal neoplasms treated with RFA was identified. In this study, 11 of the 13 lesions were treated successfully with RFA, defined by follow-up CT scans and normalization of preprocedural biochemical abnormalities.

A single-arm, retrospective, paired-comparison study (2004) evaluated the short-term efficacy of RFA in relation to pain and functional impact in patients with unresectable, painful soft tissue neoplasms recalcitrant to conventional therapies. Patients had tumors located in a variety of sites including chest wall, pelvis, breast, perirectal, renal, aortocaval, retroperitoneal, and superficial soft tissues. All had failed conventional methods of palliation or experienced dose-limiting adverse events from pain medication. Although not all Brief Pain Inventory scores were statistically significant, all mean scores trended down with increased time after ablation. Complications from RFA were minor or insignificant in all but 1 patient who had skin breakdown and infection of an ablated superficial tumor site.

Additional research has addressed the use of RFA in solid malignancies and in the pancreas. A 2015 systematic review has examined studies of ablative therapies, including RFA, in patients with locally advanced pancreatic cancer. No RCTs were identified, and conclusions limited by the sparse evidence available on RFA in this setting.

Stereotactic radiofrequency thermocoagulation for epileptogenic hypothalamic hamartomas was described in a 2009 retrospective analysis of 25 patients with gelastic seizures (a rare type of seizure). Other seizure types were exhibited in 22 (88.0%) patients, precocious puberty in 8 (32.0%), behavioral disorder in 10 (40.0%), and mental disability in 14 (56.0%). Gelastic seizures resolved in all but 2 patients. Complete seizure freedom was achieved in 19 (76.0%) patients. These patients experienced resolution of all seizure types and behavioral disorder and also demonstrated intellectual improvement.

Preliminary results of endoscopic RFA of rectosigmoid tumors have been described by Vavra et al (2009). Twelve patients were treated with the Endoblate RFA device, with 10 patients having surgical resection after ablation. Histology of the resected specimens showed that, on average, 82% (range, 60%-99%) of the tumor mass was destroyed in the ablation zone.

Small case series on RFA for colorectal and rectal carcinoma have demonstrated a debulking role for RFA. These case series did not permit comparison with an available alternative.

Section Summary: Miscellaneous Solid Tumor
Evidence on the use of RFA to treat other types of solid tumors consists of a low number of case series or retrospective comparative studies for each tumor type. Reporting on outcomes is limited. The evidence base does not support conclusion on the effects of RFA.

SUMMARY OF EVIDENCE
Bone Tumors
For individuals who have painful osteolytic bone metastases who have failed or are poor candidates for standard treatments who receive RFA, the evidence includes case series. Relevant outcomes are

symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. Case series have shown clinically significant pain relief and reduction in opioid use following treatment of painful osteolytic metastases. The population is comprised of patients with few or no treatment options, for whom short-term pain relief is an appropriate clinical outcome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have painful osteoid osteomas who receive RFA, the evidence includes numerous observational studies and a systematic review of these studies. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. In a systematic review of thermal ablation techniques, clinical success (pain-free) was achieved in 94% to 98% of patients. Most patients (89%-96%) remained pain-free when assessed during longer term follow-up. Although no randomized trials of RFA for osteoid osteomas have been performed, the uncontrolled studies have demonstrated RFA can provide adequate symptom relief with minimal complications, for a population for whom short-term symptom relief and avoidance of invasive procedures are appropriate clinical outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Localized Renal Cell Carcinoma
For individuals who have localized RCC that is no more than 4 cm in size who receive RFA, the evidence includes a RCT, a large number of observational studies, and systematic reviews of these studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. A recent meta-analysis that included only an RCT and cohort studies found that RFA was as effective as nephrectomy for small renal tumors, with a reduction in complications. Another recent meta-analysis, which included case series of stage I (≤7 cm across) renal tumors, found that the rate of local progression was greater with RFA than with nephrectomy. The differing meta-analytic results may be due to differences in tumor size in selected studies as well as potential selection bias when evaluating case series. Although inconsistent, the evidence does suggest that, for small renal tumors, RFA may result in a similar rate of disease progression with a lower complication rate than nephrectomy. However, comparative trials are needed to determine with greater certainty the effects of these treatments in the same patient population. The evidence is insufficient to determine the effects of the technology on health outcomes.

Inoperable Primary Pulmonary and Nonpulmonary Tumors
For individuals who have inoperable primary pulmonary tumors or nonpulmonary tumors metastatic to the lung who receive RFA, the evidence includes observational studies and systematic reviews of these studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. A multicenter study found that, for tumors less than 3.5 cm in size, RFA can lead to a complete response in as many as 88% of patients for at least 1 year. Two-year survival rates have been reported to range from 41% to 75% in case series, with 5-year survival rates of 20% to 27%. In general, the evidence suggests that RFA results in adequate survival and tumor control in patients who are not surgical candidates, with low morbidity rates. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Tumors
For individuals who have breast tumors who receive RFA, the evidence includes observational studies and systematic reviews of these studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. Evidence has reported varied and incomplete ablation rates with concerns about postablation tumor cell viability. Long-term improvements in health outcomes have not been demonstrated. Additionally, available studies do not permit comparisons with conventional breast-conserving procedures. Further studies, with long-term follow-up, should focus on whether RFA of the breast for small tumors can provide local control and survival rates comparable with conventional breast-conserving treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

Benign Thyroid Tumors
For individuals who have benign thyroid tumors who receive RFA, the evidence includes RCTs, case series, and systematic reviews of these studies. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. A systematic review that included 4 RCTs and 5 observational studies found significant reductions in nodule size and withdrawal from methimazole following treatment with RFA when compared to a variety of local treatment. Reports of complications have varied. The most frequent major complication in a large multicenter series of specialty centers was voice change. The evidence is insufficient to determine the effects of the technology on health outcomes.

Miscellaneous Solid Tumors
For individuals who have miscellaneous tumors (e.g., head and neck, thyroid cancer, pancreas) who receive RFA, the evidence includes a few case series and retrospective comparative studies. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related morbidity. There is a limited evidence base for each tumor type. Reporting on outcomes or comparisons with other treatments is limited. These studies do not permit conclusions on the health benefits of RFA. The evidence is insufficient to determine the impact of the technology on health outcomes.

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Policy History

Original Effective Date: 08/24/2005
Current Effective Date: 07/11/2018

07/13/2005	Medical Director review
07/19/2005	Medical Policy Committee review
08/24/2005	Managed Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/08/2006	Medical Director review
08/09/2006	Medical Policy Committee approval.
07/10/2007	Medical Director review
07/18/2007	Medical Policy Committee approval. Policy Statement added for osteoid osteoma and rationale/source updated.

Policy # 00175
Original Effective Date: 08/24/2005
Current Effective Date: 07/11/2018

07/02/2008	Medical Director review
07/16/2008	Medical Policy Committee approval. Coverage eligibility unchanged.
07/02/2009	Medical Director review
07/22/2009	Medical Policy Committee approval. Coverage statement added to indicate that use of radiofrequency ablation as treatment of osteoid osteomas that cannot be managed successfully with medical treatment may be considered eligible for coverage. Coverage statement added that treatment of localized renal cell carcinoma no more than 4cm in size may be considered eligible for coverage when specific criteria are met. Added that radiofrequency ablation for the treatment of osteoid osteomas that can be managed with medical treatment is considered to be investigational.
08/05/2010	Medical Policy Committee review
08/18/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2011	Medical Policy Committee review
08/17/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. Added options for primary and metastatic pulmonary tumors to be eligible for coverage with criteria.
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Reformatted investigational statement and added thyroid as investigational.
06/25/2015	Medical Policy Committee review
07/15/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2018	Coding update
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/31/2018	Coding update

Next Scheduled Review Date: 07/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors

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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code			
CPT	20982, 20983, 32998, 50542, 50592, 76940, 77013, 77022			
HCPCS	No codes			
ICD-10 Diagnosis	C34.90-C34.92	C50.011-C50.019	C50.111-C50.119	C50.211-C50.219
	C50.311-C50.319	C50.411-C50.419	C50.511-C50.519	C50.611-C50.619
	C50.811-C50.819	C50.911-C50.919	C64.1-C64.9	C65.1-C65.9
	C66.1-C66.9	C68.1-C68.9	C73	D16.00-D16.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.