Cryosurgery Ablation of Miscellaneous Solid Tumors other than Liver or Prostate Tumors or Breast Fibroadenomas

Policy #  00023
Original Effective Date:  01/26/2004
Current Effective Date:  09/21/2016

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: Cryoablation of Clinically Localized Prostate Tumors is addressed separately in medical policy 00022; Cryosurgical Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00220; and Cryosurgery Ablation of Breast Fibroadenomas is addressed separately in medical policy 00235.

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.

Based on review of available data, the Company may consider cryosurgery ablation as a treatment of localized renal cell carcinoma (RCC) to be eligible for coverage.

Patient Selection Criterion
Coverage eligibility for the use of cryosurgery ablation to treat localized renal cell carcinoma [RCC] (no more than 4 cm in size) will be considered when the following criterion is met:

- Preservation of kidney function is necessary (i.e., the patient has one kidney or renal insufficiency defined by a glomerular filtration rate [GFR] of < 60 mL/min/m²) and standard surgical approaches would compromise kidney function.

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 the use of cryosurgery ablation to treat localized renal cell carcinoma (RCC) when patient selection criteria are not met to be investigational.*

Based on review of available data, the Company considers cryosurgical ablation as a treatment of malignant tumors of the breast, lung, pancreas and liver, or other solid tumors other than prostate tumors and breast fibroadenomas to be investigational.*

Background/Overview
Cryosurgical ablation (hereafter referred to as cryosurgery) involves freezing of target tissues, most often by inserting into the tumor a probe through which coolant is circulated. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

The hypothesized advantages of cryosurgery include improved local control and benefits common to any minimally invasive procedure (e.g., preserving normal organ tissue, decreasing morbidity, decreasing length...
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of hospitalization). Potential complications of cryosurgery include those caused by hypothermic damage to normal tissue adjacent to the tumor, structural damage along the probe track, and secondary tumors, if cancerous cells are seeded during probe removal.

Cryosurgical treatment of various tumors including RCCs, malignant and benign breast disease, pancreatic cancer, and lung cancer has been reported in the literature.

Breast Tumors
Early stage primary breast cancers are treated surgically. The selection of lumpectomy, modified radical mastectomy, or another approach is balanced against the patient’s desire for breast conservation, the need for tumor-free margins in resected tissue, and the patient’s age, hormone receptor status, and other factors. Adjuvant radiation therapy decreases local recurrences, particularly for those who select lumpectomy. Adjuvant hormonal therapy and/or chemotherapy are added, depending on presence and number of involved nodes, hormone receptor status, and other factors. Treatment of metastatic disease includes surgery to remove the primary lesion and combination chemotherapy.

Fibroadenomas are common benign tumors of the breast that can either present as a palpable mass or a mammographic abnormality. These benign tumors are frequently surgically excised to rule out a malignancy.

Lung Tumors
Early stage lung tumors are typically treated surgically. Patients with early stage lung cancer who are not surgical candidates may be candidates for radiation treatment with curative intent. Cryoablation is being investigated in patients who are medically inoperable, with small primary lung cancers or lung metastases. Patients with more advanced local disease or metastatic disease may undergo chemotherapy with radiation following resection. This is rarely curative but rather seeks to retard tumor growth or palliate symptoms.

Pancreatic Cancer
Pancreatic cancer is a relatively rare solid tumor that occurs almost exclusively in adults and is almost always fatal. Surgical resection of tumors contained entirely within the pancreas is currently the only potentially curative treatment. However, the nature of the cancer is such that few tumors are found at such an early and potentially curable stage. Patients with more advanced local disease or metastatic disease may undergo chemotherapy with radiation following resection. This is rarely curative but rather seeks to retard tumor growth or palliate symptoms.

Renal Cell Carcinoma
Localized RCC is treated by radical nephrectomy or nephron-sparing surgery. Prognosis drops precipitously if the tumor extends outside the kidney capsule, since chemotherapy is relatively ineffective against metastatic RCC.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
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There are several cryoablation devices cleared for marketing by the FDA through the 510(k) process for use in open, minimally invasive or endoscopic surgical procedures in the areas of general surgery, urology, gynecology, oncology, neurology, dermatology, proctology, thoracic surgery and ear; nose; and throat. Examples include:
- Cryocare® Surgical System by Endocare;
- CryoGen Cryosurgical System by Cryosurgical, Inc.;
- CryoHit® by Galil Medical for the treatment of breast fibroadenoma;
- SeedNet™ System by Galil Medical; and
- Visica® System by Sanarus Medical.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

**Rationale/Source**
The following is a summary of the key literature to date. The literature search identified publications discussing applications of cryosurgery for primary and metastatic tumors outside the liver and prostate. All were uncontrolled case series with varied criteria to select patients for cryosurgery and reported limited data on long-term outcomes.

The following sections summarize those studies that adequately described baseline characteristics of the patient populations and the methods used for cryosurgery and also reported outcomes of treatment for 8 or more patients with the same diagnosis, or 8 or more procedures on the same malignancy. One article discussed cryosurgery in 429 patients with a wide variety of primary and recurrent solid tumors (e.g., head and neck, lung, genital organs, sarcomas). Although the author reported survival for some patient subsets with certain of these malignancies, the article only reported baseline tumor and patient characteristics for those with breast cancer.

**Breast Cancer**
A prospective, single-arm, phase 2 trial was published by the American College of Surgeons Oncology Group Z1072 in 2016. This trial enrolled 86 evaluable patients from 19 institutions with invasive ductal breast carcinoma that was 2 cm or less in size. The primary end point was complete ablation, defined as no residual evidence of tumor on magnetic resonance imaging. The investigators assigned a priori the success rates indicating that cryoablation would be a potentially efficacious treatment (>90%) or that the results of cryoablation would be unsatisfactory (<70%). Following cryoablation and determination of complete ablation, all patients underwent surgery according to standard protocols for treatment of early breast cancer. Of 87 cancers in 86 patients, complete ablation was achieved in 66 (75.9%; 95% confidence interval [CI], 67.1% to 83.2%). Most cases without complete ablation were the result of multifocal disease outside the targeted lesion. Success rates were intermediate, indicating neither that cryoablation is potentially efficacious, nor that the results of cryoablation were unsatisfactory.

In 2010, Zhao and Wu reported on a systematic review of minimally-invasive ablative techniques of early-stage breast cancer. The review noted that studies on cryoablation for breast cancer are primarily limited to
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pilot and feasibility studies in the research setting. Complete ablation of tumors was found to be reported within a wide range of 36-83%. Since there are many outstanding issues, including patient selection criteria and the ability to precisely determine the size of tumors and achieve 100% tumor cell death, the reviewers noted minimally-invasive thermal ablation techniques for breast cancer treatment, including cryoablation, should be limited until results from prospective, randomized clinical trials become available.

Niu et al reported on a 2013 retrospective study of 120 patients with metastatic breast cancer, including 30 metastases to the contralateral breast and other metastases to the lung, bone, liver and skin who were treated with either chemotherapy (n=29) or cryoablation (n=91, 35 of whom also received immunotherapy). After a 10-year follow-up, median overall survival (OS) of all study participants was 55 months in the cryoablation group versus 27 months in the chemotherapy group (p<0.001). Median OS was also greater in patients receiving multiple cryoablations and in those receiving immunotherapy. Complications with cryotherapy to the breast were ecchymosis and hematoma, pain, tenderness and edema, all of which resolved within 1 week to 1 month.

Three studies described the outcome of cryosurgery for advanced primary or recurrent breast cancer in 72 patients. Cryosurgery was performed percutaneously with ultrasound guidance (n = 15) or during an open surgical procedure (n = 57). Patients were treated for advanced primary disease (44%) or recurrent tumors (56%). Tanaka reported the largest retrospective series: 9 patients with advanced primary tumors and 40 with recurrent disease. The author reported 44% survival of primary breast cancer patients (n = 9) at 3 and 5 years but did not report survival duration or other outcomes for those with recurrent or metastatic disease. The report also did not adequately describe selection criteria for those enrolled in the study, details of the procedure, and procedure-related adverse events. The other studies were smaller series of patients and also were inadequate with respect to study design, analysis, and reporting of results. Furthermore, the study by Pfleiderer et al. was a pilot trial to evaluate technical limitations of the procedure. Tumors were excised and evaluated by pathology days to weeks after cryosurgery, and the authors reported incomplete necrosis in tumors greater than 23 mm in diameter.

One case series by Sabel and colleagues explored the role of cryoablation as an alternative to surgical excision as a primary treatment of early stage breast cancer. This Phase I study included 29 patients who underwent cryoablation of primary breast cancers measuring less than 2 cm in diameter, followed up 1 to 4 weeks later by standard surgical excision. Cryoablation was successful in patients with invasive ductal carcinoma less than 1.5 cm in diameter and with less than 25% ductal carcinoma in situ identified in a prior biopsy specimen. In a small series of 11 patients with breast cancer tumors less than 2 cm, Pusztaszeri, et al. found residual tumor present in 6 cases when follow-up lumpectomy was performed approximately 4 weeks after cryoablation. In a case series of 15 patients with breast cancer lesions that were 8±4 mm in diameter, percutaneous cryoablation was performed 30 to 45 days before surgical resection. Resection of the lesions confirmed complete necrosis occurred in 14 patients, but 1 lesion had residual disease considered to be probably due to incorrect probe placement.
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Breast Fibroadenomas
A variety of case series have focused on the role of cryosurgery as an alternative to surgical excision of benign fibroadenomas. Kaufman et al have published several case series on office-based ultrasound-guided cryoablation as a treatment of breast fibroadenomas. These case series reported on a range of 29 to 68 patients followed for 6 months to 2.6 years. It is likely that these case series included overlapping patients. At 1 year, patients reported 91% patient satisfaction and fibroadenomas became nonpalpable in 75% of cases. At follow-up averaging 2.6 years in 37 patients, the authors noted only 16% of 84% palpable fibroadenomas remained palpable after treatment and, of the fibroadenomas initially 2 cm or less in diameter, only 6% remained palpable. In this series, the authors also noted that cryoablation did not produce artifacts that could interfere with interpretation of mammograms. These small case series from the same group of investigators are inadequate to permit scientific conclusions. In addition, it is unclear whether “nonpalpability” is the most appropriate medical outcome. Fibroadenomas are benign lesions with only a very remote chance of malignant conversion, and thus complete surgical excision may be recommended primarily to allay patients’ concerns about harbor a palpable lesion.

Nurko et al reported on outcomes at 6 and 12 months for 444 treated fibroadenomas reported to the FibroAdenoma Cryoablation Treatment (FACT) registry involving 55 different practice settings. In these patients, before cryoablution, 75% of fibroadenomas were palpable by the patient. Follow-up at 6- and 12-month intervals showed palpable masses in 46% and 35%, respectively. When fibroadenomas were grouped by size, for lesions 2 cm or less in diameter, the treatment area was palpable in 28% at 12 months. For lesions more than 2 cm, the treatment area was palpable in 59% at 12 months.

Section Summary: Breast Disease
For the treatment of breast cancer, available evidence has shown that complete ablation can be achieved in most cases for small tumors, but studies do not include control groups or compare outcomes of cryosurgery with alternative strategies for managing similar patients. Therefore, no conclusions can be made on the net health outcomes of cryosurgery for breast cancer. For treatment of fibroadenomas, there is a small amount of evidence. This evidence has demonstrated that most fibroadenomas become “nonpalpable” following cryoablation. However, there is a lack of comparative trials. Comparative trials with adequate long-term follow-up are needed to assess this technology and determine how this approach compares with surgery, as well as with vacuum-assisted excision and with observation (approximately one-third regress over time after cryoablation).

Lung Cancer
The ECLIPSE trial is prospective, multicenter trial of cryoablation for metastatic disease in the lungs, interim results at 1-year follow-up were published in 2015. The trial enrolled 40 patients with 60 metastatic lung lesions who were treated with cryoablation and had at least 12 months of follow-up. Outcomes included survival, local tumor control, quality of life, and complications. Local tumor control was achieved in 94.2% (49/52) of treated lesions, and 1-year OS was 97.5% (39/40). There were no significant changes in quality of life over the 12-month study. The most common adverse event was pneumothorax requiring chest tube insertion in 18.8% (9/48 procedures).
Lee and colleagues conducted a systematic review of endoscopic cryoablation of lung and bronchial tumors. Included in the review were 15 case studies and one comparative, observational study. Cryoablation was performed for inoperable, advanced lung and bronchial cancers in most studies. Some studies included patients with co-morbid conditions and poor general health that would not be considered surgical candidates. Complications occurred in 11.1% of patients from 10 studies and consisted of hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea. Within 30 days of the procedure, death from hemoptysis and respiratory failure, considered to be most likely related to disease progression, occurred in 7.1% of patients. Improvements in pulmonary function and clinical symptoms occurred in studies reporting these outcomes.

In 2012, Niu et al reviewed the literature on lung cryoablation and reported on their own experience with percutaneous cryoablation in 150 patients with non-small-cell lung cancer (NSCLC) followed for 12 to 38 months. Included in the study population were stage IIIB+IV lung cancer patients. OS rates at 1, 2, and 3 years were 64%, 45% and 32%, respectively. The 30-day mortality was 2.6% and included cardiac arrest and hemopneumothorax. Complications included hemoptysis, pneumothorax, hemothorax, pleural effusion, and pulmonary infection.

An Agency for Healthcare Research and Quality comparative effectiveness review on local nonsurgical therapies for stage 1 and symptomatic obstructive NSCLC was published in 2013. Cryoablation was included in the review as a potential therapy for airway obstruction due to an endoluminal NSCLC. The reviewers were unable to draw any conclusions on local nonsurgical therapies, including cryoablation, due to lack of available quality evidence.

Available studies are limited to primarily small cohort and nonrandomized studies with relatively short-term follow-up. Complications are also reported frequently and can be severe. Because available studies do not include control groups or compare outcomes of cryosurgery with alternative strategies for managing similar patients, no conclusions can be made on the net health outcomes of cryosurgery for lung cancer.

Pancreatic Cancer

In 2012, Tao and colleagues reported on a systematic review of cryoablation for pancreatic cancer. The authors identified 29 studies from the literature search and included 5 of these studies in the review. The 5 studies were all case series and considered to be of low quality. Adverse events, when mentioned in the studies, included delayed gastric emptying (0% to 40.9% in 3 studies), pancreatic leak (0% to 6.8% in 4 studies), biliary leak (0% to 6.8% in 3 studies), and one instance of upper gastrointestinal hemorrhage. Pain relief was reported in 3 studies and ranged from 66.7% to 100%. Median survival times reported in 3 studies ranged from 13.4 to 16 months. One-year total survival rates reported in 2 studies were 57.5% and 63.6%. Keane et al reported on a systematic review of ablation therapy for locally advanced pancreatic cancer in 2014. The review noted studies have demonstrated ablative therapies, including cryoablation, are feasible but larger studies are needed. No conclusions could be made on whether ablation resulted in better outcomes than best supportive care.
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Kovach et al. reported 10 cryosurgical ablations in 9 patients with unresectable pancreatic cancer using intraoperative ultrasound guidance during laparotomy. The authors report no intraoperative morbidity or mortality and adequate pain control in all patients postoperatively. At the time of publication, all patients were dead at an average of 5 months postoperatively (range: 1–11 months).

A pilot study on the combination of cryosurgery and (125) iodine seed implantation for treatment of locally advanced pancreatic cancer was reported by Xu et al. Forty-nine patients were enrolled, 12 with liver metastases. Twenty patients received regional chemotherapy. At 3 months after therapy, most patients showed tumor necrosis with 20.4% of patients having complete response. Overall, the 6-, 12-, 24-, and 36-month survival rates were 94.9%, 63.1%, 22.8%, and 9.5%, respectively.

Li and colleagues reported on a retrospective study of 142 patients with unresectable pancreatic cancer treated with palliative bypass with (n = 68) or without cryoablation (n = 74) from 1995 to 2002. Median dominant tumor sizes decreased from 4.3 cm to 2.4 cm in 36 of 55 patients (65%) 3 months after cryoablation. Survival rates were not significantly different between groups, with the cryoablation group surviving a median of 350 days versus 257 days in the group that did not receive cryoablation. Complications overall were not significantly different between the 2 groups. However, a higher percentage of delayed gastric emptying occurred in the cryoablation group compared to the group that did not receive cryoablation (36.8% vs. 16.2%, respectively).

Because these studies did not include control groups or compare outcomes of cryosurgery to alternative strategies for managing similar patients, no conclusions can be made on the net health outcomes of cryosurgery for pancreatic cancer.

Renal Cell Carcinoma
In 2014, Tang et al reported on a systematic review and meta-analysis of laparoscopic renal cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal masses. The study identified 9 eligible trials (2 prospective, 7 retrospective) in which the 2 techniques were assessed and included 555 cases and 642 controls. Laparoscopic cryoablation was associated with statistically significant shorter operative time, less blood loss, and fewer overall complications; however, it was estimated that laparoscopic partial nephrectomy may still have a significantly lower local recurrence rate (odds ratio [OR], 13.03; 95% confidence interval [CI], 4.20 to 40.39; p<0.001) and lower distant metastasis rate (OR=9.05; 95% CI, 2.31 to 35.51; p=0.002).

In 2014, Klatte et al reported on a systematic review and meta-analysis of laparoscopic cryoablation versus laparoscopic partial nephrectomy for small renal tumors. Thirteen nonrandomized studies were included in the analysis, which found laparoscopic cryoablation was associated with better perioperative outcomes than laparoscopic partial nephrectomy. Oncologic outcomes, however, were inferior with cryoablation, which was significantly associated with greater risk of local and metastatic tumor progression with relative risks of 9.39 and 4.68, respectively. Tang et al also reported on a systematic review and meta-analysis of laparoscopic cryoablation versus laparoscopic partial nephrectomy for small renal tumors in 2014. This review included 2 prospective and 7 retrospective studies. Similar results to the Klatte analysis were found including better
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perioperative outcomes and inferior oncologic outcomes occurring with laparoscopic cryoablation than laparoscopic partial nephrectomy. Local recurrence and distant metastasis rates were significantly lower with laparoscopic partial nephrectomy (OR=13.03; 95% CI, 4.20 to 40.39; p<0.001; OR=9.05; 95% CI, 2.31 to 35.51; p=0.002, respectively).

In an earlier 2011 systematic review, Klatte et al reviewed 98 studies published through December 2010 to compare treatment of small renal masses with laparoscopic cryoablation or partial nephrectomy. Partial nephrectomy was performed in 5347 patients and laparoscopic cryoablation was performed in 1295 patients. Renal cell carcinoma was proven in 159 (2.9%) of patients. After cryoablation, local tumor progression of RCC occurred at a rate of 8.5% (70/821; range, 0%-17.7%). After partial nephrectomy, 1.9% (89/4689; range, 0%-4.8%) experienced local tumor progression. Distant metastasis occurred more frequently in partial nephrectomy patients than cryoablation patients, although not significantly (91 patients vs 9 patients, respectively; p=0.126). However, mean tumor size for cryoablation patients was smaller than the partial nephrectomy patients (2.4 cm vs 3.0 cm; p<0.001). Fewer patients receiving cryoablation experienced perioperative complications than partial nephrectomy patients (17% [range, 0%-42%] vs 23.5% [range, 8%-66%]; p<0.001).

Long et al. reported on a 2011 systematic review comparing percutaneous cryoablation to surgical cryoablation of small renal masses. A total of 42 studies treating small renal masses (pooled total of 1,447 lesions) were reviewed including 28 articles on surgical cryoablation and 14 articles on percutaneous cryoablation. The authors concluded percutaneous and surgical cryoablation for small renal masses have similar, acceptable short-term oncologic outcomes, and each technique is relatively equivalent. Long-term data are needed to ultimately compare ablation techniques to the gold standard of partial or radical nephrectomy.

In 2011, Van Poppel et al. conducted a review of the literature on localized RCC treatment published between 2004 and May 2011. In this review, the authors concluded cryoablation is a reasonable treatment option for low-grade renal tumors less than 4 cm (mostly less than 3 cm) in patients who are not candidates for surgical resection or active surveillance. The authors noted the need for long-term prospective studies to compare ablative techniques for renal ablation, such as radiofrequency ablation (RFA) versus cryoablation.

Martin and Athreya reported on a meta-analysis of cryoablation versus microwave ablation for small renal tumors in 2013. The analysis included 51 studies and did not reveal any significant differences between microwave ablation and cryoablation in primary effectiveness (93.75% vs 91.27%, respectively; p=0.4), cancer-specific survival (98.27% vs 96.8%, respectively; p=0.47), local tumor progression (4.07% vs 2.53%, respectively; p=0.46), or progression to metastases (0.8% vs 0%, respectively; p=0.12). In the microwave ablation group, the mean tumor size was significantly larger (p=0.03) and open access was used more often than in the cryoablation group (12.20% vs 1.04%, respectively; p<0.001). In the cryoablation group, percutaneous access was used more often than in the microwave ablation group (88.64% vs 37.20%, respectively; p=0.002).
In 2012, El Dib and colleagues conducted a meta-analysis evaluating cryoablation and RFA for small renal masses. Included in the review were 20 cryoablation (totaling 457 patients) and 11 RFA (totaling 426 patients) case series studies published through January 2011. Mean tumor size was 2.5 cm (range from 2 to 4.2 cm) in the cryoablation group and 2.7 cm (range from 2 to 4.3 cm) in the RFA group. Mean follow-up times for the cryoablation group and RFA group were 17.9 and 18.1 months, respectively. Clinical efficacy, defined as cancer-specific survival rate, radiographic success, no evidence of local tumor progression, or distant metastases, was not significantly different between groups. The pooled proportion of clinical efficacy for cryoablation was 89% (95% confidence interval [CI]: 0.83–0.94) and 90% (95% CI: 0.86–0.93) for RFA.

In a 2010 Cochrane review, Nabi and colleagues review evidence on the management of localized RCC. No randomized trials comparing cryoablation to open radical or partial nephrectomy were identified. One nonrandomized study compared laparoscopic partial nephrectomy with laparoscopic cryoablation using a matched paired-analysis and 3 retrospective studies. The review notes percutaneous cryoablation can successfully destroy small RCC and may be considered a treatment option in patients with serious comorbidities that pose surgical risks. The review concluded that high-quality, randomized controlled trials (RCTs) are required in the management of localized RCC and that one area of emphasis should be the role of renal surgery compared to minimally invasive techniques for small tumors (< 4 cm).

Kunkle and Uzzo conducted a comparative meta-analysis evaluating cryoablation and RFA as primary treatment for small renal masses in 2008. Forty-seven case series representing 1,375 renal tumors were analyzed. Of 600 lesions treated with cryoablation, 494 were biopsied before treatment versus 482 of 775 treated with RFA. The incidence of RCC with known pathology was 72% in the cryoablation group and 90% in the RFA group. The mean duration of follow-up after cryoablation was 22.5 months. Most studies used contrast enhanced imaging to determine treatment effect. Local tumor progression was reported in 31 of 600 (5%) lesions after cryoablation and in 100 of 775 (13%) lesions after RFA. Progression to metastatic disease was described in 6 of 600 (1%) lesions after cryoablation versus 19 of 775 (2.5%) after RFA. The authors caution that minimally invasive ablation generally has been performed selectively on older patients with smaller tumors, possibly resulting in selection bias; series of ablated lesions tend to have shorter post-treatment follow-up compared with tumors managed by surgical excision or active surveillance, and treatment efficacy may be overestimated in series that include tumors with unknown pathology.

Matin and Ahrar reviewed studies of cryoablation and RFA with at least 12-month follow-up and found that recently published 3- and 5-year outcomes show 93–98% cancer-specific survival in small cohorts. They caution that, while studies suggest satisfactory outcomes, given the limitations of imaging and the indolent nature of the tumors, stringent selection criteria and rigorous follow-up is required.

Strom and colleagues reported on a retrospective comparison of 145 patients who underwent laparoscopic (n = 84) or percutaneous (n = 61) cryoablation of small renal masses at 5 academic medical centers in the United States. These patients were offered cryoablation because they were considered to be at higher risk for complications from partial nephrectomy or were not surgical candidates due to comorbidities. Mean tumor size was 2.7 cm in the laparoscopic group versus 2.5 cm in the percutaneous group. Patients were followed for a longer period of time in the laparoscopic group (mean of 42.3 ± 21.2 months) compared to the
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percutaneous group (31.0 ± 15.9 months \( p = 0.008 \)). Complications in both treatment groups were similar and did not occur with any significant difference in frequency. At a mean intermediate follow-up of 37.6 months, local tumor recurrence was significantly more frequent in the percutaneous group at 16.4% (10/61) compared to 5.9% (5/84) in the laparoscopic group. However, disease-free survival and overall survival were not significantly different at last follow-up in the laparoscopic group compared to the percutaneous group (91.7% and 89.3% vs. 93.7% and 88.9%, respectively).

Case Series
The individual case series do not add substantially to the evidence on efficacy, but a number have reported intermediate or longer term outcomes for cryoablation with RCC. Caputo et al reported on long-term outcomes on 138 patients with 142 tumors, with a mean follow-up of 98.8 months. Perioperative complications occurred in 15 patients, for a rate of 10.6%. Recurrence-free survival was 91.4% at 3 years, 86.5% at 5 years, and 86.5% at 10 years. The latest recurrence occurred 4.4 years posttreatment.

Weld et al reported on 3-year follow-up for 36 (22 malignant) renal tumors treated with laparoscopic cryoablation. In this series, the 3-year cancer-specific survival rate was 100%, and no patient developed metastatic disease. The authors concluded that these intermediate-term data seemed equivalent to results obtained with extirpative therapy. Hegarty et al reported results on 164 laparoscopic cryoablutions and 82 percutaneous RFAs for localized renal tumors. Mean tumor size was 2.5 cm. Cancer-specific survival following cryotherapy was 98% at a median follow-up of 3 years and 100% for RFA at just 1-year median follow-up. Studies have also reported results for small numbers of patients who had laparoscopic cryoablation or laparoscopic partial nephrectomy for treatment of renal masses.

In a prospective, single-institution study, Rodriguez et al reported on 113 patients consecutively treated with percutaneous cryoablation for 117 renal lesions. The average renal lesion size in the study was 2.7 cm (83 [71%] were RCC). Patients were selected for cryoablation over surgery when tumors were 4 cm or less in diameter and percutaneously approachable or if the patient could not tolerate surgery when tumors were greater than 4 to 7 cm. Technical success was reported as 100%, with 93% of patients having no or only mild complications. At a median follow-up of 2 years (59 patients), efficacy was 98.3% and 92.3% at 3 years (13 patients). Metastatic disease did not occur in any patients during follow-up, and cancer-specific survival was 100%.

Nguyen et al evaluated options for salvage of ipsilateral tumor recurrence after previous ablation. Recurrence rates at their center were 13 (7%) of 175 after cryoablation and 26 (25%) of 104 after RFA. Extensive perinephric scarring was encountered in all salvage operations following cryoablation, leading authors to conclude that cryoablation in particular can lead to extensive perinephric fibrosis, which can complicate salvage attempts.

Section Summary: Renal Cancer
There is a large body of single-arm studies reporting on cryoablation outcomes for small renal tumors, most of which involved patients who are inoperable or at high surgical risk. The success rate for cryoablation is high, likely greater than 95%, and the long-term disease-free survival is more than 90%. Some meta-
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analyses have performed indirect comparisons of cryoablation with surgery, but they had selection bias and did not definitively provide evidence of comparative effectiveness. Prospective controlled trials are needed to determine whether cryoablation achieves equivalent outcomes and/or reduced complications, compared to surgical treatment.

Other Cancers
Meller et al. report a retrospective analysis of a single center experience of 440 bone tumor cryosurgery procedures performed between 1988 and 2002, two-thirds of them for primary benign-aggressive and low-grade malignant lesions, and one-third for primary high-grade and metastatic bone tumors. At median follow-up of 7 years (range 3–18 years), overall recurrence rate was 8%. Based on their experience, the authors suggest that the ideal case for cryosurgery is a young adult with involvement of long bone, a benign-aggressive or low-grade malignant bone tumor, a good cavity with greater than 75% thick surrounding walls, none or minimal soft tissue component, and at least +/-1 cm of subchondral bone left near a joint surface after curettage and burr drilling.

In 2013, Callstrom et al reported on 61 patients treated with cryoablation for pain from 69 tumors (size, 1-11 cm) metastatic to the bone. Before treatment, patients rated their pain with a 4 or more on a 1 to 10 scale using the Brief Pain Inventory with a mean score of 7.1 out of 10 for worst pain in a 24-hour period. The mean pain score gradually decreased after cryoablation to 1.4 of 10 (p<0.001) 24 weeks for worst pain in a 24-hour period. A major complication of osteomyelitis was experienced by 1 patient (2%).

Other articles identified in the literature search related to use of cryoablation in other cancers either involved small numbers of patients or limited follow-up.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received from 2 Physician Specialty Societies (5 reviews) and from 2 Academic Medical Centers (3 reviews) while this policy was under review for February 2009. There was strong reviewer support for use of cryoablation in the treatment of select patients with renal tumors. There also was support for use in the treatment of benign breast disease. Reviewers generally agreed this was investigational in the treatment of pancreatic cancer.

Summary
For individuals who have solid tumors of the breast, lung, pancreas, or kidney who receive cryosurgical ablation, the evidence includes nonrandomized comparative studies, case series, and systematic reviews of these nonrandomized studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. There is a lack of randomized controlled trials and high-quality comparative studies to determine the efficacy and comparative effectiveness of cryoablation. The largest amount of evidence is for renal cell carcinoma in select patients, ie, those with small tumors who are not surgical candidates or who have baseline renal insufficiency such that standard surgical procedures would impair their kidney function. Cryoablation results in short-term tumor control and less morbidity than surgical resection, but long-term outcomes may be inferior to surgery. For other indications, there is less evidence, with single-arm series reporting high rates of local control. Due to the lack of prospective controlled trials, it
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is difficult to draw conclusions whether cryoablation improves outcomes for any indication better than alternative treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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Policy History
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Current Effective Date: 09/21/2016
10/21/2003 Medical Policy Committee review
01/26/2004 Managed Care Advisory Committee approval
12/07/2005 Medical Director review
12/20/2005 Medical Policy Committee review. Format revision. FDA approval information added to policy.
02/23/2006 Quality Care Advisory Council approval
10/10/2007 Medical Director review
10/17/2007 Medical Policy Committee approval. No change to coverage eligibility.
03/04/2009 Medical Director review
03/18/2009 Medical Policy Committee approval. Changed localized renal cell carcinoma from investigational to eligible for coverage with criteria. Breast fibroadenomas removed from this policy and made into a separate policy.
03/05/2010 Medical Policy Committee review
03/19/2010 Medical Policy Implementation Committee approval. Added benign tumors of the breast to be investigational.
03/03/2011 Medical Policy Committee review
03/16/2011 Medical Policy Implementation Committee approval. Renal cell carcinomas in patients who are surgical candidates was added as investigational.
03/01/2012 Medical Policy Committee review
03/21/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/07/2013 Medical Policy Committee review
03/20/2013 Medical Policy Implementation Committee approval. Title changed from “Cryosurgery Ablation of Miscellaneous Solid Tumors other than Liver or Prostate” to “Cryosurgery Ablation of Miscellaneous Solid Tumors Other than Liver or Prostate Tumors or Breast Fibroadenomas”. Removed the second criteria bullet for treatment of renal cell carcinoma requiring that the patient not be considered as a surgical candidate due to co-morbid disease. Lung cancer added to investigational statement. The investigational statement was revised for clarification.
03/06/2014 Medical Policy Committee review
03/19/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015 Medical Policy Committee review
09/08/2016 Medical Policy Committee review
09/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Next Scheduled Review Date: 09/2017

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 2015 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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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
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</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0340T, 19105, 20983, 50250, 50542, 50593</td>
</tr>
<tr>
<td>HCPCS</td>
<td>C2618</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*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. 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.

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