Whole Gland Cryoablation of Prostate Cancer

Policy # 00022
Original Effective Date: 06/24/2002
Current Effective Date: 11/21/2018

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: Focal Treatments for Prostate Cancer are addressed separately in medical policy 00484.

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 whole gland cryoablation of the prostate when patient selection criteria are met to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for whole gland cryoablation of the prostate as treatment of clinically localized (organ-confined) prostate cancer will be considered when any of the following criteria are met:

- As an initial treatment; or
- As salvage treatment of disease that recurs following radiotherapy.

When Services Are Considered Investigational
Note: 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 whole gland cryoablation of the prostate as treatment of clinically localized (organ-confined) prostate cancer when patient selection criteria are not met to be **investigational.***

Background/Overview

PROSTATE CANCER
Prostate cancer is the most commonly diagnosed cancer and the third leading cause of cancer deaths among men in the United States, with an estimated 161,360 new cases and 26,730 deaths in 2017. The diagnosis and grading of prostate cancer are performed by taking a biopsy of the prostate gland.

Treatment
Whole gland (also known as total) cryoablation is one of several methods used to treat clinically localized prostate cancer and may be considered an alternative to radical prostatectomy or external-beam radiotherapy. Additionally, whole gland cryoablation may be used for salvage of nonmetastatic relapse

following initial therapy for clinically localized disease. Using percutaneously inserted cryoprobes, the glandular tissue is rapidly frozen and thawed to cause tissue necrosis. Cryosurgical ablation is less invasive than radical prostatectomy and recovery time may be shorter. External-beam radiotherapy requires multiple treatments, whereas cryoablation usually requires a single treatment.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Cryoablation of prostate cancer is a surgical procedure that uses previously approved and available cryoablation systems; and as a surgical procedure, it is not subject to regulation by the U.S. FDA.

Centers for Medicare and Medicaid Services (CMS)
The Centers for Medicare & Medicaid Services have indicated total cryotherapy is medically necessary and appropriate as primary treatment for clinically localized prostate cancer in stages T1 to T3. Salvage cryoablation is only medically necessary and appropriate in localized disease when radiotherapy has failed as primary treatment, and the patient meets 1 of 3 criteria: stage T2B or below, Gleason score less than 9, or prostate-specific antigen level of less than 8 ng/mL. Salvage cryoablation after failure of other therapies is not covered.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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

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PRIMARY PROSTATE CRYOABLATION
Clinical Context and Test Purpose
The purpose of whole gland cryoablation in patients considered initial treatment for localized prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of whole gland cryoablation improve the net health outcomes in patients with localized prostate cancer?

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

Patients
The relevant population of interest is individuals considering initial treatment for localized prostate cancer.

Interventions
The intervention of interest is cryoablation of the whole prostate gland. Cryoablation uses freezing to destroy tumor cells in a relatively noninvasive procedure, which can be conducted under spinal anesthesia.

Comparators
The following therapies and practices are currently being used to make decisions about localized prostate cancer: radiotherapy, radical prostatectomy, and active surveillance.

Outcomes
The general outcomes of interest are overall survival (OS), disease-free survival, cancer recurrence, and treatment-related adverse events (eg, sexual dysfunction, incontinence).

Timing
Follow-up for treatment-related morbidity is months post-procedure. Follow-up to monitor for recurrence measured in years of follow-up.

Setting
Cryoablation is administered by urologists in a tertiary care setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Gao et al (2016) reported the results of a systematic review and meta-analysis comparing cryoablation with radiotherapy and radical prostatectomy for the treatment of localized prostate cancer. The search included articles published up to December 2015. Because the pooled estimates combined primary and salvage treatment, the individual studies are presented in the following sections in lieu of pooled data here. Six studies described primary treatment (2 RCTs, 2 prospective observational, 2 retrospective). Cryotherapy had a similar OS and disease-specific survival rates as radiotherapy and radical prostatectomy in trials of primary treatment. There was significantly more sexual bother for cryoablation (compared with radiotherapy) at all times reported ($p<0.01$).

Ramsay et al (2015) prepared a health technology assessment for the National Institute for Health Research. Reviewers compared the clinical effectiveness of ablative therapies with radical prostatectomy, external-beam radiotherapy (EBRT), and active surveillance. The literature search included RCTs and non-RCTs published through March 2013. Meta-analyses were performed using a Bayesian indirect mixed-treatment comparison. Fourteen case series, 1 RCT, and 4 non-RCT comparative studies (total N=3995 patients) evaluated cryoablation. Reviewers included studies of primary and salvage treatment as well as whole and focal cryoablation. All studies were considered at high risk of bias. Only pooled estimates of primary, whole cryoablation are described here. Two publications provided data on OS for cryoablation vs EBRT; there was no evidence of a difference in OS for cryotherapy and EBRT at 4 years. The probability that cryoablation was superior to EBRT was 0.73. The predicted survival rate in the mixed-treatment comparison model at 4 years was 93% for cryoablation and 91% for EBRT. Reviewers concluded that there was insufficient evidence to form any clear recommendations on the use of ablative therapies.

A network meta-analysis by Xiong et al (2014) evaluated the comparative efficacy and safety of radical prostatectomy for several regimens of EBRT, cryoablation, and observational management. Evidence from 2005 to 2012 was included. This analysis incorporated evidence from 21 RCTs (total N=7350 patients) that reported on OS and prostate cancer–specific survival rates at 5 years, and late gastrointestinal (GI) and late genitourinary toxicities at 3 years. Reviewers used Bayesian network analysis with informative prior distributions based on external evidence for heterogeneity variances to compute odds ratios with 95% confidence intervals for all pairwise comparisons of interventions. The rank order of superiority of each intervention was compared with all the others using the surface under the cumulative ranking (SUCRA) curve statistic. The SUCRA curve is expressed as a percentage that ranges from 0% if an intervention is certainly the worst to 100% if an intervention is certainly the best. If all interventions are equal, all SUCRA curve values will approximate a percentage of 50%. Overall, the network analysis showed no evidence of the superiority of any treatment for OS (based on SUCRA curve values that ranged from 18% [observational management] to 69% [conformal low-dose EBRT]). Cryoablation had a SUCRA curve value of 50%, which yielded a ranking of fourth best treatment. However, the SUCRA curve values for late GI (99%) and genitourinary (77%) events with cryoablation rated this intervention in first place for those

specific outcomes. These analyses are consistent with a positive balance of benefits and harms associated with total cryoablation compared with radical prostatectomy, EBRT, and observational management.

In a comparative effectiveness report from the Prostate Cancer Results Study Group (2012), which included studies published between 2000 and 2010, treatment effectiveness measured by prostate-specific antigens (PSA) levels following various prostate cancer treatments, including cryoablation, was noted to be difficult to evaluate, because very few studies comparing results from treatment options were identified. Additionally, variations in methods of evaluating outcomes and reporting results complicated the analysis. No recommendations for cryoablation were made by the Prostate Cancer Results Study Group.

A systematic review by Chou et al (2011) assessed localized prostate cancer treatments on behalf of the Agency for Healthcare Research and Quality. In a search of literature from 2002 to July 2011, reviewers found no studies comparing cryoablation with watchful waiting (surveillance) and no randomized trials or cohort studies evaluating OS or prostate cancer–specific survival outcomes. The available evidence was mostly from uncontrolled studies and found to be very limited and not sufficiently reliable to estimate the benefits or harms of cryoablation.

A comparative effectiveness review by Wilt et al (2008), which evaluated therapies for clinically localized prostate cancer on behalf of the Agency for Healthcare Research and Quality, also found that no randomized trials had evaluated cryoablation. Reviewers noted that, in general, neither OS nor prostate cancer–specific survival was reported for this technique. Progression-free survival in patients with T1 or T2 stages ranged from 29% to 100%.

A Cochrane review by Shelley et al (2007), which assessed cryoablation for localized prostate cancer, found no randomized trials comparing cryoablation with other therapies for the primary treatment of localized prostate cancer; studies identified included case series. The patients recruited in the case series (total N=1483 patients) ranged in age from 41 to 84 years, and their conditions were classified by stage: stages T1: 0% to 43%; T2: 24% to 88%; T3: 1% to 41%; and T4: 0% to14%. The mean preoperative PSA level ranged from 9.7 to 39 ng/mL, with Gleason scores less than 7 in 9% to 37% of patients. Reviewers concluded that cryoablation offered a potential alternative to standard therapies for the primary treatment of localized prostate cancer and that patients who select cryoablation as their therapeutic option should be informed of the relevant data (eg, efficacy, complications, low-grade evidence) associated with such treatment; however, due to the poor quality of the available studies, it was difficult to determine the relative benefits of cryoablation.

Randomized Controlled Trials

Chin et al (2008, 2012) reported on a randomized trial comparing cryoablation with EBRT in patients who had clinical stage T2C-T3B prostate cancer. These patients had node-negative disease and had received 6 months of hormonal therapy, starting 3 months before treatment. Only 64 of the planned 150 patients were accrued; entry was limited due to changes in practice and difficulty beginning cryoablation at one of the

sites. Twenty-one (64%) of 33 in the cryoablation group and 14 (45%) of 31 in the EBRT-treated group were classified as treatment failures. The mean biochemical disease-free survival (bDFS) was 41 months for the EBRT group and 28 months for the cryoablation group. The 4-year bDFS rate for the EBRT and cryoablation groups were 47% and 13%, respectively. The 8-year bDFS rate for the EBRT and cryoablation groups were 59.1% and 17.4%, respectively. Disease-specific survival rates and OS rates were very similar and, at the 8-year follow-up, the rates still did not differ significantly. Serious complications were uncommon in both groups. EBRT patients exhibited adverse GI effects more frequently. The trialists concluded that taking into account the relative deficiency in numbers and the original trial design, this prospective randomized trial indicated that the results of cryoablation were less favorable than those of EBRT and that cryoablation was suboptimal primary therapy in locally advanced prostate cancer.

Donnelly et al (2010) reported on a randomized trial of 244 patients with newly diagnosed localized prostate cancer, during the period from 1997 through 2003, to compare cryoablation with EBRT. All patients began neoadjuvant androgen-deprivation therapy before local treatment and continued for a period of 3 to 6 months. The median follow-up was 100 months. At 36 months, the biochemical failure rate (PSA nadir + 2 ng/mL) was 17.1% in the cryoablation group and 13.2% in the radiotherapy group. The OS rate at 5 years was 89.7% in the cryoablation group, and 88.3% in the radiotherapy group (p=0.78). At 36 months, radiotherapy patients had significantly more positive prostate biopsies (22/76 patients) than the cryoablation group (7/91 patients; p<0.001). Observed failure rates at 60 months were similar in both groups but were less likely with cryoablation at 84 months. Using the National Cancer Institute of Canada Common Toxicity Criteria, 12 cryoablation patients experienced 13 grade 3 adverse events vs 16 grade 3 adverse events in 14 radiotherapy patients. Urinary retention was the most common grade 3 adverse event in both treatment arms. The trialists were unable to establish that cryoablation was noninferior to radiotherapy at 36 months due to the wide confidence interval. The trialists also noted several issues that limited interpretation of trial results, including the use of uncommonly low radiation dosages (68 gray, 70 gray, 73.5 gray, respectively), and early trial closure due to lack of patient enrollment.

In a second article from the Donnelly trial (2010), Robinson et al (2009) reported on the quality of life outcomes in the same 244 patients. With few exceptions, study participants reported the quality of life at high levels in both the cryoablation and radiotherapy treatment arms. Acute urinary dysfunction, which eventually resolved, occurred more often with cryoablation, as measured using the University of California at Los Angeles Prostate Cancer Index (mean urinary function after cryoablation was 69.4 vs 90.7 after EBRT; p<0.001; higher scores indicate better function and less bother). The University of California at Los Angeles Prostate Cancer Index sexual function decreased in both arms at 3 months. However, reduced sexual function was reported more frequently in the cryoablation arm (mean cryoablation, 7.2 vs mean EBRT, 32.9; p<0.001). Decreased sexual function continued at the 3-year evaluation, with the mean score 15 points lower in the cryoablation group.

Nonrandomized Comparative Studies
Many nonrandomized studies have assessed cryoablation for localized prostate cancer. A sample is discussed here.

Aus (2008) reported that cryoablation using third-generation equipment and that long-term follow-up from these newer devices, which emerged around 2000, would be needed. The newer devices use more ultra-thin probes and argon gas (as opposed to liquid nitrogen) and create smaller ice balls. Lian et al (2011) reported on early results of cryoablation using third-generation technology as a primary treatment for 102 patients with localized prostate cancer during the period of 2006 through 2009. Only 1 patient developed biopsy-confirmed prostate cancer recurrence. The PSA levels were elevated in 7 patients; however, biopsies were negative. Mild incontinence, urethral sloughing, and erectile dysfunction occurred in 4%, 4.9%, and 64%, respectively.

Ball et al (2006) reported on the quality of life outcomes on a subset of 719 patients with localized prostate cancer treated with various techniques including cryosurgical ablation. They reported that, in an older population, the tissue destruction resulting from cryoablation appeared to relieve obstructive and irritative urinary symptoms but at the sacrifice of sexual function compared with palladium 103 brachytherapy.

Registry Studies
Williams et al (2012) compared data from the U.S. Surveillance, Epidemiology, and End Results Medicare-linked data on 10,928 patients with localized prostate cancer treated with primary cryoablation or brachytherapy. Urinary and erectile dysfunction occurred significantly more frequently after cryoablation (41.4% and 34.7%) than brachytherapy (22.2% and 21%), respectively. Androgen-deprivation therapy was also used significantly more often after cryoablation than after brachytherapy, suggesting a higher rate of recurrence after cryoablation (1.4 vs 0.5 per 100 person-years). Bowel complications, however, occurred significantly more frequently with brachytherapy (19%) than cryoablation (12.1%).

The Cryo Online Data Registry is a database established and supported by a cryoablation manufacturer. The data are maintained independently. Physicians submit standardized forms to the database and participation is voluntary. The Registry contains case report forms of pretreatment and posttreatment information for patients undergoing whole gland or partial gland (focal) prostate cryoablation. Patients are stratified into low-, intermediate-, and high-risk groups. Jones et al (2008) reported the initial outcome for 1198 men with primary whole gland prostate cryoablation. Mean follow-up was 24.4 months; 136 men had 5-year data. The 5-year bDFS rate (Phoenix definition) for the entire population was 73%; rates by category were 91%, 79%, and 62%, for the low-, intermediate-, and high-risk groups, respectively. The rectal fistula rate was 0.4%. Incontinence was reported by 5% of men, with 3% of men using pads. Twenty-five percent of men reported having sexual intercourse, but only 9% did so without pharmaceutical or device assistance. Outcomes for 300 men in the Cryo Online Data Registry who underwent primary whole gland cryotherapy for high-grade (Gleason score ≥8), localized prostate cancer were published by Tay et al (2016). Mean follow-up was 28.4 months. The estimated 2- and 5-year bDFS rates were 77% (95% confidence interval,

71% to 88%) and 59% (95% confidence interval, 50% to 67%), respectively. At 12-month follow-up, complete continence was reported by 91% of men and potency by 17% of men. The incidence of recto-urethral fistulae was 1.3%. Urinary retention requiring intervention beyond temporary catheterization was reported by 3% of men.

Section Summary: Primary Prostate Cryoablation
Evidence for the use of whole gland cryoablation to treat localized prostate cancer comes from several systematic reviews, 2 RCTs, and many comparative and noncomparative observational studies. Earlier systematic reviews, with literature searches through mid-2011 did not find evidence supporting the use of whole gland cryoablation; however, more recent systematic reviews have reported similar OS and disease-specific survival rates for whole gland cryoablation compared with radical prostatectomy and EBRT.

SALVAGE PROSTATE CRYOABLATION
Clinical Context and Test Purpose
The purpose of whole gland cryoablation in patients who have recurrent localized prostate cancer following radiotherapy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of whole gland cryoablation improve the net health outcomes in patients with recurrence of localized prostate cancer following radiotherapy?

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

Patients
Individuals in need of salvage treatment for recurrent localized prostate cancer after radiotherapy.

Interventions
The intervention of interest is cryoablation of the whole prostate gland. Cryoablation uses freezing to destroy tumor cells in a relatively noninvasive procedure, which can be conducted under spinal anesthesia.

Comparators
The following therapies and practices are currently being used to make decisions about recurrent localized prostate cancer: radical prostatectomy and brachytherapy.

Outcomes
The general outcomes of interest are OS, disease-free survival, cancer recurrence, and treatment-related adverse events (eg, sexual dysfunction, incontinence).

Timing
Follow-up for treatment-related morbidity is months post-procedure. Follow-up to monitor for recurrence measured in years of follow-up.

Setting
Cryoablation is administered by urologists in a tertiary care setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Systematic Reviews
The health technology assessment by Ramsay et al (2015), described previously, identified 2 studies (Chin et al [2001]; Robinson et al [2006]) assessing salvage whole gland cryoablation. Both were single-arm studies. One reported 1- and 4-year bDFS rates of 71% and 54%, respectively. Both reported functional outcomes. With a median follow-up of 19 months, the incontinence rate was 20%, bladder neck stenosis rate was 25%, and the recto-urethral fistula rate was 3%. The sexual dysfunction rate was 69% at 1 year, and 52% at 2 years.

Mouraviev et al (2012) reviewed literature published between 1991 and 2012 to compare salvage cryoablation for radio-recurrent prostate cancer with other salvage treatments. Reviewers found comparisons difficult to make because no prospective, randomized studies were identified and PSA failure was defined variously. However, they noted that studies had reported salvage cryoablation outcomes as being comparable to those for salvage radical prostatectomy (for an intermediate term). The following criteria were identified as favorable prognostic factors for defining patients for salvage cryoablation: a PSA level less than 10 ng/mL, a Gleason score 8 or less, and a clinical stage T1c or T2 before salvage cryoablation therapy.

In a systematic review, Punnen et al (2013) evaluated management approaches, including cryoablation, for salvage treatment (biochemical recurrence) after primary treatment for localized prostate cancer. Reviewers identified 6 studies using salvage cryoablation and concluded that while there was limited evidence, cryoablation was a treatment option for salvage therapy; randomized trials are needed.

Nonrandomized Comparative Studies
Peters et al (2013) reported on results of retrospective data from 129 men from 5 Dutch centers. Forty-four men underwent salvage prostatectomy, 54 underwent salvage cryoablation, and 31 underwent salvage brachytherapy. The mean follow-up for each procedure was 29 months, 22 months, and 14 months, respectively. Biochemical failure occurred in 25 (81%) men in the brachytherapy group, 29 (66%) men in the prostatectomy group, and 33 (61%) men in the cryoablation group. Severe genitourinary and GI toxicity (grade >3) using the Common Toxicity Criteria for Adverse events (v.3.0), definition was observed in up to 30% of patients in all 3 groups. There were 12 (27%), 5 (9%), and 14 (45%) deaths in the prostatectomy, cryoablation, and brachytherapy groups, respectively.

Case Series
Siddiqui et al (2016) reported long-term outcomes for 157 men undergoing salvage cryoablation for biopsy-proven, localized radio-recurrent prostate cancer at a single institution from 1995 to 2004. Median follow-up was 117 months (interquartile range, 55-154 months). OS rates at 5 and 10 years were 93% and 76%, respectively. The bDFS rates at 10 and 15 years were 35% and 23%, respectively. Recto-urethral fistula developed in 2.5% of patients and was successfully repaired in all cases. Fifty-two percent of men reported no incontinence while 44% required 0 or 1 pad per day.

Wenske et al (2013) reported on salvage cryoablation in a series of 396 consecutively treated patients who had failed cryoablation or radiotherapy. Data were analyzed from 328 patients, with a median follow-up of 47.8 months (range, 1.6-203.5 months). Fifty-five (16.7%) of these patients received subtotal (focal) salvage cryoablation. At the 5- and 10-year follow-ups, disease-free survival rates were 63% and 35%, disease-specific survival rates were 91% and 79%, and OS rates were 74% and 45%, respectively. After salvage cryoablation, the median PSA nadir was 0.2 ng/mL (range, 0.01-70.70 ng/mL) at a median follow-up of 2.6 months (range, 2.0-67.3 months). The PSA nadir was the only predictor of recurrence ($p<0.001$) and disease-specific survival ($p=0.012$) based on multivariate analyses. Complications occurred in 0.6% to 4.6% of patients.

Williams et al (2011) retrospectively reviewed 176 patients receiving salvage cryoablation for locally recurrent prostate cancer during the period of 1995 to 2004. Patients were followed a mean of 7.46 years, with 52 patients having been followed for more than 10 years. The 10-year disease-free survival rate was 39%. The authors identified certain risk factors for prostate cancer recurrence following salvage cryoablation, including presalvage PSA levels, preradiation, and presalvage Gleason scores. Early recurrence was highly predicted by a PSA nadir greater than 1.0 ng/dL after salvage cryoablation.

Ng et al (2007) reported on a series of 187 patients with locally recurrent prostate cancer after radiotherapy who underwent salvage cryoablation, with a mean follow-up of 39 months. Serum PSA level at cryoablation was a predictive factor for biochemical recurrence on univariate and multivariate analyses ($p<0.001$). Patients with a precryoablation PSA level less than 4 ng/mL had 5- and 8-year bRFS rates of 56% and 37%, respectively. In contrast, patients with precryoablation PSA levels of 10 ng/mL or greater had 5- and

8-year bRFS rates of only 1% and 7%, respectively. Patients with precryoablation PSA levels ranging from 4 to 9.99 ng/mL had intermediate survival outcomes. Five- and 8-year OS rates were 97% and 92%, respectively. The authors concluded that salvage cryoablation was a viable treatment option for patients with prostate cancer for whom radiotherapy has failed; they further concluded that salvage cryoablation should be performed when the serum PSA level is still relatively low because, in these patients, the repeat procedure may potentially be curative.

Ismail et al (2007) reported on 100 patients treated between 2000 and 2005 with cryoablation for recurrent prostate cancer after radiotherapy; the mean follow-up was 33.5 months. All patients had biopsy-confirmed recurrent prostate cancer. Biochemical RFS was defined using a PSA level of less than 0.5 ng/mL and using the American Society for Therapeutic Radiology and Oncology definition for biochemical failure. Patients were stratified into 3 risk groups: high-risk (68 men), intermediate-risk (20 men), and low-risk (12 men). There was no surgery- or cancer-related deaths; the 5-year actuarial bRFS rates were 73%, 45%, and 11% for the low-, intermediate- and high-risk groups, respectively. Complications included incontinence (13%), erectile dysfunction (86%), lower urinary tract symptoms (16%), prolonged perineal pain (4%), urinary retention (2%), and recto-urethral fistula (1%). The authors concluded that salvage cryoablation was a safe and effective treatment for localized prostate cancer recurrence after radiotherapy.

Registry Studies
Friedlander et al (2014) compared salvage cryoablation with salvage radical prostatectomy in 440 men retrospectively identified in the U.S. Surveillance, Epidemiology, and End Results database who were treated between 1992 and 2009. The authors used propensity score analyses to compare overall and prostate cancer–specific mortality. Overall mortality was significantly higher (21.6 vs 6.1 deaths/100 person-years, p<0.001) for prostatectomy than for cryoablation. Prostate cancer–specific death rates were numerically higher for prostatectomy than for cryoablation (6.5 vs 1.4 deaths/100 person-years, p=0.061).

Spiess et al (2013) reported on outcomes from the Cryo Online Data Registry for 156 men with data on who underwent salvage cryoablation without neoadjuvant hormonal ablative therapy. The bDFS rates at 1, 2, and 3 years were 89.0%, 73.7%, and 66.7%, respectively. For men with presalvage PSA levels less than 5 ng/mL, the bDFS rates were 95.3%, 86.7%, and 78.3% vs 81.4%, 58.4%, and 52.9% for those with PSA levels of 5 ng/mL or more.

Section Summary: Salvage Prostate Cryoablation
The evidence for the use of salvage prostate cryoablation in men with localized, recurrent prostate cancer following radiotherapy primarily includes noncomparative case series. A small number of retrospective comparative studies have compared salvage cryoablation with salvage prostatectomy but with contradictory findings. Men in this group have few other options and prostatectomy can be difficult in tissue that has been irradiated.

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SUMMARY OF EVIDENCE

For individuals who are considering initial treatment for localized prostate cancer who receive whole gland cryoablation, the evidence includes several systematic reviews, 2 RCTs, and many comparative and noncomparative observational studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. High-quality data comparing cryoablation with external-beam radiotherapy, radical prostatectomy, or active surveillance are lacking, but available data have suggested similar overall survival and disease-specific survival rates compared with radical prostatectomy and external-beam radiotherapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have salvage treatment for recurrence of localized prostate cancer following radiotherapy who receive whole gland cryoablation, the evidence includes primarily noncomparative case series and a few retrospective studies comparing salvage cryoablation with salvage prostatectomy. Relevant outcomes are overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. High-quality data comparing cryoablation with prostatectomy was mixed, and evidence comparing cryotherapy with brachytherapy is lacking. Men in this group have few options and prostatectomy can be difficult in tissue that has been irradiated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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Policy History

Original Effective Date: 06/24/2002
Current Effective Date: 11/21/2018

06/20/2002	Medical Policy Committee review
06/24/2002	Managed Care Advisory Council approval. Format revision. No substance change to policy.
08/31/2004	Medical Director review
09/21/2004	Medical Policy Committee review. Format revision. No substance change to policy.
09/27/2004	Managed Care Advisory Council approval
09/07/2005	Medical Director review
09/20/2005	Medical Policy Committee review. Format revision. Coverage eligibility unchanged. The following clarification statement was added: "Based on review of available data, the Company considers other uses of cryoablation of the prostate to be investigational."
09/22/2005	Quality 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.
10/04/2006	Medical Director review
10/18/2006	Medical Policy Committee approval. Format revision, including addition of information added to FDA and or other governmental regulatory approval. References updated and additional references added. Coverage eligibility unchanged.
11/07/2007	Medical Director review
11/15/2007	Medical Policy Committee approval. No change to coverage eligibility.
11/05/2008	Medical Director review
11/18/2008	Medical Policy Committee approval. No change to coverage eligibility. Rationale updated.
05/07/2009	Medical Director review
05/20/2009	Medical Policy Committee approval. Revised two criteria bullets in coverage section as follows: • "As an initial treatment of clinically localized (organ-confined) primary prostate cancer; or • As salvage treatment of recurrent (following radiation therapy) localized prostate cancer." Added investigational statement as follows, "Based on review of available data, the Company considers subtotal prostate cryoablation in the treatment of prostate cancer to be investigational.*"
06/03/2010	Medical Policy Committee review
06/16/2010	Medical Policy Implementation Committee approval
05/05/2011	Medical Policy Committee review
05/18/2011	Medical Policy Implementation Committee approval. No change.
05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. No change to coverage.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. No change to coverage.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. No change to coverage. Added FDA section.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. No change to coverage.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Title change, policy statements adjusted to address whole gland treatment.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 11/2019

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.

Whole Gland Cryoablation of Prostate Cancer

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

Code Type	Code
CPT	55873
HCPCS	C2618
ICD-10 Diagnosis	C61 C79.82 D07.5 Z85.46

*****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 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.

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