Whole Gland Cryoablation of Prostate Cancer

Policy # 00022
Original Effective Date: 06/24/2002
Current Effective Date: 11/16/2016

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: 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 of clinically localized (organ-confined) prostate cancer; or
- As salvage treatment of recurrent (following radiation therapy) disease.

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
Cryoablation, also known as cryotherapy or cryosurgery, of prostate cancer is a technique in which cryoprobes are inserted percutaneously into the prostate gland to rapidly freeze and thaw tissue causing necrosis. Whole gland (also known as total) cryoablation is one of several methods available to treat clinically localized prostate cancer and may be considered an alternative to radical prostatectomy or external beam radiotherapy (EBRT). It also 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 such that tissue necrosis follows. Cryosurgical ablation is less invasive than radical prostatectomy and recovery time may be shorter. While EBRT requires multiple treatments, typically only one treatment is required for cryoablation.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
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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)
CMS indicates cryotherapy is medically necessary and appropriate as primary treatment for clinically localized prostate cancer in stages T1-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 (PSA) less than 8 ng/mL. Salvage cryotherapy after failure of other therapies is not covered.

Rationale/Source
This policy has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed for the period of through July 8, 2016.

Primary Prostate Cryoablation
Systematic reviews
This policy was initially based on a 2001 Technology Evaluation Center (TEC) Assessment focused on cryoablation for primary treatment of clinically localized prostate cancer. At that time, available evidence was heterogeneous with insufficient information on baseline characteristics of enrolled patients. Where data were available, outcomes appeared to be generally comparable across treatment methods. However, data from cryoablation studies were sparse and did not permit conclusions on oncologic outcomes. Perioperative mortality and acute life-threatening consequences of cryoablation appeared negligible. Patients had the highest likelihood of impotence after cryoablation compared with radical prostatectomy or 3-dimensional conformal radiotherapy (3D-CRT). The frequency of incontinence appeared similar to that after 3D-CRT, and potentially less than that after radical prostatectomy. Adverse gastrointestinal (GI) consequences typical of 3D-CRT were not noted after cryoablation. Long-term consequences of cryoablation were uncertain because follow-up was inadequate.

The conclusions of the 2001 TEC Assessment contrasted with an analysis from the CMS supporting Medicare’s decision that cryosurgical ablation is eligible for coverage. While the TEC Assessment sought data on health outcomes, the CMS assessment used an intermediate outcome, changes in PSA levels. As noted in the CMS assessment, “Data shows that a significant number of patients are able to sustain undetectable levels of PSA for a period of time of at least 24 months. This compares favorably with the biopsy data following external beam irradiation.”

A 2007 Cochrane review of cryoablation for localized prostate cancer found no randomized trials comparing cryoablation with other therapies for primary treatment of localized prostate cancer. Studies identified were case series. The patients recruited (n=1,483) 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 and ranging from 6% to 37%. The authors concluded the following: cryoablation offers a potential alternative to standard therapies for the primary treatment of localized prostate cancer; however, the poor quality of the available studies makes it difficult to determine the relative benefits of this modality; patients selecting cryoablation as
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their therapeutic option should be made fully aware of the reported efficacy, complications, and low-grade
evidence from which these data are derived.

A 2008 comparative effectiveness review of therapies for clinically localized prostate cancer from the
Agency for Healthcare Research and Quality (AHRQ) also found that no randomized trials had evaluated
cryoablation. The report also noted that in general neither overall survival (OS) nor prostate-cancer-specific
survival was reported for this technique. Progression-free survival (PFS) in patients with T1–T2 stages
ranged from 29% to 100%.

A subsequent systematic review of localized prostate cancer treatments prepared for AHRQ was published
in late 2011. The review found no studies comparing cryoablation with watchful waiting and no randomized
trials or cohort studies evaluating OS or prostate cancer-specific mortality 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.

In a 2012 comparative effectiveness report from the international Prostate Cancer Results Study Group
(PCRSG), PSA-free survival following various prostate cancer treatments, including cryoablation, was noted
to be difficult to evaluate, since 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 PCRSG.

A network meta-analysis published in 2014 evaluated the comparative efficacy and safety of radical
prostatectomy, several regimens of EBRT, cryoablation, and observational management. This analysis
incorporated 21 randomized controlled trials (RCTs; total N=7350 patients) that reported OS and prostate
CSS rates at 5 years, and late GI and late genitourinary (GU) toxicities at 3 years. It used Bayesian network
analysis with informative prior distributions based on external evidence for heterogeneity variances to
compute odd ratios (ORs) with 95% confidence intervals (CIs) for all pairwise comparisons of interventions.
The rank order of superiority of each intervention was compared to all others using the surface under the
cumulative ranking (SUCRA) curve statistic. The latter 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 would approximate 50%. Overall, the network analysis showed no evidence
of 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 GU
(77%) events with cryoablation placed 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 2015, a Health Technology Assessment (HTA) was reported by the National Institute for Health
Research. The review compared the clinical effectiveness of ablative therapies to radical prostatectomy,
EBRT, and active surveillance. The 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. The
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review 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 versus 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. The reviewers concluded that there was insufficient evidence to form any clear recommendations on the use of ablative therapies.

In 2016, Gao et al reported results of a systematic review and meta-analysis comparing cryoablation to radiotherapy (RT) and radical prostatectomy for treatment of localized prostate cancer. The search included articles published up to December 2015. Because the pooled estimates combined primary and salvage treatment, we present the individual studies in the following sections and do not present pooled data here. Six studies described primary treatment (2 RCTs, 2 prospective observational, 2 retrospective). Cryotherapy had similar OS and disease-specific survival (DSS) rates as RT and radical prostatectomy in trials of primary treatment. There was significantly more sexual bother for cryoablation compared to RT at all times reported (p<0.01).

Randomized Controlled Trials
Chin and colleagues reported on a randomized trial of cryoablation compared to EBRT in patients with clinical stage T2C-T3B prostate cancer. These patients had node-negative disease and also 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 cryosurgery at one of the sites. Twenty-one of 33 (64%) in the cryoablation group and 14 of 31 (45%) in the EBRT-treated group were classified as treatment failure. The mean biochemical disease-free survival (bDFS) was 41 months for the EBRT group compared to 28 months for the cryoablation group. The 4-year bDFS for EBRT and cryoablation groups were 47 and 13%, respectively. Disease-specific survival and OS for both groups were very similar and at 8 years’ follow-up, were not significantly different. Serious complications were uncommon in either group. EBRT patients exhibited adverse GI effects more frequently. The authors 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 compared to those of EBRT and that cryoablation was suboptimal primary therapy in locally advanced prostate cancer.

Donnelly and colleagues reported on a randomized trial of 244 patients with newly diagnosed localized prostate cancer, during the period of December 1997 through February 2003, to compare cryoablation to EBRT. All patients began neoadjuvant antiandrogen therapy prior to local treatment and continued for a period of 3-6 months. 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 versus 13.2% in the radiotherapy group. Overall survival at 5 years was 89.7% in the cryoablation group versus 88.3% in the radiotherapy group and did not differ statistically (p=0.78). At 36 months, radiotherapy patients had significantly more positive prostate biopsies than the cryoablation group (22 of 76 vs. 7 of 91 patients, respectively [p<0.001]). Observed failure rates at 60 months were equal in both groups but favored cryoablation at 84 months. Twelve cryoablation patients experienced 13 grade 3 adverse events versus 16 grade 3 adverse events in 14 radiotherapy
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patients using National Cancer Institute of Canada Common Toxicity Criteria. Urinary retention was the most common grade 3 adverse event in both treatment arms. The authors indicated they were unable to establish that cryoablation was noninferior to radiotherapy at 36 months due to the wide confidence interval. However, they noted several issues which limit interpretation of the study results, including the use of lower radiation dosages (68 Gy, 70 Gy, and 73.5 Gy, respectively) than are common today and early trial closure due to lack of patient enrollment.

In a second article from the Donnelly study, Robinson et al. reported on quality-of-life (QOL) outcomes in the same 244 patients. With only a few exceptions, the authors found study participants reported QOL 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 (UCLA) Prostate Cancer Index (mean urinary function in cryoablation was 69.4 vs. 90.7 in EBRT; p<0.001; higher scores meaning better function and less bother). UCLA Prostate Cancer Index sexual function decreased in both arms at 3 months. However, reduced sexual function was reported more in the cryoablation arm (mean cryoablation: 7.2 vs. 32.9 in EBRT; 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 reported on cryoablation for localized prostate cancer. The largest single-institution series reported the 7-year actuarial rate of bDFS for 590 consecutively treated patients. However, 59% of the patients were treated using an older liquid nitrogen system, which the authors asserted “… yields inferior results compared with the argon-based cryomachines we now use….” Even so, reported results combined outcomes obtained from both systems.

Aus reported that cryoablation is now using third-generation equipment and that long-term follow-up from these devices, which emerged around 2000, will be needed. These newer devices use more ultrathin probes and argon gas (as opposed to liquid nitrogen) and create smaller ice balls. Lian and colleagues reported early results of cryoablation using third-generation technology as primary treatment for 102 patients with localized prostate cancer during the period of 2006 through 2009. Only one patient developed biopsy-confirmed prostate cancer recurrence. 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 and colleagues reported on QOL outcomes on a subset of 719 patients with localized prostate cancer treated with a variety of 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. compared data from the United States Surveillance, Epidemiology, and End Results (SEER) 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 with cryoablation than brachytherapy (41.4% and 34.7% vs. 22.2% and 21%, respectively). The use of androgen deprivation
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therapy also occurred significantly more often after cryoablation than 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 (COLD) 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 reported 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 (Phoenix definition) for the entire population was 73%; 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. In 2016, outcomes for 300 men registered in COLD who underwent primary whole gland cryotherapy for high-grade (Gleason score ≥8), localized prostate cancer were published.32 Mean follow-up was 28.4 months. The estimated 2- and 5-year bDFS rates were 77% (95% CI, 71% to 88%) and 59% (95% CI, 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 rectourethral 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 for treatment localized prostate cancer comes from several systematic reviews, 2 RCTs, and many comparative and noncomparative observational studies. High-quality data comparing cryoablation to other treatments are lacking, but available data suggest similar OS and DSS rates compared to radical prostatectomy and EBRT.

Salvage Prostate Cryoablation
Studies have described results from using cryoablation for patients with recurrent, localized prostate cancer following RT.

Systematic Reviews
The 2015 HTA (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 median follow-up of 19 months, the incontinence rate was 20%, bladder neck stenosis rate was 25%, and the rectourethral fistula rate was 3%. The sexual dysfunction rate was 69% at 1 year and 52% at 2 years.

In 2012, Mouraviev and colleagues reviewed literature published between 1991 and 2012 to compare salvage cryoablation for radio-recurrent prostate cancer to other salvage treatments. The authors reported comparisons were difficult to make since no prospective, randomized studies were identified and PSA failure is defined in various ways. However, the authors noted studies have reported salvage cryoablation outcomes that are comparable to salvage radical prostatectomy on an intermediate term. PSA level less
than 10 ng/mL, Gleason score less than or equal to 8, and clinical stage T1c or T2 before salvage cryoablation therapy were identified as favorable prognostic factors. In a 2013 systematic review, Punnen et al evaluated management approaches, including cryoablation, for salvage treatment (biochemical recurrence) after primary treatment for localized prostate cancer. The reviewer noted while there is limited evidence available, cryotherapy is a possible treatment option for salvage therapy although randomized trials are needed.

**Nonrandomized Comparative Studies**

Peters et al reported results of retrospective data from 129 men from 5 high-volume Dutch centers. Forty-four men underwent salvage prostatectomy, 54 underwent salvage cryoablation, and 31 underwent salvage brachytherapy. Mean follow-up 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 cryosurgery group. Severe GU and GI toxicity (grade >3) using 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, respectively.

Pisters et al compared retrospective data for 38 men who underwent salvage radical prostatectomy at the Mayo Clinic between 1990 and 1999 and for 34 men who underwent salvage cryoablation at M.D. Anderson Cancer Center between 1992 and 1995. Mean follow-up was 7.8 years in the prostatectomy group and 5.5 years in the cryoablation group. The bDFS rate was 42% for cryoablation and 66% for prostatectomy at 5 years (p=0.002). OS rate at 5 years was 85% for cryoablation and 95% for prostatectomy (p=0.001). There was no significant difference in DSS at 5 years (96% cryoablation vs 98% prostatectomy, p=0.283).

**Nonrandomized Noncomparative Studies**

Wenske et al reported on salvage cryoablation in a series of 396 consecutively treated patients who had failed cryoablation or RT. 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, DFS was 63% and 35%, DSS was 91% and 79%, and OS was 74% and 45%, respectively. After salvage cryoablation, 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). PSA nadir was the only predictor of recurrence and DSS based on multivariate analyses (p<0.001 and p=0.012, respectively). Complications occurred in 0.6% to 4.6% of patients.

Ng et al reported on a series of 187 patients with locally recurrent prostate cancer after RT who underwent salvage cryoablation, with a mean follow-up of 39 months. Serum PSA levels 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 biochemical recurrence-free survival (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. Overall 5- and 8-year survival rates were 97% and 92%, respectively. The authors concluded that salvage cryoablation was a viable treatment option for patients with prostate cancer for whom RT has failed and that...
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Salvage cryoablation should be performed when the serum PSA level is still relatively low because, in these patients, the procedure may potentially be curative.

Ismail et al. reported on 100 patients treated between May 2000 and November 2005 with cryoablation for recurrent prostate cancer after RT; mean follow-up was 33.5 months. All patients had biopsy-confirmed recurrent prostate cancer. bRFS was defined using a PSA level of less than 0.5 ng/mL and by applying the American Society for Therapeutic Radiology and Oncology (ASTRO) 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 were no surgery- or cancer-related deaths; the 5-year actuarial bRFS was 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 RT.

Williams et al. 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 DFS rate was 39%. The authors found risk factors for prostate cancer recurrence following salvage cryoablation were 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.

In 2016, Siddiqui et al. 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. Rectourethral fistula developed in 2.5% of patients and successfully repaired in all cases. Fifty-two percent of men reported no incontinence while 44% required 0 or 1 pad per day.

Registry Studies

Friedlander et al. compared salvage cryoablation to salvage radical prostatectomy in 440 men retrospectively identified in the SEER 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).

In 2013, Spiess et al. reported outcomes for 156 men who underwent salvage cryoablation without neoadjuvant hormonal ablative therapy from the COLD registry. 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% versus 81.4%, 58.4%, and 52.9% for those with PSA levels of 5 ng/mL or more.
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Section Summary: Salvage Prostate Cryoablation
The evidence for use of salvage prostate cryoablation in men with localized, recurrent prostate cancer following RT includes primarily noncomparative case series. A small number of retrospective comparative studies have compared salvage cryoablation to 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.

Ongoing Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>Ongoing</td>
<td>NCT01398657 Cryotherapy With or Without Short-term Adjuvant Androgen-Deprivation Therapy for High-Risk Localized Prostate Cancer — Open-Label Randomized Clinical Study</td>
<td>182</td>
<td>Jun 2016 (unknown)</td>
</tr>
<tr>
<td>Unpublished</td>
<td>NCT00824928* A Prospective Multicenter Registry of Salvage Cryotherapy in Recurrent Prostate Cancer Study (SCORE)</td>
<td>60</td>
<td>Dec 2012 (terminated)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2009. There was strong agreement that cryoablation should be considered medically necessary as 1 option in the initial treatment of organ-confined prostate cancer, as well as for use as salvage therapy for disease that recurs after radiotherapy.

Summary
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 OS, DSS, symptoms, functional outcomes, QOL, and treatment-related morbidity. High-quality data comparing cryoablation to EBRT, radical prostatectomy, or active surveillance are lacking, but available data suggest similar OS and DSS rates compared to radical prostatectomy and EBRT. The evidence is sufficient to conclude that cryoablation leads to improvement in net health outcome.

For individuals who need salvage treatment for recurrence of localized prostate cancer following radiotherapy who receive whole gland cryoablation, the evidence includes primarily noncomparative case
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Evidence is sufficient to conclude that cryoablation leads to better results compared to prostatectomy, though outcomes are OS, DSS, symptoms, functional outcomes, QOL, and treatment-related morbidity. High-quality data comparing cryoablation to prostatectomy is mixed and evidence comparing cryotherapy to brachytherapy is lacking. Men in this group have few other options and prostatectomy can be difficult in tissue that has been irradiated. The evidence is sufficient to conclude that cryoablation leads to improvement in net health outcome.

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40. Wenske S, Quartier S, Katz AE. Salvage Cryosurgery of the Prostate for Failure After Primary Radiotherapy or Cryosurgery: Long-term Clinical, Functional, and Oncologic Outcomes in a Large Cohort at a Tertiary Referral Centre. Eur Urol 2012 [Epub ahead of print]

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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
08/18/2014 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

Next Scheduled Review Date: 11/2017
Whole Gland Cryoablation of Prostate Cancer

Policy # 00022  
Original Effective Date: 06/24/2002  
Current Effective Date: 11/16/2016

Coding

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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>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>55873</td>
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<tr>
<td>HCPCS</td>
<td>C2618</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>C61 C79.82 D07.5 Z85.46</td>
</tr>
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*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
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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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