Cryoablation of Clinically Localized Prostate Cancer

**Policy #** 00022
**Original Effective Date:** 06/24/2002
**Current Effective Date:** 06/18/2014

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.

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

**Patient Selection Criteria**
Coverage eligibility of cryoablation therapy for prostate cancer will be considered when any of the following criteria are met:

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

**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 subtotal prostate cryoablation in the treatment of prostate cancer to be **investigational**. *

Based on review of available data, the Company considers the use of cryoablation therapy for 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. While most studies use total cryoablation, subtotal cryoablation is an emerging technique.

Cryoablation is one of several methods available to treat clinically localized prostate cancer and may be considered an alternative to radical prostatectomy or radiation therapy. It also may be used for salvage of non-metastatic 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 external-beam radiation therapy (EBRT) requires multiple treatments, typically only one treatment is required for cryoablation.
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Subtotal prostate cryoablation is also being evaluated as a form of more localized therapy (referred to by some as focal or organ-preserving therapy or male lumpectomy) for small localized prostate cancers.

**FDA or Other Governmental Regulatory Approval**

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

A number of cryoablation systems and cryoprobes have general surgical FDA 510(k) marketing clearance. Examples of cryoablation devices that specifically mention treatment of prostate cancer in their marketing clearance are Endocare’s Cryocare CS and Cryocare CN2 systems, and Galil Medical's Visual-ICE Cryoablation System and IceRod CX Cryoablation Needle.

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-T-3. Salvage cryotherapy is only medically necessary and appropriate in localized disease when radiation therapy 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**
The most recent literature search was performed for the period of March 2013 through April 25, 2014.

**Primary Prostate Cryoablation**

**Systematic reviews**
This policy was initially based on a 2001 TEC Assessment focused on cryoablation for primary treatment of clinically localized prostate cancer. The TEC Assessment arrived at the following conclusions:

- No studies compared outcomes of cryoablation to outcomes of radical prostatectomy or conformal external-beam radiotherapy in randomized or otherwise similar patient populations. In addition, follow-up times were limited to 2 years or less in most cryoablation studies. Available studies reported only surrogate outcomes: PSA and biopsy failure rates, and rates of second treatment.
- Of 34 studies reporting efficacy outcomes after prostate cryoablation, only 6 (total n=2,352) met the TEC Assessment’s inclusion criteria. Problems with available evidence included short follow-up times, heterogeneous patient populations, and 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 comparison of patient populations that may have had different risk distributions, both within and across treatment methods, did not permit conclusions.
- One study presented a retrospective comparison of data from the CaPSURE [Cancer of the Prostate Strategic Urologic Research Endeavor] database, a longitudinal observational database of patients with prostate cancer. Adjusted overall rates of second treatment indicated that patients receiving cryoablation were 1.9 times more likely to have a second treatment than patients who received radical prostatectomy, and 1.4 times more likely than patients who received EBRT. When
rates of second treatment were stratified by prognostic factors, the rates for cryoablation compared to those for radical prostatectomy tended to be significantly increased for low-risk disease but not for high-risk disease. The same was true for EBRT compared to radical prostatectomy, but to a lesser extent. Thus, these results did not suggest an advantage for cryoablation and may have indicated poorer outcomes for low-risk disease.

- Perioperative mortality and acute life-threatening consequences of cryoablation appeared to be negligible. Patients had the highest likelihood of impotence after cryoablation, compared to radical prostatectomy or 3-dimensional conformal radiation therapy (3D-CRT). The frequency of incontinence appeared similar to that after 3D-CRT, and potentially less than that after radical prostatectomy. However, other genitourinary complications were unique to cryoablation. Adverse gastrointestinal 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 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%.

In October 2011, a systematic review of localized prostate cancer treatments prepared for AHRQ to update the 2002 U.S. Preventive Services Task Force Recommendation was published. 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.
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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.

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. The 8-year bDFS for EBRT and cryoablation groups were 59.1% and 17.4%, respectively. Disease-specific survival (DSS) 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 gastrointestinal (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 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 concluded 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...
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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. While some, but not all, studies collected data prospectively in consecutive patients, none included a concurrent comparison group treated with an established alternative. In addition, it was unclear whether “consecutive” meant patients meeting eligibility criteria or those consenting to enroll in a study. Furthermore, retrospective comparisons used historical data collected using different guidelines to assign risk groups or monitor for recurrence (e.g., frequency of follow-up PSA measurements and PSA thresholds for recurrence). The largest single institution series reported the 7-year actuarial rate of bDFS of 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 with 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.

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 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%).

Salvage Prostate Cryoablation
Studies have described results from using cryoablation for patients with recurrent, localized prostate cancer following a course of radiation therapy. In 2012, Mouraviev and colleagues reviewed literature published
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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.

Wenske and colleagues reported on salvage cryoablation in a series of 396 consecutively treated patients who had failed cryoablation or radiotherapy. Data was analyzed from 328 patients with a median follow-up of 47.8 months (range: 1.6-203.5). Fifty-five (16.7%) of these patients received subtotal (focal) salvage cryoablation. At 5- and 10-years’ follow-up, disease-free survival (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 in multivariate analyses (p<0.001 and p=0.012, respectively). Complications occurred in 0.6-4.6% of patients. In the 55 patients that received subtotal (focal) salvage cryoablation, median PSA nadir was 0.44 ng/mL (range: 0.04-20.1 ng/mL) and recurrence was seen in 27 patients (49%). At 5- and 10-years’ follow-up, DFS was 47% and 42%, DSS was 100% and 83%, and OS was 87% and 81%, respectively.

Ng and colleagues reported on a series of 187 patients with locally recurrent prostate cancer after radiotherapy who underwent salvage cryoablation of the prostate and were studied after a mean follow-up of 39 months. Serum PSA at cryoablation was a predictive factor for biochemical recurrence on univariate and multivariate analysis (p <0.001). Patients with a pre-cryoablation PSA value less than 4 ng/mL had a 5- and 8-year bRFS of 56% and 37%, respectively. In contrast, patients with a pre-cryoablation PSA of 10 ng/mL or greater had a 5- and 8-year bRFS of only 1% and 7%, respectively. Patients with a pre-cryoablation PSA in the range of 4 to 9.99 ng/mL had intermediate survival outcomes. Overall 5- and 8-year survival was 97% and 92%, respectively. The authors concluded that salvage cryoablation is a viable treatment option for patients with prostate cancer in whom radiation therapy has failed and that salvage cryoablation should be performed when the serum PSA level is still relatively low because, in these patients, the procedure may potentially be curative. Similarly, Ismail and colleagues reported on 100 patients treated between May 2000 and November 2005 with cryoablation for recurrent prostate cancer after radiotherapy; 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, i.e., high-risk (68 men), intermediate-risk (20 men), and low-risk (12 men). There were no operative 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 is a safe and
effective treatment for localized prostate cancer recurrence after radiotherapy. Williams and colleagues reported on a retrospective review of 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 PSA nadir greater than 1.0 ng/dL after salvage cryoablation.

**Subtotal (Focal) Prostate Cryoablation**

There is minimal evidence for use of the technique of subtotal prostate cryoablation for treatment of localized disease. In one representative publication on focal therapy, Truesdale and colleagues reported on a retrospective chart review of 77 patients with unilateral prostate cancer treated with primary focal cryosurgery between 2002 and 2009. Using D'Amico risk classifications, 44 patients were considered low-risk, 31 were intermediate-risk, and 2 were high-risk disease. Patients were followed for a median time of 24 months, and the biochemical (PSA) progression-free survival rate was 72.7% overall. Prostate cancer was confirmed by biopsy in 10 of 22 patients suspected of having recurrent disease (2 ipsilateral, 7 contralateral, and 1 bilateral disease). The overall pathologic progression-free survival rate was 87%. Disease progression was correlated with pretreatment PSA levels, pretreatment Gleason scores, number of positive cores, and total tumor lengths. Comparative data from studies with longer follow-up are needed to evaluate this technology.

Bahn and coworkers reported on use of focal prostate cryoablation with "less-than-complete" ablation of the gland with ice, which spares contralateral prostate tissue and surrounding structures. Results on 31 men with a mean follow-up of 70 months showed biochemical disease-free status of 92.8%. Potency (either with or without oral medications) was 88.9%. The authors indicated that further investigation is needed. Bahn and colleagues subsequently reported on a retrospective review of 73 patients with low-intermediate risk, unilateral prostate cancer followed for a median of 3.7 months (range 1-8.5 years) after focal cryotherapy. Mean PSA level decreased 70% from 5.9 ng/mL to 1.6 ng/mL after cryoablation of one lobe (p<0.001). Prostate biopsy was performed in 48 patients after focal cryotherapy and was negative in 36 (75%) patients. Incontinence was not documented in any patient, and impotence was noted in 14% of patients.

Ward and Jones reported on a retrospective review of 1,160 patients with localized prostate cancer treated with focal cryoablation between 1997 and 2007 from the national Cryo On-Line Database (COLD) Registry. At 36 months, the biochemical recurrence-free rate (bDFS) was 75.7%. Prostate biopsy was positive in 43 (26.3%) of 164 patients biopsied for suspected cancer recurrence or 3.7% of all cryoablation patients. Incontinence and impotence were each documented in 1.6% of patients. Six patients (1.1%) experienced urinary retention for more than 30 days.

**Ongoing Trials**

A search of ClinicalTrials.gov identified 7 active studies on cryotherapy for prostate cancer. The only phase 3 study began in July 2011 and will randomize high-risk localized prostate cancer patients to receive cryoablation either with or without androgen deprivation therapy (NCT01398657). This study is expected to enroll 182 patients and be completed in June 2016. In another study, biochemical failure and quality-of-life...
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Outcomes will be evaluated in an estimated 800 patients in the prospective, multicenter registry of salvage cryotherapy in recurrent prostate cancer (SCORE) trial (NCT00824928). This study began in January 2007 and is expected to be completed in June 2014.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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

Summary

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.

The available evidence for use of cryotherapy in the treatment of clinically localized (organ-confined) prostate cancer when performed as initial treatment or as salvage treatment of disease that recurs following radiation therapy is sufficient to demonstrate improvement in net health outcome. This conclusion is based on the extensive data from cohort studies and clinical input including an indirect chain of evidence and the recognition that the data for this long-used technique are similar to data for a number of accepted techniques. While the data for treatment of recurrence after radiation therapy are limited, these patients have few options; one option with recurrence is prostatectomy, which can be difficult in tissue that has been irradiated. However, for patients with recurrence after radiation therapy who elect further treatment, based on the limited data available, cryosurgical treatment does appear to produce anti-tumor activity.

Given the lack of long-term follow-up data, including a lack of comparative studies, subtotal prostate cryoablation is considered investigational.

References

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

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Policy History
Original Effective Date: 06/24/2002
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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
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<td>09/20/2005</td>
<td>Medical Policy Committee review. Format revision. Coverage eligibility unchanged. The following clarification statement was added: &quot;Based on review of available data, the Company considers other uses of cryoablation of the prostate to be investigational.&quot;</td>
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<td>09/22/2005</td>
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<td>Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.</td>
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<td>10/04/2006</td>
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<td>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.</td>
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<tr>
<td>05/07/2009</td>
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| 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. |

*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.
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**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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