

<b>MEDICAL POLICY</b>		<b>Prostate: High-Intensity Focused Ultrasound (HIFU) (All Lines of Business Except Medicare)</b>	
<b>Effective Date: 1/1/2021</b>		Section: SUR	Policy No: 420
 1/1/2021		Medical Policy Committee Approved Date: 8/18; 9/18; 11/19; 04/2020	
Medical Officer	Date		

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

## SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

## APPLIES TO:

All lines of business except Medicare

## BENEFIT APPLICATION

### Medicaid Members

*Oregon:* Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

### **POLICY CRITERIA**

High-intensity focused ultrasound (HIFU) for treatment of prostate cancer is considered **investigational and is not covered.**

Link to [Policy Summary](#)

## CPT/HCPCS CODES

### All Lines of Business Except Medicare

Not Covered

€9747

TERMED 12/31/2020

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	Ablation of prostate, transrectal, high intensity focused ultrasound (hifu), including imaging guidance
<b>Unlisted Codes</b> All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be <b>denied as not covered</b> .	
55899	Unlisted procedure, male genital system

**DESCRIPTION**

**Prostate Cancer**

In the United States, prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in men. Prostate cancer is more common in older men and men of African American ethnicity. Approximately 1 in 7 men will be diagnosed with prostate cancer in his lifetime. In 2018, it is estimated that 164,690 men will be diagnosed with prostate cancer and 29,430 will die of the disease in the United States.<sup>1</sup>

Although almost all prostate cancers are adenocarcinomas, there are several other types of prostate cancer, including sarcomas, small cell carcinomas, neuroendocrine tumors and transitional cell carcinomas. Prostate cancer is a heterogeneous disease with tumors ranging from indolent to very aggressive. Survival differs according to disease stage at diagnosis. The majority of prostate cancers are discovered prior to becoming metastatic and therefore the 5-year relative survival rate is close to 100%. However, men with metastatic disease have a 5-year survival rate of approximately 30%.<sup>2</sup>

Currently, the treatment of prostate cancer varies depending on the stage and grade of disease. Usual treatment options include surgery, radiation therapy, hormone therapy, chemotherapy, biologic therapy, and bisphosphonate therapy.

**High-Intensity Focused Ultrasound (HIFU)**

HIFU is a minimally invasive prostate cancer treatment that ablates abnormal prostatic tissue using high-intensity convergent ultrasound deliver via an endorectal probe. The entire prostate gland is ablated using a series of ultrasonic shots, which causes a sharp rise in temperature. Visualization of the procedure is possible through real-time guidance provided by diagnostic ultrasound or MRI. During real-time monitoring, computer software calculates target volume, with the aim of delivering a wave beam with a high degree of precision. This may be beneficial due to minimizing the impact on surrounding tissue and intervening structures. Since ultrasound has no maximum dose, HIFU can be repeated as needed.

**REVIEW OF EVIDENCE**

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A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of high-intensity focused ultrasound (HIFU) for treatment of prostate cancer. Below is a summary of the available evidence identified through March of 2020.

**High-Intensity Focused Ultrasound for Primary Treatment of Localized Prostate Cancer**

In 2016 (updated 2019), Hayes published an evidence review that evaluated ultrasound-guided high-intensity focused ultrasound (HIFU) for primary treatment of localized prostate cancer.<sup>3</sup> The literature review identified 19 nonrandomized uncontrolled studies (12 nonrandomized comparative studies included 6 prospective comparative cohort studies, 5 retrospective comparative cohort studies, and 1 retrospective matched-pair analysis) as eligible for inclusion. Sample sizes ranged from 40 to 1002 patients and follow-up times varied from 6 months to 43 months for comparative studies and 47 to 120 months for noncomparative studies. Outcomes of interest included serum prostate specific antigen (PSA), negative prostate biopsy rate, prostate cancer survival, disease-free survival (DFS), recurrence, postoperative urinary and sexual function, quality of life, prostate cancer mortality, and treatment related complications.

Evidence regarding the effectiveness of HIFU for primary treatment of localized prostate cancer was limited and, “(n)one of the comparative studies evaluated the efficacy and safety of HIFU compared with standard radical prostatectomy, external beam radiotherapy (EBRT), or active surveillance—therapies that are considered usual care for patients with localized, early-stage prostate cancer. No randomized controlled trials evaluating HIFU for prostate cancer were identified in the literature searches.”<sup>3</sup>

*Summary of Outcomes in Comparative Studies*

Outcome	Evidence
Postoperative PSA	<ul style="list-style-type: none"> <li>● Mixed results:               <ul style="list-style-type: none"> <li>○ In 4 studies, PSA was significantly lower for HIFU; however, in 4 other studies HIFU had similar efficacy for reducing PSA as its comparator.</li> </ul> </li> </ul>
Negative Prostate Biopsy Rate	<ul style="list-style-type: none"> <li>● Results do not favor HIFU:               <ul style="list-style-type: none"> <li>○ In 2 studies, the negative prostate biopsy rate was significantly higher for HIFU; however, there was no difference in rates between HIFU and comparator groups in 4 other studies.</li> </ul> </li> </ul>
Disease-free Survival Rate	<ul style="list-style-type: none"> <li>● Mixed results:               <ul style="list-style-type: none"> <li>○ The rate was significantly higher for HIFU plus ADT (androgen deprivation therapy) versus HIFU alone (78.0% versus 53.8%) and for HIFU with prostatic compression versus HIFU alone (92.6% versus 76.5%) in 2 studies. Whole-gland versus focal HIFU was similar in efficacy in 2 studies.</li> </ul> </li> </ul>
Recurrence-free Survival Rate	<ul style="list-style-type: none"> <li>● Results do not favor HIFU:               <ul style="list-style-type: none"> <li>○ The rate was significantly lower for HIFU relative to brachytherapy in 1 study; however, rates did</li> </ul> </li> </ul>

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	not differ between HIFU and other therapies in 3 other studies.
Prostate Cancer-Specific Survival	<ul style="list-style-type: none"> <li>• Similar results <ul style="list-style-type: none"> <li>○ HIFU and brachytherapy had similar outcomes in 1 comparative study.</li> </ul> </li> </ul>
Overall Survival Rate	<ul style="list-style-type: none"> <li>• Similar results <ul style="list-style-type: none"> <li>○ HIFU and brachytherapy had similar outcomes in 1 comparative study.</li> </ul> </li> </ul>
Biochemical Recurrence	<ul style="list-style-type: none"> <li>• Similar results <ul style="list-style-type: none"> <li>○ In 2 studies there was no significant difference between HIFU and comparator therapies.</li> </ul> </li> </ul>
Prostate Cancer Mortality	<ul style="list-style-type: none"> <li>• Similar results <ul style="list-style-type: none"> <li>○ Rates were very low (0% to 0.4%) and similar for HIFU and the comparator therapy in 5 studies.</li> </ul> </li> </ul>
Urinary Incontinence	<ul style="list-style-type: none"> <li>• Similar results <ul style="list-style-type: none"> <li>○ Postoperative rates were similar after HIFU and comparator therapies in 7 studies.</li> </ul> </li> </ul>
Prostate and Urinary Symptoms	<ul style="list-style-type: none"> <li>• Mixed results: <ul style="list-style-type: none"> <li>○ Reflecting differences in early and late effects between HIFU and its comparators in 7 studies.</li> </ul> </li> </ul>
Sexual Function and Erectile Dysfunction	<ul style="list-style-type: none"> <li>• Similar results <ul style="list-style-type: none"> <li>○ Outcomes were similar in 7 studies between HIFU and its comparator; 6 studies compared variations of HIFU and 1 study compared HIFU with brachytherapy.</li> </ul> </li> </ul>

Overall, HIFU was relatively safe with no major treatment-related complications or deaths reported for HIFU or its comparators. The overall quality of evidence was determined to be low due to individual study limitations and the absence of well-designed, randomized controlled trials. Individual factors that contributed to the low quality of evidence include that lack of randomization, the lack of control or comparator groups, retrospective analyses, small or unequal sample sizes between groups, lack of statistical analysis for some outcomes, and lack of blinded assessment of results in most studies.

The Hayes review concluded that, “additional, well-designed studies are needed to further compare HIFU for localized prostate cancer with alternative and established therapies before a determination can be made as to its long-term safety and effectiveness, particularly with regard to survival and prostate cancer mortality.”<sup>3</sup> The following rating was assigned:

- C (potential but unproven benefit): For use of ultrasound-guided high-intensity focused ultrasound (HIFU) for treatment of localized prostate cancer.

**High-Intensity Focused Ultrasound for Salvage Therapy of Recurrent Prostate Cancer**

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In 2017 (updated 2019), Hayes published an evidence review that evaluated high-intensity focused ultrasound (HIFU) for salvage therapy of recurrent prostate cancer.<sup>4</sup> The literature review identified 14 studies (1 retrospective comparative study and 13 noncomparative studies) as eligible for inclusion. All studies involved patients with prostate cancer recurrence following primary external beam radiation therapy (EBRT)(12 studies) or radical prostatectomy (RP)(2 studies). Sample sizes ranged from 19 to 418 patients and follow-up times varied from 14 to 53 months. Outcome measures included serum prostate specific antigen (PSA), negative prostate biopsy rate, disease-free survival (DFS), prostate cancer-specific survival, overall survival, recurrence-free survival, recurrence, treatment-related complications, and quality of life.

Evidence evaluating the effectiveness of HIFU for salvage treatment of localized, recurrent prostate cancer is limited and of poor quality.

*Salvage HIFU for Recurrent Prostate Cancer Following EBRT*

Outcome	Evidence
Treatment Failure	Rates ranged from 33% to 60.9%.
Serum PSA Level	Mean serum PSA levels post-HIFU were consistently lower than baseline.
Negative Biopsy	Rates ranged from 73% to 83%.
Overall Survival	Rates ranged from 52% to 100%.
Prostate Cancer Mortality	Rates ranged from 2.7% to 10%.
Recurrence	Rates range from 31.1% to 70%.
Prostate and Urinary Symptoms	<ul style="list-style-type: none"> <li>• In the one comparative study, salvage HIFU resulted in lower rates of morbidity compared with cryoablation. In noncomparative studies, urinary incontinence ranged from 20% to 49% and lower urinary tract symptoms ranged from 1.4% to 76.5%.</li> <li>• In general, prostate symptoms increased following HIFU.</li> </ul>
Sexual Function and Erectile Dysfunction	In general, there was a decline in sexual and erectile function from baseline.

*Salvage HIFU for Recurrent Prostate Cancer Following RP*

Outcome	Evidence
Treatment Failure	Rates ranged from 10.5% at 3 months to 47% to 54.5% at later follow-ups.
Disease Free Survival	Only one study reported. Rate of 47.4%.
Prostate Cancer Mortality	Only one study reported. Rate of 0%.
Prostate and Urinary Symptoms	Urinary incontinence rates were 21% and 22% and urinary retention rates were 4.5% and 10.5%.

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Sexual Function and Erectile Dysfunction	In 1 study, 28.5% of patients with an International Index of Erectile Function (IIEF) score $\geq 20$ before HIFU reported erectile dysfunction after HIFU salvage therapy.
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Overall, HIFU for salvage therapy was relatively safe with no major treatment-related complications or deaths reported. The overall quality of evidence was determined to be low (HIFU following EBRT) or very low (HIFU following RP) due to individual study limitations and the absence of well-designed, randomized controlled trials. Individual factors that contributed to the low quality of evidence include lack of randomization, lack of control or comparator groups, retrospective design, small sample sizes, lack of statistical analysis, loss to follow-up, and lack of blinding.

The Hayes review concluded, “(a)dditional, well-designed studies are needed to further compare HIFU for localized, recurrent prostate cancer with alternative and established salvage therapies before a determination can be made as to its long-term safety and effectiveness, particularly with regard to prostate cancer recurrence and mortality.”<sup>4</sup> The following ratings were assigned:

- C (potential but unproven benefit): For use of ultrasound-guided high-intensity focused ultrasound (HIFU) for salvage therapy of localized, recurrent prostate cancer in patients with no signs of metastatic disease who were treated with primary external beam radiotherapy.
- D2 (insufficient evidence): For use of ultrasound-guided HIFU for salvage therapy of localized, recurrent prostate cancer in patients with no signs of metastatic disease who were treated with primary radical prostatectomy.

**CLINICAL PRACTICE GUIDELINES**

The American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology (AUA/ASTRO/SUO)

The 2017 AUA/ASTRO/SUO evidence-based clinical practice guideline for localized prostate cancer gave the following recommendations regarding HIFU:

- “The Panel recommends that if HIFU is offered as an alternative treatment modality for localized prostate cancer, it should be done within the context of a clinical trial. Prospective randomized or comparative trials with other treatment modalities are lacking.
- Clinicians should inform **low-risk** prostate cancer patients who are considering focal therapy or high intensity focused ultrasound (HIFU) that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)
  - As most men with low-risk disease have favorable outcomes with active surveillance, it is unclear whether focal therapy or HIFU improve survival outcomes or provide comparable QoL as the preferred management for most low-risk men. Prospective randomized or comparative trials of HIFU with active surveillance or other treatment modalities are lacking. Published five year oncologic outcomes are variable and attributable to the lack of consensus on objective response criteria. The Panel awaits the results of well-designed comparative clinical trials in order to define the appropriate role of this technology in the management of low-risk prostate cancer.

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- Clinicians should inform **intermediate-risk** prostate cancer patients who are considering focal therapy or HIFU that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)
  - The Panel recognizes that novel therapies including HIFU and focal prostate ablation may provide QoL advantages for patients in comparison to surgery and radiotherapy. However, there are no prospective randomized or comparative effectiveness data versus traditional treatments available. Published five year oncologic outcomes for HIFU are variable and attributable to the lack of consensus on objective response criteria. The Panel awaits the results of well-designed comparative clinical trials of HIFU in order to define the appropriate role of this technology in the management of intermediate risk prostate cancer.
- Panel recommends that if focal therapy or HIFU is offered as an alternative treatment modality for intermediate risk prostate cancer, it should preferably be offered within the context of a clinical trial.
- Cryosurgery, focal therapy and HIFU treatments are not recommended for men with **high-risk** localized prostate cancer outside of a clinical trial. (Expert Opinion)
- Clinicians should inform those localized prostate cancer patients considering focal therapy or HIFU that these treatment options lack robust evidence of efficacy. (Expert Opinion)
- Clinicians should inform localized prostate cancer patients who are considering HIFU that even though HIFU is approved by the FDA for the destruction of prostate tissue, it is not approved explicitly for the treatment of prostate cancer (Expert Opinion).
- Clinicians should advise localized prostate cancer patients considering HIFU that tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)<sup>1</sup>

### National Comprehensive Cancer Network

The NCCN guidelines for prostate cancer (v4.2019) recommend HIFU for patients with prostate-specific antigen (PSA) persistence/recurrence or positive digital rectal exam (DRE) who are TRUS biopsy positive with studies negative for distant metastases.<sup>5</sup> The guideline discussion states that only cryosurgery and HIFU are recommended as options for radiation therapy recurrence in the absence of metastatic disease. Although the NCCN recommends HIFU in select patients, this recommendation is based off of eight poor-quality nonrandomized studies.<sup>6-13</sup>

### American College of Radiology

The 1996 (updated 2016) ACR appropriateness criteria for locally advanced, high-risk prostate cancer stated, "(a)blative treatments including cryotherapy and high-intensity focused ultrasound (HIFU) are other options available for men with high-risk prostate cancer, though data are limited for these modalities... The results of HIFU are similar to those of cryotherapy... The morbidity of HIFU is considerable, with rates of urinary obstruction up to 24% and impotency in previously potent men of 45%."<sup>14</sup>

### National Institute for Health and Care Excellence (NICE)

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The 2012 evidence-based NICE guideline for focal therapy using high-intensity focused ultrasound for localized prostate cancer states the following:

“Current evidence on focal therapy using high-intensity focused ultrasound (HIFU) for localized prostate cancer raises no major safety concerns. However, evidence on efficacy is limited in quantity and there is a concern that prostate cancer is commonly multifocal. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. NICE encourages further research into focal therapy using HIFU for localized prostate cancer. This should take the form of controlled studies comparing the procedure against other forms of management. Studies should clearly define patient selection criteria and should report outcomes including local recurrence in the long term.”<sup>15</sup>

**POLICY SUMMARY**

The available evidence does not support the long-term efficacy and safety of high intensity focused ultrasound (HIFU) compared to other established therapies for prostate cancer. Additional long-term studies of good methodological quality are required to establish the clinical utility and safety of this treatment. Additionally, the December 2017 AAU/ASTRO/SUO evidence-based guideline for prostate cancer recommends HIFU only be used in the context of a clinical trial and that additional prospective randomized studies are needed. Although the NCCN recommends HIFU, this recommendation is based on a very weak and poor quality body of evidence. All eight studies referenced in the NCCN recommendation were nonrandomized studies encompassing small sample sizes and short follow-up periods (< 4 years). For these reasons, HIFU is considered investigational for the treatment of prostate cancer.

**INSTRUCTIONS FOR USE**

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

**REGULATORY STATUS**

Mental Health Parity Statement

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Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

U.S. Food and Drug Administration (FDA)

In 2015 FDA approved two high-intensity focused ultrasound devices for use in the prostate: Sonablate® 450 (SonaCare Medical, LLC) and Ablatherm® (Maple Leaf; Toronto, Canada).

Device & Manufacturer	Indications for Use
Sonablate® 450 (SonaCare Medical, LLC) <sup>16</sup>	The Sonablate® is indicated for transrectal high intensity focused ultrasound (HIFU) ablation of prostatic tissue.
Ablatherm® (Maple Leaf; Toronto, Canada) <sup>17</sup>	The Ablatherm® Integrated Imaging device is indicated for transrectal high intensity focused ultrasound ablation of prostate tissue.

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