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Prostate Biopsy Specimen Analysis

Policy Number: AHS – G2007 – Prostate Biopsy Specimen Analysis	Original Effective Date: 05/15/2022 Current Effective Date: 02/01/2026

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I. Policy Description

Prostate cancer is characterized by a malignancy of the small walnut-shaped gland that produces seminal fluid. This malignancy can present with a wide clinical range, from only being a microscopic, well-differentiated tumor that may never be clinically significant all the way to being an aggressive, high-grade cancer.[1]

II. Related Policies

Policy Number	Policy Title
AHS-G2008	Prostate Specific Antigen (PSA) Testing
AHS-G2013	Testosterone
AHS-G2124	Serum Tumor Markers for Malignancies

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) In the initial diagnosis of prostate cancer as a follow-up to abnormal PSA results, presence of a palpable nodule on digital rectal examination, **or** suspicious radiologic findings, pathological examination of tissue obtained from a prostate biopsy involving 12 core extended sampling (see Note 1 below) **MEETS COVERAGE CRITERIA**.

2) When the clinical suspicion of prostate cancer remains in an individual for whom an initial biopsy was negative for prostate cancer, pathological examination of tissue from a follow-up prostate biopsy (excluding prostate saturation biopsy) **MEETS COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

3) Pathological examination of tissue obtained from a prostate saturation biopsy **DOES NOT MEET COVERAGE CRITERIA** for the diagnosis, staging, or management of prostate cancer.

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NOTES:

Note 1: One vial per sextant, with no more than two core samples per vial. Each vial, regardless of the number of cores enclosed, is considered a single specimen for billing purposes.

IV. Table of Terminology

Term	Definition
ACR	American College of Radiology
ACS	American Cancer Society
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
CC	Cubic centimeters
CLIA '88	Clinical Laboratory Improvement Amendments Of 1988
CMS	Centers For Medicare and Medicaid
CS	Clinically significant
csPCa	All clinically significant cases of prostate cancer
DRE	Digital rectal examination
EAU	European Association of Urology
ESMO	European Society for Medical Oncology
FBx	Fusion biopsy
FDA	Food And Drug Administration
GG2	Grade 2 or greater
LDT	Laboratory-developed test
MicroUS	Micro-Ultrasound
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NPV	Negative predictive value
NYU	New York University
PI-RADS	Prostate imaging reporting and data system
PPV	Positive predictive value
PROMIS	Prostate magnetic resonance imaging study
PSA	Prostate specific antigen
RP	Radical prostatectomy
SBx	Transrectal ultrasound biopsy
SUO	Society Of Urologic Oncology
TPM	Template prostate mapping
TRUS	Transrectal ultrasound
UCLA	University Of California, Los Angeles
US	Ultrasound
USPSTF	United States Preventive Services Task Force

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V. Scientific Background

Prostate cancer is one the most common cancers in American individuals with a prostate and the second leading cause of death in individuals with a prostate who are 65 years of age or older with an estimated 313,780 new cases and 35,770 deaths in the US in 2025.[2] About 11% of individuals with a prostate will be diagnosed with prostate cancer during their lifetime.[1]

Many cases of prostate cancer do not become clinically evident, as indicated in autopsy series of individuals with a prostate- prostate cancer is detected in approximately 30% of these individuals at age 55 and approximately 60% of these individuals by age 80.[3] These data suggest that prostate cancer often grows so slowly that most affected individuals die of other causes before the disease becomes clinically advanced. Prostate cancer survival is related to many factors, especially the extent of tumor at the time of diagnosis. The five-year relative survival among individuals with cancer confined to the prostate (localized) or with just regional spread is 100%, compared with 31% among those diagnosed with distant metastases.[4]

Findings on digital rectal examination (DRE) including the presence of nodules, induration, or asymmetry or elevated prostate specific antigen (PSA) levels indicate the need for prostate biopsy. Although considered safe, prostate biopsy is an invasive procedure and recommendations for its use are limited to a subset of patients. Screening the general population for prostate cancer remains a controversial issue.[4] Screening may reduce the risk of distant-stage prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC) enrolled 162,243 individuals with a prostate aged 50 to 69 years. The cumulative incidence rate of metastatic disease in the regular screening group was 0.67 percent compared to the control group of 0.86 percent. The absolute risk reduction of metastatic disease was 3.1 per 1000 individuals randomized.[4]

Multiple sampling schemes have been developed to improve the accuracy of prostate biopsy in the detection of cancer. Systematic prostate sampling is performed and augmented by additional sampling of any abnormal areas found on ultrasound or rectal examination.[5] During transrectal ultrasound (TRUS)-guided biopsy, a six-core, or sextant biopsy technique, takes one sample each from the apex, base, and mid-prostate on each side.[6] However, this method may miss approximately 30% of clinically significant cancers and has been replaced by extended core biopsy which obtains five to seven evenly-distributed specimens from each side, sampling more extensively from the lateral aspects of the prostate.[7] A meta-analysis by Eichler, et al. (2006) found that schemes with 12 core samples that took additional laterally directed cores detected 31% more cancers compared with a six-core approach, with increasing number of cores significantly associated with increased detection of prostate cancer.[8] This biopsy method has been used to obtain up to 18 cores for evaluation.[7]

Saturation biopsy involves extensive sampling of the prostate, obtaining up to 24 core samples. Saturation biopsy is not appropriate for initial screening as it does not provide increased cancer detection when used for first-time biopsy but may provide increased sensitivity when repeat biopsies are performed and can be considered after one or more negative TRUS-biopsies. Saturation biopsy detects prostate cancer in approximately 22% to 33% of patients undergoing repeat biopsy, but it is associated with a higher incidence of complications.[7]

Complications may occur with biopsy. Firstly, the samples from a biopsy may be inadequate to make a diagnosis; the cores obtained may not be of high enough quality or more cores may be needed. Other findings such as an abnormal but nonmalignant histology may warrant a repeat biopsy. Clinical

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complications such as inflammation, bleeding, infection, and urinary obstruction are also possible.[7] Pepe and Aragona (2007) estimated the rate of clinical complication after a transperineal biopsy to be as high as 40%.[9]

Clinical Utility and Validity

Thompson, et al. (2015) studied whether saturation or transperineal biopsy altered oncological outcomes as compared with standard transrectal biopsy. In total, 650 individuals with a prostate were analyzed, and saturation biopsy was associated with "increased objective biopsy progression requiring treatment" on both the Kaplan-Meier analysis and multivariate Cox analysis. A logistic regression analysis of 179 individuals undergoing a radical prostatectomy (RP) found that transperineal biopsy was associated with lower likelihood of "unfavourable" RP pathology. The authors concluded that "saturation biopsy increased progression to treatment on AS; longer follow-up is needed to determine if this represents beneficial earlier detection of significant disease or over-treatment. Transperineal biopsy reduced the likelihood of unfavourable disease at RP, possibly due to earlier detection of anterior tumours."[10]

Zaytoun, et al. (2011) "compared saturation and extended repeat biopsy protocols after initially negative biopsy." The study included 1,056 individuals with a prostate- 393 of these individuals underwent a 1,214 core biopsy ("extended") and 663 of these individuals underwent a 20-24 core biopsy ("saturated"). Overall, prostate cancer was detected in 315 patients, but saturated biopsy detected a third more cancers and identified more cancers in a benign initial biopsy. In total, 119 biopsies identified clinically "insignificant" cancer. The authors concluded, "Compared to extended biopsy, office-based saturation biopsy significantly increases cancer detection on repeat biopsy. The potential for increased detection of clinically insignificant cancer should be weighed against missing significant cases."[11]

The Prostate Magnetic Resonance Imaging Study (PROMIS) study assessed the ability of multiparametric MRI (mpMRI) to identify individuals with a prostate who could safely avoid an "unnecessary biopsy" and compared mpMRI to TRUS-guided biopsy.[12] A TPM-biopsy was included for comparison, and 576 individuals with a prostate underwent all three tests. Clinically significant cancer was defined as "a Gleason score of $\geq 4+3$ and/or cancer core length of ≥ 6 mm." For CS cancer, TRUS-guided biopsy showed a sensitivity of 48%, specificity of 96%, PPV of 90%, and NPV of 74%. The sensitivity of mpMRI was 93%, specificity was 41%, PPV was 51%, and NPV was 89%. A negative mpMRI scan was recorded for 158 individuals with a prostate (27%). Of these, 17 were found to have CS cancer on TPM-biopsy. The authors also found that the most cost-effective strategy involved testing all individuals with a prostate with "mpMRI, followed by MRI-guided TRUS-guided biopsy in those patients with suspected CS cancer, followed by rebiopsy if CS cancer was not detected."[12]

Sidana, et al. (2018) compared the yield of MRI fusion biopsy (FBx) to 12-core TRUS biopsy (SBx) in patients with prior negative biopsies. The study included 779 patients, and a total of 346 cancers were detected with 239 of 346 considered clinically significant. FBx diagnosed a total of 205 patients with SBx diagnosing an additional 34 patients. FBx identified high proportions of clinically significant cancers over all amounts of prior negative biopsies. The authors stated that "SBx added a relatively small diagnostic value to FBx for detecting CS disease" and concluded that "repeat SBx alone in patients with multiple prior negative biopsies will be hindered by lower yield and FBx should be utilized concurrently in these patients."[13]

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Pepe, et al. (2018) investigated the diagnostic accuracies for clinically significant prostate cancer, multiparametric magnetic resonance imaging (MRI) and transperineal saturation prostate biopsy. Lesions with PI-RADS (Prostate Imaging Reporting and Data System) scores of three or higher were subjected to additional targeted fusion prostate biopsy. A total of 1,032 patients were included, with 372 deemed to have T1c prostate cancer. Further, 272 of these cases were considered "clinically significant." Saturation biopsy missed 12 of 272 clinically significant cancers, and targeted fusion prostate biopsy with the score cutoff of three missed 44 cases. However, the authors noted that using multiparametric MRI in combination with a score cutoff of three in PI-RADS would have prevented 49.3% of biopsies, and a score cutoff of four would have prevented 73.6% of biopsies, although the score cutoff of four missed 108 of 272 clinically significant cases. The authors concluded that multiparametric MRI could "significantly reduce the number of unnecessary repeat prostate biopsies in about 50% of cases in which a PI-RADS score of three or greater is used."[14]

Pepe, et al. (2020) investigated the number of cores (combined with multiparametric MRI [mpMRI]) needed to diagnose all clinically significant cases of prostate cancer (csPCa) in individuals with a prostate who were subject to transperineal saturation biopsy (SPBx; 30 cores). The study included 875 patients and stage 1 prostate cancer was found in 306 of these patients, with 222 of these classified as clinically significant. The initial 20 needle cores obtained from SPBx identified all 222 cases of clinically significant prostate cancer, although it missed 84 of 129 indolent cases. Overall, the "diagnostic accuracy, sensitivity, and specificity [were] equal to 83.1%, 100%, and 65.1%, respectively." The authors concluded that in individuals with a prostate who were "subject to mpMRI and/or TPBx, a maximum of 20 systematic transperineal needle cores detected all cases of csPCa and minimized the diagnosis of indolent cancers."[15]

Klotz, et al. (2021) investigated MRI with targeted biopsy against TRUS-guided biopsy to determine whether MRI with a targeted biopsy was as effective in detecting a grade two or greater prostate cancer. In total, 453 individuals underwent tests and were randomized to receive TRUS biopsy or MRI-TB. Cancers of grade two or greater (GG2) were identified in 67 of 225 individuals (30%) who underwent TRUS biopsy vs 79 of 227 (35%) allocated to MRI-TB. The authors concluded that "magnetic resonance imaging followed by selected targeted biopsy is noninferior to initial systemic biopsy in [individuals] at risk for prostate cancer in detecting GG2 or greater cancers."[16]

Lokeshwar, et al. (2022) studied the clinical utility of mpMRI guided prostate biopsy. The study started with a retrospective analysis of 415 individuals with low risk prostate cancer that was being managed with active surveillance. Then, 125 participants were selected based on having a mpMRI visible index lesions score of two or three according to PI-RADS version 2. Clinically significant prostate cancer, defined as Gleason grade group of at least two, was found in 22 of 125 patients (17.6%). The authors found that the only significant variable that could predict detection was "higher PSAD." The authors conclude that "integration of PSAD may be a useful adjunctive tool in identifying patients at highest risk for upgrade despite favorable imaging findings."[17]

Pier Paolo, et al. (2025) evaluated micro-ultrasound (microUS) for prostate cancer detection in a prospective single-center study of 1,423 individuals with a prostate. All participants underwent both microUS- and mpMRI-targeted biopsies. Clinically significant cancer (Gleason ≥3+4) was detected in 116 individuals. MicroUS demonstrated a sensitivity of 85% and negative predictive value of 79%. MicroUS findings were concordant with mpMRI in 96% of cases. Among individuals diagnosed through targeted cores, 25 cases were identified by microUS alone compared to four by mpMRI alone. Systematic biopsy

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detected 22% of clinically significant cancers missed by both targeted approaches. The authors concluded that microUS improved detection and may reduce reliance on systematic biopsy.[18]

VI. Guidelines and Recommendations

The American Urological Association (AUA)

The AUA published a paper on Optimal Techniques of Prostate Biopsy and Specimen Handling which recommended: "12-core systematic sampling methodology that incorporates apical and far-lateral cores in the template distribution. The results of our literature review suggest that collecting more than 12 cores or sampling the transition zone offer no benefit for initial diagnostic biopsies. However, such approaches might be useful for resampling following a negative biopsy."[19]

The AUA/American Society for Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO) published guidelines which state:[20]

- "Localized prostate cancer patients who elect active surveillance should have accurate disease staging including systematic biopsy with ultrasound or MRI-guided imaging."

- "Localized prostate cancer patients undergoing active surveillance should be encouraged to have a confirmatory biopsy within the initial two years and surveillance biopsies thereafter."

In 2018, the American Society of Clinical Oncology (ASCO) endorsed the above 2017 AUA/ASTRO/SUO joint guideline, with only a minor disagreement on two cryosurgery recommendations.[21]

In 2020, The American Urological Association and the Society of Abdominal Radiology Prostate Disease Focus Panel published a guideline on standard operating procedures for multiparametric MRI in the diagnosis, staging, and management of prostate cancer.[22] The guideline states:

- "mpMRI of the prostate allows for risk stratification of [individuals] at risk for prostate cancer including its ability to predict cancer aggressiveness prior to biopsy."
- "The performance of prostate mpMRI in [individuals] with no prior biopsy is now supported by randomized clinical trials, while its use in [individuals] with a prior negative biopsy continues to be endorsed by consensus statements and national guidelines."[22]

In 2023, the AUA and SUO released guidelines on early detection of prostate cancer.[23] They recommend the following regarding prostate biopsies.

In terms of PSA screening:

- "For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy."
- "For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy."
- "Clinicians and patients may use validated risk calculators to inform the SDM process regarding prostate biopsy."
- "When the risk of clinically significant prostate cancer is sufficiently low based on available clinical, laboratory, and imaging data, clinicians and patients may forgo near-term prostate biopsy."

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In terms of initial biopsy:

- "Clinicians should inform patients undergoing a prostate biopsy that there is a risk of identifying a cancer with a sufficiently low risk of mortality that could safely be monitored with active surveillance (AS) rather than treated."
- "Clinicians may use magnetic resonance imaging (MRI) prior to initial biopsy to increase the detection of Grade Group (GG) 2+ prostate cancer."
- "For biopsy-naïve patients who have a suspicious lesion on MRI, clinicians should perform targeted biopsies of the suspicious lesion and may also perform a systematic template biopsy. "
- "For patients with both an absence of suspicious findings on MRI and an elevated risk for GG2+ prostate cancer, clinicians should proceed with a systematic biopsy."
- "Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy."
- "For patients with a PSA > 50 ng/mL and no clinical concerns for infection or other cause for increased PSA (e.g., recent prostate instrumentation), clinicians may omit a prostate biopsy in cases where biopsy poses significant risk or where the need for prostate cancer treatment is urgent (e.g., impending spinal cord compression)."

In terms of repeat biopsy:

- Clinicians should communicate with patients following biopsy to review biopsy results, reassess risk of undetected or future development of GG2+ disease, and mutually decide whether to discontinue screening, continue screening, or perform adjunctive testing for early reassessment of risk."
- "Clinicians should not discontinue prostate cancer screening based solely on a negative prostate biopsy."
- "After a negative biopsy, clinicians should not solely use a PSA threshold to decide whether to repeat the biopsy."
- "If the clinician and patient decide to continue screening after a negative biopsy, clinicians should re-evaluate the patient within the normal screening interval (two to four years) or sooner, depending on risk of clinically significant prostate cancer and life expectancy."
- "At the time of re-evaluation after negative biopsy, clinicians should use a risk assessment tool that incorporates the protective effect of prior negative biopsy."
- "After a negative initial biopsy in patients with low probability for harboring GG2+ prostate cancer, clinicians should not reflexively perform biomarker testing."
- "After a negative biopsy, clinicians may use blood, urine, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management."
- "In patients with focal (one core) high-grade prostatic intraepithelial neoplasia (HGPIN) on biopsy, clinicians should not perform immediate repeat biopsy."
- "In patients undergoing repeat biopsy with no prior prostate MRI, clinicians should obtain a prostate MRI prior to biopsy."
- "In patients with indications for a repeat biopsy who do not have a suspicious lesion on MRI, clinicians may proceed with a systematic biopsy."

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- "In patients undergoing repeat biopsy and who have a suspicious lesion on MRI, clinicians should perform targeted biopsies of the suspicious lesion and may also perform a systematic template biopsy."

In terms of biopsy technique:

- "Clinicians may use software registration of MRI and ultrasound images during fusion biopsy, when available."
- "Clinicians should obtain at least two needle biopsy cores per target in patients with suspicious prostate lesion(s) on MRI."
- "Clinicians may use either a transrectal or transperineal biopsy route when performing a biopsy."

The AUA 2025 Quality Summit reinforced their 2023 guideline recommendations with only minor refinements, reaffirming the use of 12-core systematic sampling (including apical and far-lateral cores), continued use of mpMRI prior to biopsy, allowance for both transrectal and transperineal approaches with a preference for transperineal due to lower infection risk, and ongoing support for combined targeted and systematic biopsies, repeat biopsies during surveillance, and shared decision-making aided by risk calculators and biomarkers.[24]

National Comprehensive Cancer Network (NCCN)

The NCCN Guidelines on Early Detection for prostate cancer state that "image-guided biopsy with targeting (preferred) or without targeting of lesions seen on pre-biopsy MRI is the recommended technique for prostate biopsy." It recommends the use of an extended pattern at least 12 core biopsies as it has been validated and results in enhances cancer detection compared to sextant biopsy schemes. Moreover, the NCCN states,

- "Anteriorly directed biopsy is not supported in routine biopsy. However, this can be added to an extended biopsy protocol in a repeat biopsy if PSA is persistently elevated."
- "A negative biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy. If clinical suspicion of cancer persists after a negative biopsy, consideration can be given to the use of multiparametric MRI followed by an appropriate targeted biopsy technique based on the results."
- Despite this emerging evidence, the panel does not recommend a saturation biopsy strategy for all individuals with a prostate with "previous negative biopsies at this time given the benefits seen for MRI and MRI-targeted biopsy in this patient population."
- "After one or more negative image-guided biopsies, individuals who are considered at high risk (eg, those with persistently elevated or rising PSA) can be considered for MRI followed by targeted biopsy based on several studies showing improved detection of clinically significant prostate cancer in this setting." The NCCN notes that targeted biopsy techniques include "cognitive or visual targeting, TRUS-MRI fusion platforms, and direct in-bore magnetic resonance-guided biopsy.
- "Overall, the panel believes that the data for the use of MRI and MRI-targeted biopsies in the initial biopsy setting are increasingly compelling. However, studies using both targeted and systematic sampling routinely demonstrate higher yield of clinically significant cancer with the combined approach and improved sensitivity. Therefore, a combination of systematic and

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targeted procedures is preferred when MRI-targeting capabilities are available, at least at initial biopsy."[25]

The NCCN recommends considering age, life expectancy, family history, African ancestry, inherited mutations, and prior test results—along with a clear understanding of the risks and benefits—when deciding whether to initiate early prostate cancer detection. The following recommendations are included for early detection and screening criteria:

- "Black/African American individuals, individuals with a suspicious family or personal cancer history, and those with a known genetic predisposition represent groups at high risk for the development of prostate cancer. . . The panel recommends that baseline PSA testing for healthy, well-informed individuals with African ancestry, germline mutations that increase the risk for prostate cancer, and/or a suspicious family history should be offered at ages 40 to 75 years.
- The panel recommends that baseline PSA testing should be offered to healthy, well-informed individuals deemed to be at average risk aged 45 to 75 years based on the results of RCTs. Baseline testing may be complemented by DRE. An elevated PSA should be confirmed by repeat testing.
- The panel recommends that frequency of testing be 2 to 4 years for
  - those <75 years with serum PSA values below 1 ng/mL considered to be at average risk for prostate cancer.
  - For those with PSA of 1 to 3 ng/mL at average risk, testing should occur at 1- to 2-year intervals.
  - For those with elevated prostate cancer risk, the recommended testing interval for those with PSA ≤3 ng/mL is 1 to 2 years."[25]

The NCCN also addressed prostate biopsy in their prostate cancer guideline. The NCCN remarks that repeat prostate biopsy (and/or repeat multiparametric MRI) no more often than every 12 months unless clinically indicated (such as PSA increase). Most patients on active surveillance should undergo prostate biopsies every two to five years as part of their monitoring. Patients should be transitioned out of active surveillance to observation when life expectancy is less than ten years.[26]

American College of Radiology (ACR)

The ACR rated TRUS-guided biopsy a nine, and MRI-targeted prostate biopsy a seven in the most recent ACR Appropriateness Criteria for Prostate Cancer Pretreatment Detection, Surveillance and Staging for "clinically suspected prostate cancer with no prior biopsy." A rating of seven, eight, or nine is usually appropriate. MRI-targeted biopsy was rated an eight and repeat TRUS biopsy rated a seven in "clinically suspected prostate cancer, prior negative TRUS biopsy" as well as "clinically established low risk prostate cancer for active surveillance."[27] The 2023 ACR update reconfirmed the above recommendations.[28]

They note that "Overall, the clinical paradigm for prostate cancer diagnosis is rapidly moving towards MRI-targeted transrectal biopsy, based on substantial evidence from several centers (notably the National Institutes of Health; New York University [NYU]; University of California, Los Angeles [UCLA]; and Nijmegen) that this approach can transform baseline cancer evaluation when compared with traditional systematic biopsy, with fewer false negatives, better tumor characterization, improved tumor localization, and better treatment stratification, especially stratification to lower-risk cohorts that may be appropriate for active surveillance or focal therapy."[27]

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The 2023 ACR update also added that "the clinical paradigm for prostate cancer diagnosis undoubtedly is rapidly moving toward MRI-targeted biopsies, based on abundant evidence that this can improve pretreatment evaluation of prostate cancer in many aspects, such as MRI-targeted biopsies are more concordant with radical prostatectomy in determining Gleason score; better selected candidates for active surveillance; and improved risk stratification."[28]

American Cancer Society (ACS)

The ACS published guidelines which state:[29]

"A PSA level of 4.0 ng/mL or greater historically has been used to recommend referral for further evaluation or biopsy, which remains a reasonable approach for [individuals] at average risk for prostate cancer."

"For PSA levels between 2.5 ng/mL and 4.0 ng/mL, health care providers should consider an individualized risk assessment that incorporates other risk factors for prostate cancer, particularly for high-grade cancer, that may be used to recommend a biopsy. Factors that increase the risk of prostate cancer include African American race, family history of prostate cancer, increasing age, and abnormal DRE. A previous negative biopsy lowers the risk. Methods are available that merge this information to achieve an estimate of a man's overall risk of prostate cancer and, more specifically, of his risk of high-grade prostate cancer."[29]

According to the ACS, an update to the guidelines for prostate cancer was initiated in 2019.[30]

United States Preventive Services Task Force

Within the 2018 USPSTF recommendation statement regarding prostate screening, they state that for individuals with a prostate "with a positive PSA test result may undergo a transrectal ultrasound-guided core-needle biopsy of the prostate to diagnose prostate cancer… Although protocols vary, active surveillance usually includes regular, repeated PSA testing and often repeated digital rectal examination and prostate biopsy, with potential for exposure to repeated harms from biopsies."[31]

European Society for Medical Oncology (ESMO)

The ESMO includes recommendations for prostate biopsies:

- "Transperineal biopsies are recommended, rather than transrectal ultrasound (TRUS)-guided biopsies." ESMO further noted that "Targeted transperineal biopsies, in comparison with systematic transrectal biopsies, result in an increased detection rate of clinically significant prostate cancer, a decreased detection rate of clinically insignificant prostate cancer, and fewer adverse events."
- When multiparametric MRI is positive (defined as [PI-RADS] ≥3), ESMO recommends performing a targeted (systematic or non-systematic) biopsy. However, when multiparametric MRI is negative (PI-RADS ≤2) and clinical suspicion of cancer is low, the biopsy can be omitted.[32]

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European Association of Urology

The EAU's recommendations on prostate biopsy include the following:

- Perform MRI before prostate biopsy in individuals with suspected organ confined disease.
- The follow-up strategy during active surveillance should be based on serial DRE (at least once yearly), prostate specific antigen (at least once, every six months) and repeated biopsy.
- "Perform magnetic resonance imaging (MRI) and repeat biopsy if PSA is rising (PSA- doubling time < 3 years)."
- For asymptomatic individuals with a prostate with a "PSA level between 3 and 20 ng/mL and a normal DRE, use one of the following tools for biopsy indication:
  - magnetic resonance imaging of the prostate;
  - risk-calculator, provided it is correctly calibrated to the population prevalence;
  - an additional serum, urine biomarker test."[33]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

The FDA has cleared numerous devices including needles, reagents, instrumentation, and imaging systems for use in prostate biopsy. Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
88305	Level IV – Surgical pathology, gross and microscopic examination
G0416	Surgical pathology, gross and microscopic examinations, for prostate needle biopsy, any method

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
02/01/2026	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following changes were made for clarity and consistency: Note 1, added "Each vial, regardless of the number of cores enclosed, is considered a single specimen for billing purposes." for clarity on unit restrictions for prostate biopsy.
01/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
05/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: Title changed to "Prostate Biopsy Specimen Analysis" Addition of "pathological examination of tissue obtained from a" before "prostate biopsy" in CC1, 2, and 3, as this policy focuses on the laboratory test performed, not the surgical procedure to get the sample. Removed asterisk before "Note 1" in CC1.
03/10/2023	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: CC1 and CC3 edited for clarity and consistency Addition of new CC2: "When the clinical suspicion of prostate cancer remains in an individual for whom an initial biopsy was negative for prostate cancer, follow-up biopsy (excluding prostate saturation biopsy) MEETS COVERAGE CRITERIA."
05/15/2022	Initial Policy Implementation

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