Prostate Biopsies

Policy Number: **APEA – G2007** – Prostate Biopsies

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Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request:

1. Prostate biopsy involving 12 core extended sampling* (see Note 1 below) **MEETS COVERAGE CRITERIA** 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.
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 a patient’s illness.

2. Prostate saturation biopsy **DOES NOT MEET COVERAGE CRITERIA** in the diagnosis, staging and management of prostate cancer.

*Note 1: One vial per sextant, with no more than two core samples per vial.

**Scientific Background**

Prostate cancer is the most common cancer in American men and the second leading cause of death in men aged 65 years or older (Balducci, Pow-Sang, Friedland, & Diaz, 1997; Tabayoyong & Abouassaly, 2015) with an estimated 174,650 cases and 31,620 deaths in the US in 2017 (Siegel, Miller, & Jemal, 2019). About 1 man in 9 will be diagnosed with prostate cancer during his lifetime (Kantoff et al., 2018).

Many cases of prostate cancer do not become clinically evident, as indicated in autopsy series, where prostate cancer is detected in approximately 30 percent of men age 55 and approximately 60 percent of men by age 80 (Bell, Del Mar, Wright, Dickinson, & Glasziou, 2015). These data suggest that prostate cancer often grows so slowly that most men 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 men with cancer confined to the prostate (localized) or with just regional spread is 100 percent, compared with 29.3 percent among those diagnosed with distant metastases (Hoffman, 2019).

Findings on digital rectal examination including the presence of nodules, induration, or asymmetry or elevated prostate specific antigen (PSA) levels indicate the need for prostate biopsy. Although generally 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 since improved patient outcomes have not been demonstrated (Andriole et al., 2009; Hoffman, 2019; NCCN, 2017; Schroder et al., 2009).

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 (Gosselaar et al., 2008). 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 (Hodge, McNeal, Terris, & Stamey, 1989). However, this method may miss approximately 30 percent 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 (Benway, 2018). A meta-analysis by Eichler et al found that schemes with 12 core samples that took additional laterally directed cores detected 31 percent more cancers compared with a six-core approach, with increasing number of cores significantly associated with increased detection of prostate cancer (Eichler et al., 2006). This biopsy method has been used to obtain up to 18 cores for evaluation (Benway, 2018).

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 should be considered after two negative TRUS-biopsies. Saturation biopsy detects prostate cancer in approximately 22 to 33 percent of patients undergoing repeat biopsy, but it is associated with a higher incidence of complications (Benway, 2018).
Several 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 complications such as inflammation, bleeding, infection, and urinary obstruction are also possible (Benway, 2018). Pepe et al estimated the rate of clinical complication after a transperineal biopsy to be as high as 40% (Pepe & Aragona, 2007).

Clinical Validity and Utility

Thompson et al (2015) studied whether saturation or transperineal biopsy altered oncological outcomes as compared with standard transrectal biopsy. 650 men 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 men 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 (Thompson et al., 2015).”

Zaytoun et al (2011) “compared saturation and extended repeat biopsy protocols after initially negative biopsy.” 1056 men were included, with 393 men undergoing a 12-14 core biopsy (“extended”) and 663 men undergoing 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. 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 (Zaytoun et al., 2011).”

The PROstate Magnetic resonance Imaging Study (PROMIS) study (Brown et al., 2018) “assessed the ability of multi-parametric MRI (mpMRI) to identify men who can safely avoid unnecessary biopsy” and compared mpMRI to TRUS-guided biopsy. A TPM-biopsy was included for comparison, and 576 men underwent all three tests. Clinically significant (CS) cancer was defined as “a Gleason score of ≥ 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 men (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 men 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 (Brown et al., 2018).”

Sidana et al compared the yield of MRI fusion biopsy (FBx) to 12-core TRUS biopsy (SBx) in patients with prior negative biopsies. 779 patients were included, 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” (Sidana et al., 2018).
Guidelines and Recommendations

The American Urological Association (AUA)

The AUA published a paper (2015) 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”

The AUA/ASTRO/SUO published guidelines (Sanda et al., 2017) which state:

- “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.”

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines (NCCN, 2019) state that “systematic prostate biopsy under TRUS guidance with or without targeted 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 saturation biopsy strategies and/or the use of multiparametric MRI followed by an appropriate targeted biopsy technique based on the results.”
- “Based on emerging evidence, the panel believes that a saturation biopsy strategy can be considered for very high-risk men with previous negative biopsies”.
- “After 1 or more negative TRUS biopsies, men who are considered high-risk (e.g. those with persistently elevated or rising PSA) can be considered for MRI followed by targeted biopsy”. The NCCN notes that targeted biopsy techniques include “cognitive or visual targeting, TRUS-MRI fusion platforms, and direct in-bore magnetic resonance biopsy-guided biopsy.
- “Overall, the panel believes that targeted biopsy techniques may help regions of cancer missed on prior biopsies and should be strongly considered in patients with a prior negative biopsy and persistent concern for cancer”.
- “The panel believes that MRI-guided targeted biopsies can be considered in place of standard 12-core TRUS biopsies in initial biopsy setting...however...more information is needed about the generalizability of the findings of the trials mentioned above”.

American College of Radiology (ACR)

The ACR (Coakley et al., 2017) rated TRUS guided biopsy a 9, and MRI targeted prostate biopsy a 7 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 7, 8 or 9 are usually appropriate. MRI targeted biopsy was rated an 8 and repeat TRUS biopsy rated a 7 in clinically suspected prostate cancer, prior negative TRUS biopsy as well as Clinically established low risk prostate cancer for active surveillance.

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”.

**American Cancer Society (ACS)**

The American Cancer Society published guidelines (Wolf et al., 2010) which state:

- “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 men 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.”

According to the ACS, an update to the guidelines for prostate cancer is planned in 2019 (Smith et al., 2018).

**US Preventive Services Task Force (USPSTF, 2018)**

Within the 2018 USPSTF recommendation statement regarding prostate screening, they state, “Men 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.”

**European Association of Urology (EAU, 2019)**

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

- The need for biopsy is based on PSA level or suspicious DRE/imaging, although limited PSA elevation alone should not prompt biopsy.
- “Ultrasound (US)-guided biopsy is now the standard of care…transurethral resection of the prostate should not be used as a tool for cancer detection”.
- “Sextant biopsy is no longer considered adequate. At least eight systematic [core] biopsies are recommended in prostates with a size of about 30 cc. Ten to twelve core biopsies are recommended in larger prostates, with > twelve cores not being significantly more conclusive” (EAU, 2019).

**State and Federal Regulations, as applicable**

The FDA has cleared numerous devices including needles, reagents, instrumentation, and imaging systems for use in prostate biopsy as of July 24, 2019. Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.
Applicable CPT/HCPCS Procedure Codes

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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.*

Evidence-based Scientific References


**Policy Implementation/Update Information**

7/1/20 New Policy
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.