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## aetna®

# Prostate Saturation Biopsy

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

**Number: 0698**

## Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers a transperineal stereotactic template-guided saturation prostate biopsy medically necessary for the following indications in men with 2 prior extended transrectal prostate biopsies negative for invasive cancer:

- Men with an elevated prostate specific antigen (PSA) that is persistently rising; or
- Men with histologic evidence of atypia on prior prostate biopsy; or
- Men with histologic findings of high-grade prostatic intraepithelial neoplasia (PIN) on prior biopsy.

Aetna considers prostate saturation biopsy experimental and investigational for all other indications (e.g., surveillance of persons with a positive prostate biopsy) because there is insufficient evidence on the clinical utility of this procedure for indications other than the ones listed above in the peer-reviewed medical literature.

**Note**: The know error® DNA Specimen Provenance Assay, a forensic assay to confirm that a surgical specimen belongs to the patient evaluated for treatment, is considered to be part of the laboratory's quality control for specimens. Use of this test is considered an integral part of the biopsy and is not separately reimbursed.

## Policy History

Last Review

 03/01/2019
Effective: 01/31/2006
Next
Review: 07/25/2019

Review History

Definitions

Additional Information

See also CPB 0001 - Transrectal Ultrasound
(../1_99/0001.html); CPB 0168 - Tumor Scintigraphy
(../100_199/0168.html); CPB 0521 - Prostate Cancer Screening
(../500_599/0521.html).

## Background

Prostate cancer is the second leading cause of cancer death in men, exceeded only by lung cancer. It accounts for 33 % of all male cancers and 10 % of male cancer-related deaths. The disease is histologically evident in as many as 34 % of men during their fifth decade of life and in up to 70 % of men aged 80 years old and older.

Transperineal template-guided stereotactic saturation prostate biopsy, typically using 30 to 80 cores, is being proposed as a method to detect prostate cancer in high-risk men with multiple negative extended prostate biopsies, including men with an elevated prostate-specific antigen (PSA) that is persistently rising, men with histologic evidence of atypia on prior prostate biopsy, or men with histologic findings of high-grade prostate intraepithelial neoplasia (PIN) on prior biopsy.

Digital rectal exam (DRE) and PSA tests detect prostate abnormalities, but they cannot determine whether these abnormalities are cancer or benign; only a biopsy can confirm a diagnosis of prostate cancer. Prostate cancer risk factors include persistent elevated PSA, atypia, or high grade prostatic intraepithelial neoplasia (PIN) on prior biopsy.

A core needle biopsy of the prostate under transrectal ultrasound guidance is the main method used to diagnose prostate cancer. A narrow needle is placed through the wall of the rectum into the prostate gland. The needle removes a cylinder of tissue, usually about 1/2-inch long and 1/16-inch across. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Usually 6 to 18 cores are removed to get a good sample and tell how much of the gland (if any) is affected by cancer; however, 10 to 12 tissue cores are considered the standard of care (Wilson and Crawford, 2004).

It has been reported that 38 % of prostate cancers are missed by prostate biopsy (Patel et al, 2004). There is some evidence that the sensitivity of needle biopsy could improve by 30 % to 35 % by increasing the number of biopsy cores beyond 6

(e.g., 14 to 45 cores) (Stewart et al, 2001).   Some investigators have proposed even more extensive sampling (30 to 80 cores). This improvement in sensitivity, however, has been at the cost of doubling the rate of cancer detection of less than 0.5 cm3 in volume identified. The extent to which an increase in detection rate would reduce morbidity and mortality from prostate cancer or increase the percentage of men treated unnecessarily is unknown.

Epstein et al (2005) reported the results of prostate saturation biopsy on 103 men who were predicted to have insignificant cancer in their radical prostatectomy (RP) specimen. All had limited cancer on routine needle biopsy (no core with more than 50 % involvement; Gleason score less than 7, and fewer than 3 cores involved) with a serum PSA density of 0.15 or less. Insignificant tumor at RP was considered organ-confined tumor, no Gleason pattern 4 or 5, and a tumor volume of less than 0.5 cm3.   Saturation biopsy (average 44 cores) versus an alternate biopsy saturation protocol with half the number of cores was performed on RP specimens. Of the tumors examined, 97 % were organ confined. The RP Gleason score was less than 7 in 84 % of the cases. The RP tumor volume was 0.01 to 2.39 cm3 (median 0.14).   Overall, 71 % of cancers were insignificant; however, 29 % had been incorrectly classified before surgery using a standard biopsy protocol. The authors calculated that with the saturation biopsy method, the false-positive rate for significant disease was 11.5 %. Similarly, the false-negative rate for insignificant tumors was 11.5 % (sensitivity 71.9 % and specificity 95.8 %). Using the alternate biopsy protocol, with half the number of cores, the false-positive rate was 8 % and the false-negative rate was 11.4 % (sensitivity 71.9 % and specificity 97.1 %). The authors stated that in comparison, using a 12-core biopsy protocol, a false-negative rate of 11.7 % would have been achieved with a false-positive rate of 41.9 %, and lowering the false-positive rate to 28.65 % increased the false-negative rate to 16.0 %.

A systematic review of the diagnostic value of systematic prostate biopsy methods in the investigation for prostate cancer, prepared by the Centre for Reviews and Dissemination (2005) found that "[s]chemes with 18 and more cores of the 5-region pattern showed the highest cancer yield (RPR 1.48; 95 % confidence interval [CI]: 1.32 to 1.66).  However, the difference in the cancer yield of this scheme to the yield of the 12-core scheme from pattern mid-lobar peripheral zone + lateral peripheral zone (RPR 1.31; 95 % CI: 1.25 to 1.37) and the 10-core scheme of the 5-region pattern (RPR 1.38; 95 % CI: 1.08 to 1.76) was not statistically significant."

The assessment concluded that "[i]t still has to be demonstrated that extended biopsy schemes with a higher cancer yield do lead to a survival benefit due to early cancer detection."

An update to this systematic evidence review on the diagnostic value of biopsy methods in the investigation of prostate cancer reached similar conclusions. Eichler et al (2006) searched 13 electronic databases, screened relevant urological journals and the reference lists of included studies, and contacted experts. These researchers included studies that compared different systematic prostate biopsy methods using sequential sampling or a randomized design in men scheduled for biopsy due to suspected prostate cancer. They pooled data using a random effects model when appropriate; and analyzed 87 studies with a total of 20,698 patients. These investigators pooled data from 68 studies comparing a total of 94 extended schemes with the standard sextant scheme. An increasing number of cores were significantly associated with the cancer yield. Laterally directed cores increased the yield significantly ($p = 0.003$), whereas centrally directed cores did not. Schemes with 12 cores that took additional laterally directed cores detected 31 % more cancers (95 % CI: 25 to 37) than the sextant scheme. Schemes with 18 to 24 cores did not detect significantly more cancers. Adverse events for schemes up to 12 cores were similar to those for the sextant pattern. Adverse event reporting was poor for schemes with 18 to 24 cores. The authors concluded that prostate biopsy schemes consisting of 12 cores that add laterally directed cores to the standard sextant scheme strike the balance between the cancer detection rate and adverse events. Taking more than 12 cores added no significant benefit.

Prostate saturation biopsy may provide increased accuracy in the predictability of prostate tumor volume and grade to select suitable candidates for watchful waiting therapy; however, it is not clear whether early detection and subsequent earlier treatment leads to any change in the natural history and outcome of individuals with prostate cancer. Randomized controlled trials are needed to determine the clinical utility of prostate saturation biopsy.

Jones et al (2006) reported on the results of a sequential cohort study comparing office-based saturation prostate biopsy to traditional 10-core sampling as an initial biopsy. Based on improved cancer detection of office-based saturation prostate biopsy repeat biopsy, the authors adopted the technique as an initial biopsy strategy to improve cancer detection. Two surgeons performed 24-core saturation prostate biopsies in 139 patients undergoing initial biopsy under peri-prostatic local

anesthesia.   Indication for biopsy was an increased PSA of 2.5 ng/dl or greater in all patients. Results were compared to those of 87 patients who had previously undergone 10-core initial biopsies. Cancer was detected in 62 of 139 patients (44.6 %) who underwent saturation biopsy and in 45 of 87 patients (51.7 %) who underwent 10-core biopsy (p > 0.9). Breakdown by PSA level failed to show benefit to the saturation technique for any degree PSA increase. Men with PSA 2.5 to 9.9 ng/dl were found to have cancer in 53 of 122 (43.4 %) saturation biopsies and 26 of 58 (44.8 %) 10-core biopsies. Complications included 3 cases of prostatitis in each group. Rectal bleeding was troublesome enough to require evaluation only in  3 men in the saturation group and 1 in the 10-core group. These investigators concluded that although saturation prostate biopsy improves cancer detection in men with suspicion of cancer following a negative biopsy, it does not appear to offer benefit as an initial biopsy technique. These findings suggest that further efforts at extended biopsy strategies beyond 10 to 12 cores are not appropriate as an initial biopsy strategy.

In an accompanying editorial, Moon and Theodorescue (2006) reported that the literature shows average cancer detection rates on first repeat biopsy using standard techniques of 22 %, compared with detection rates ranging from 14 to 34 % on first repeat biopsy using saturation  techniques.

Merrick et al (2007) ascertained the prostate cancer incidence, anatomical distribution, Gleason score profile, and tumor burden in patients diagnosed by transperineal template-guided saturation biopsy (TTSB). A total of 102 patients underwent TTSB; all but 1 patient had undergone at least 1 prior negative transrectal ultrasound (TRUS) biopsy.  Criteria for inclusion included an elevated PSA and/or the diagnosis of atypical small acinar proliferation or high-grade PIN on prior biopsy. The prostate gland was divided into 24 regional biopsy locations. The median number of biopsy cores was 50.  Multiple clinical parameters were assessed as predictors for prostate cancer diagnosis. The mean patient age was 64.8 years with a mean PSA of 9.1 ng/ml and a prostate volume of 78.6 cm (3). On average, patients had undergone 2.1 prior negative TRUS biopsies with a mean of 22.4 core biopsies. Prostate cancer was diagnosed in 43 patients (42.2 %) with a Gleason score distribution of 6 to 9.   No anatomical region of the prostate gland was spared of cancer.  In patients with prostate cancer, an average of 9.9 cores were involved. In multi-variate analysis, prostate volume was the best predictor for prostate cancer diagnosis. The authors concluded that TTBS diagnosed prostate cancer in 42.2 % of patients. Considerable anatomical variability in  prostate cancer

distribution was documented. They also noted that TTBS "results in promising diagnostic yields for patients with prior negative TRUS biopsies. However, ideal patient selection, optimal transperineal saturation biopsy technique, number of biopsy cores, and regions to be sampled remains to be clarified".

Stav et al (2008) evaluated the diagnostic value of saturation prostate biopsy in patients with PSA greater than 10 ng/ml, PSA velocity greater than 0.75 ng/ml/year, free PSA ratio less than 0.2, and at least 3 sets of negative biopsy specimens. A total of 27 patients underwent the procedure with the use of a transrectal approach under general or regional anesthesia. A systematic coverage of the peripheral zone (PZ) was accomplished by maintaining a fixed distance between punctures (5 mm). In addition, multiple cores were obtained from the transition zone bilaterally, bladder neck, and midline according to a strict pre-planned template. The mean number of cores obtained per patient was 61.7 +/- 9.5 (range of 41 to 76). Average PSA was 19.4 +/- 8.5 ng/ml (range of 10.1 to 49). Prostate cancer (Gleason score 3+3) was found in 3 patients (11.1 %). All 3 patients who received a diagnosis of cancer had minimal disease affecting less than 1 % of a single core sampled from the PZ. Two patients were designated for watchful waiting and 1 patient chose radical prostatectomy. His pathologic specimen contained carcinoma of prostate (Gleason 3+3) in less than 1 % of the total prostate volume. All patients were discharged within 24 hours after the procedure. Asymptomatic bacteremia was documented in 1 patient. Two patients had epididymitis develop and were treated conservatively. The authors concluded that according to their findings, saturation prostate biopsy has low diagnostic yield in patients who previously had at least 3 sets of negative traditional biopsy specimens. In all the cases that prostate cancer was found, it had histologic features consistent with biologically insignificant disease.

Lane et al (2008) stated that it has been reported that the prostate cancer detection rate in men with PSA 2.5 ng/ml or greater undergoing saturation (20 cores or greater) prostate biopsy as an initial strategy is not higher than that in men who undergo 10 to 12 core prostate biopsy. At a median follow-up of 3.2 years, these investigators reported the cancer detection rate on subsequent prostate biopsy in men who underwent initial saturation prostate biopsy. Saturation prostate biopsy was used as an initial biopsy strategy in 257 men between January 2002 and April 2006. Cancer was initially detected in 43 % of the patients who underwent saturation prostate biopsy. In the 147 men with negative initial saturation prostate biopsy follow-up including DRE and repeat PSA measurement was recommended

at least annually. Persistently increased PSA or an increase in PSA was seen as an indication for repeat saturation prostate biopsy. During the median follow-up of 3.2 years after negative initial saturation prostate biopsy 121 men (82 %) underwent subsequent evaluation with PSA and DRE. Median PSA remained 4.0 ng/ml or greater in 57 % of the men and it increased by 1 ng/ml or greater in 23 %. Cancer was detected in 14 of 59 men (24 %) undergoing repeat prostate biopsy for persistent clinical suspicion of prostate cancer. No significant association was demonstrated between cancer detection and initial or follow-up PSA, or findings of atypia and high grade prostatic intra-epithelial neoplasia on initial saturation prostate biopsy. Cancers detected on repeat prostate biopsy were more likely to be Gleason 6 and organ confined at prostatectomy than were those diagnosed on initial saturation prostate biopsy. The authors concluded that previous experience suggested that while office-based saturation prostate biopsy improves cancer detection in men who have previously undergone a negative prostate biopsy, it does not improve cancer detection as an initial biopsy technique. Moreover, false-negative rate on subsequent prostate biopsy after initial saturation prostate biopsy is equivalent to that following traditional prostate biopsy. These data provide further evidence against saturation prostate biopsy as an initial strategy.

Simon et al (2008) reported the findings of using an extensive saturation biopsy in men with negative prostate biopsies but in whom there is still a clinical suspicion for carcinoma. A total of 40 patients (median age of 63 years) were offered an extensive saturation biopsy if there was clinical suspicion of prostate cancer after previous negative prostate biopsies. The median (range) number of cores taken was 64 (39 to 139) and was adjusted to the size of the prostate. All patients received general or spinal anesthesia. Of the 40 patients, 18 (45 %) had carcinoma in at least 1 core; 16 had a radical prostatectomy, which showed pT2a, pT2b, pT2c, pT3a and pT3b adenocarcinoma of the prostate in 3, 4, 6, 2 and 1 patients, respectively. Brachytherapy and external radiation were the therapies of choice in the other patients. A total of 16 patients had marked hematuria after the biopsy procedure. The authors concluded that there is no significant increase in the cancer detection rate in an extensive saturation-biopsy regimen compared to published series with fewer cores, but the morbidity increased.

Delongchamps and colleagues (2009) assessed a 36-core saturation biopsy scheme on autopsied prostate glands to estimate the detection rate based on the true cancer prevalence, and compared the cancer features on biopsy with whole-mount pathological analysis, as saturation biopsies have been proposed as a tool

to increase the prostate cancer detection rate, and as a staging tool to identify potentially insignificant cancers before surgery. These investigators took 36-core needle biopsies in 48 autopsied prostates from men who had no history of prostate cancer. The first 18 cores corresponded to an extended biopsy protocol including 6 cores each in the mid peripheral zone (PZ), lateral PZ and central zone. An additional 6 cores were then taken in each of these three locations. They compared the histological characteristics of step-sectioned prostates with the biopsy findings. Tumors were considered clinically insignificant if they were organ- confined with an index tumor volume of less than 0.5 ml and Gleason score of less than or equal to 6. The pathological evaluation identified 12 (25 %) cases of prostate cancer and 22 tumor foci; 7 prostate cancers were significant. Of the 22 tumor foci, 16 (73 %) were in the PZ. The first 18 cores detected 7 cancers (58 %), of which 5 were clinically significant. The last 18 cores detected 4 cancers, all of which were already detected by the first 18 cores. Of the 5 cancers remaining undetected by biopsies, 2 were clinically significant and 3 were insignificant.

Comparison of the histological characteristics between biopsies and step-sectioned prostates showed an over-estimation of Gleason score by saturation biopsies in 3 of 7 cases. The authors concluded that the evaluation of saturation biopsies based on the true prevalence of prostate cancer showed no increase in detection rate over a less extensive 18-core biopsy. Also, saturation biopsies might over-estimate the final Gleason score on whole-mount analysis.

Guidelines from the National Comprehensive Cancer Network (NCCN, 2009) state that for men at high risk for prostate cancer and multiple negative biopsies, consideration may be given to a saturation biopsy strategy. NCCN guidelines recommend, in men with 2 negative extended biopsies, but persistently rising PSA values, a saturation biopsy may be considered. The NCCN Guidelines cited a study by Stewart et al (2001) that found a prostate cancer detection rate of 34 % in a cohort of patients with an average of 2 previous negative sextant prostate biopsies.

Presti (2009) stated that repeat biopsies should include a minimum of 14 cores, the 12 cores recommended for an initial biopsy and 2 additional cores obtained from the right and left anterior apex. In patients for whom repeat biopsies fail to identify cancer, yet the clinical suspicion remains high, consideration for a saturation biopsy approach seems warranted.

Scattoni and colleagues (2010) noted that prostate biopsy techniques have significantly changed since the original Hodge's "sextant scheme", which should now be considered obsolete. The feasibility of performing a biopsy scheme with a high number of cores in an out-patient setting is a result of the great improvement and effectiveness of local anesthesia. Peri-prostatic nerve block with lidocaine injection should be considered the "gold standard" because it provides the best pain relief to patients undergoing prostate biopsy. The optimal extended protocol should now include the sextant template with an additional 4 to 6 cores directed laterally (anterior horn) to the base and medially to the apex.  Saturation biopsies (i.e., template with greater than or equal to 20 cores, including transition zone) should be carried out only when biopsies are repeated in patients where there is a high suspicion of prostate cancer. Complementary imaging methods (e.g., color- Doppler and power-Doppler imaging, with or without contrast enhancement, and elastography) could be used in order to increase the accuracy of biopsy and reduce the number of unnecessary procedures.  However, the routine use  of these methods is still under evaluation.

Guidance from the National Instutute for Clinical Excellence (NICE, 2010) states that current evidence on the efficacy of transperineal template biopsy of the prostate shows an increase in diagnostic yield in patients with suspected prostate cancer who have had negative or equivocal results from other biopsy methods. The guidance states that there are no major safety concerns. Therefore, this procedure may be used for this indication provided that normal arrangements are in place for clinical governance, consent and audit.

NICE (2010) states that evidence was not found to support the use of transperineal template biopsy of the prostate as a mapping technique to determine the exact location and extent of prostate cancer in order to guide focal therapy, nor as part of an active surveillance regime. Therefore, the procedure should be used with these intentions only with special arrangements for clinical governance, consent and audit or research.

NCCN guidelines on prostate cancer early detection (2012) state that prostate saturation biospy should be considered for high-risk men with multiple negative biopsies. The guidelines state that, in patients with two negative extended prostate biopsies, yet persistently rising PSA values, a saturation biopsy may be considered.

Nelson et al (2013) stated that there is no consensus on how to investigate men with negative transrectal ultrasound guided prostate biopsy (TRUS-B) but ongoing suspicion of cancer. Three strategies used are (i) transperineal (TP-B), (ii) transrectal saturation (TS-B) and (iii) MRI-guided biopsy (MRI-B). These researchers compared cancer yields of these strategies. Papers were identified by search of PubMed, Embase and Ovid Medline.  Included studies investigated biopsy diagnostic yield in men with at least 1 negative TRUS-B and ongoing suspicion of prostate cancer (PCa). Data including age, PSA, number of previous biopsy episodes, number of cores at re-biopsy, cancer yield, and Gleason score of detected cancers were extracted. Meta-regression analyses were used to analyze the data. A total of 46 studies were included; 12 of TS-B, 14 of TP-B, and 20 of MRI-B, representing 4,657 patients.   Mean patient age, PSA and number of previous biopsy episodes were similar between the strategies.   The mean number   of biopsy cores obtained by TP-B and TS-B were greater than MRI-B. Cancer detection rates were 30.0 %, 36.8 %, and 37.6 % for TS-B, TP-B, and MRI-B, respectively. Meta-regression analysis showed that MRI-B had significantly higher cancer detection than TS-B. There were no significant differences however between MRI-B and TP-B, or TP-B and TS-B. In a sensitivity analysis incorporating number of previous biopsy episodes (36 studies) the difference between MRI-B and TP-B was not maintained resulting in no significant difference in cancer detection between the groups.  There were no significant differences in median Gleason scores detected comparing the 3 strategies. The authors concluded that in the re- biopsy setting, it is unclear which strategy offers the highest cancer detection rate. MRI-B may potentially detect more prostate cancers than other modalities and can achieve this with fewer biopsy cores. However, they stated that well-designed prospective studies with standardized outcome measures are needed to accurately compare modalities and define an optimum re-biopsy approach.

Li and associates (2014) identified the ability of transrectal saturation prostate biopsy (SPBx) as the initial diagnostic approach to reduce the likelihood of finding previously unrecognized PCa during repeat prostate biopsy. These investigators reviewed PCa detection in 561 men who underwent 1st repeat SPBx after initial negative biopsy between March 2002 and April 2012. They divided the patients on the basis of the number of cores retrieved on initial biopsy (group 1, initial negative SPBx [n = 81] and group 2, initial negative extended prostate biopsy [n = 480]). The yield of repeat SPBx was compared between the 2 groups. Insignificant PCa and low-risk PCa were defined according to Epstein criteria and D'Amico risk criteria, respectively. Prostate cancer detection on 1st repeat SPBx was 43.1 % lower in group 1 (19.8 % versus 34.8 %; p = 0.008). Moreover, lower rate of

significant PCa (31.3 % versus 74.3 %; p < 0.001) and intermediate- and/or high-risk PCa (25.0 % versus 50.9 %; p = 0.048) in group 1. Multi-variate analysis confirmed that initial negative SPBx decreased PCa detection on 1st repeat SPBx (odds ratio [OR] = 0.41, 95 % CI: 0.22 to 0.78). The authors concluded that men whose initial biopsy was per transrectal saturation technique were less likely to have cancer identified during repeat biopsy. Furthermore, PCa diagnosed after negative initial SPBx was much more likely to be clinically insignificant. These findings suggested that SPBx may be less likely to miss clinically significant cancer during initial prostate biopsy. They stated that if confirmed in other studies, this suggests that initial biopsy by saturation technique may eliminate the need for most men to undergo repeat biopsy.

Thompson et al (2015) examined if saturation or transperineal biopsy altered medium-term oncologic outcomes compared with standard transrectal biopsy in active surveillance (AS) for low-risk PCa. These researchers performed a retrospective analysis of prospectively collected data from 2 cohorts with localized PCa (1998 to 2012) undergoing AS. Prostate cancer-specific, metastasis-free and treatment-free survival, unfavorable disease and significant cancer at RP were compared for standard (6 to 12 core, median of 10) versus saturation (greater than 12 core, median of 16), and transrectal versus transperineal biopsy, using multi-variate analysis. A total of 650 men were analyzed; median (mean) follow-up of 55 (67) months. Prostate cancer-specific, metastasis-free and BCR-free survival were 100 %, 100 % and 99 %, respectively. Radical treatment-free survival at 5 and 10 years were 57 % and 45 % respectively (median time to treatment of 7.5 years). On KM analysis, saturation biopsy was associated with increased objective biopsy progression requiring treatment (log rank $x2 = 5.87$, p = 0.01). On multi-variate pH analysis, saturation biopsy (HR = 1.68, p < 0.01) but not transperineal approach (p = 0.89) was associated with increased objective biopsy progression requiring treatment. On logistic regression analysis of 179 men who underwent RP for objective progression, transperineal biopsy was associated with lower likelihood of unfavorable RP pathology (OR = 0.42, p = 0.03) but saturation biopsy did not alter the likelihood (p = 0.25). Neither transperineal nor saturation biopsy altered the likelihood of significant versus insignificant cancer at RP (p = 0.19 and p = 0.41, respectively). The authors concluded that active surveillance achieved satisfactory oncologic outcomes. They stated 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 unfavorable disease at RP, possibly due to earlier detection of anterior tumors.

Isbarn et al (2015) stated that prostate biopsy (PB) is the gold standard for the diagnosis of PCa. However, the optimal number of biopsy cores remains debatable. These researchers compared contemporary standard (10 to 12 cores) versus saturation (18 cores) schemes on initial as well as repeat PB. A non- systematic review of the literature was performed from 2000 through 2013. Studies of highest evidence (randomized controlled trials [RCT], prospective non- randomized studies, and retrospective reports of high quality) comparing standard versus saturation schemes on initial and repeat PB were evaluated. Outcome measures were overall PCa detection rate, detection rate of insignificant PCa, and procedure-associated morbidity. On initial PB, there is growing evidence that a saturation scheme is associated with a higher PCa detection rate compared to a standard one in men with lower PSA levels (less than 10 ng/ml), larger prostates (greater than 40 cc), or lower PSA density values (less than 0.25 ng/ml/cc).
However, these cut-offs are not uniform and differ among studies. Detection rates of insignificant PCa do not differ in a significant fashion between standard and saturation biopsies. On repeat PB, PCa detection rate is likewise higher with saturation protocols. Estimates of insignificant PCa vary widely due to differing definitions of insignificant disease. However, the rates of insignificant PCa appear to be comparable for the schemes in patients with only 1 prior negative biopsy, while saturation biopsy seems to detect more cases of insignificant PCa compared to standard biopsy in men with 2 or more prior negative biopsies. Very extensive sampling is associated with a high rate of acute urinary retention, whereas other severe adverse events, such as sepsis, appear not to occur more frequently with saturation schemes. The authors concluded that current evidence suggested that saturation schemes are associated with a higher PCa detection rate compared to standard ones on initial PB in men with lower PSA levels or larger prostates, and on repeat PB. They noted that since most data are derived from retrospective studies, other end-points such as detection rate of insignificant disease -- especially on repeat PB -- showed broad variations throughout the literature and must, thus, be interpreted with caution. They stated that future prospective RCTs should be conducted to compare extended templates with newer techniques, such as image-guided sampling, in order to optimize PCa diagnostic strategy.

Kato and colleagues (2016) noted that saturation prostate biopsy protocols have been developed to improve the PCa detection rate, particularly in the setting of repeat biopsies. These investigators clarified the association between PCa detection and various risk factors in repeat saturation biopsies. A retrospective analysis was conducted on 78 Japanese patients for whom findings had caused suspicion of PCa despite previous negative prostate biopsies, and who consecutively underwent a 24-core TP repeat biopsy; PCa was confirmed histologically in 16 of the 78 patients (20.5 %). A univariate analysis revealed that PSA level at repeat biopsy was higher (p < 0.01), the free PSA/total PSA ratio was lower (p = 0.04), the total prostate volume was smaller (p = 0.01) and the PSA density was higher (p < 0.01) in PCa patients than in patients with benign prostatic disease (BPD). Histological inflammation was more frequently observed in BPD patients than in PCa patients (p < 0.01). A multivariate analysis revealed that histological inflammation was the only independent predictor of the presence of a malignant lesion on repeat biopsy (OR, 0.027; p = 0.01). The authors concluded that it must be considered that inflammation may cause a PSA increase in some patients with a negative initial biopsy, leading to unnecessary repeat biopsy.

Ting and associates (2016) compared the performance of multi-parametric MRI/US fusion targeted biopsy (MRI/US-TBx) to a combined biopsy strategy (MRI/US-TBx plus 24-core TP template saturation mapping biopsy (TTMB)). Between May 2012 and October 2015, all patients undergoing MRI/US-TBx at the authors' institution were included for analysis. Patients underwent MRI/US-TBx of suspicious lesions detected on multi-parametric MRI +/- simultaneous TTMB. Subgroup analysis was performed on patients undergoing simultaneous MRI/US-TBx + TTMB. Primary outcome was PCa detection. Significant PCa was defined as greater than or equal to Gleason score (GS) 3 + 4 = 7 PCa. McNemar's test was used to compare detection rates between MRI/US-TBx and the combined biopsy strategy. A total of 148 patients underwent MRI/US-TBx and 80 patients underwent MRI/US-TBx + TTMB. In the MRI/US-TBx versus combined biopsy strategy subgroup analysis (n = 80), there were 55 PCa and 38 significant PCa. The detection rate for the combined biopsy strategy versus MRI/US-TBx for significant PCa was 49 % versus 40 % (p = 0.02) and for insignificant PCa was 20 % versus 10 % (p = 0.04), respectively; 11 cases (14 %) of significant PCa were detected exclusively on MRI/US-TBx and 7 cases (8.7 %) of significant PCa were detected exclusively on TTMB. The authors concluded that a combined biopsy approach (MRI/US-TBx + TTMB) detects more significant PCa than MRI/US-TBx alone; however, it will double the detection rate of insignificant PCa.

An UpToDate review on "Saturation biopsy" (Benway and Andriole, 2017) states that "Saturation biopsy is typically performed in the outpatient setting under regional or general anesthesia due to concerns for pain control, and because it is thought to be associated with an increased incidence of morbidity (e.g., severe hematuria) requiring hospital admission. However, a systematic review that identified 8 studies comparing saturation with extended biopsy found no significant differences in infection, hematuria, or bleeding between the groups … Saturation biopsy is not appropriate for initial screening but may be performed after a second negative TRUS-biopsy in the patient for whom clinical suspicion for prostate cancer remains high.  Saturation biopsy detects prostate cancer in 22 to 33 % of patients   undergoing repeat biopsy but is associated with a higher incidence of complications".

**know error DNA Specimen Provenance Assay**

DNA Specimen Provenance Assignment (DSPA) Testing (eg, Know Error System) is a molecular diagnostic test intended for the protection and control of tissue samples to purportedly decrease the incidence of diagnostic mistakes due to an individual's misidentification, specimen transposition or cell contamination, known as specimen provenance complications (SPCs). Breast and prostate tissues are most often tested but other tissue types may also be examined including, but not limited to, bone marrow.

The know error® DNA Specimen Provenance Assay is a forensic assay to confirm that a surgical specimen belongs to the patient evaluated for treatment. According to the manufacturer, the know error system features a DNA verification test that is intended to eliminate diagnostic mistakes due to specimen provenance complications. This testing incorporates three steps: (1) before a biopsy procedure, a reference sample of the patient's DNA is taken by swabbing the inside of the patient's cheek; the swab is sent to an independent forensic DNA lab; (2) the patient's biopsy tissue samples are placed in bar coded specimen containers from the biopsy kit and sent to the pathology lab for evaluation; (3) if the biopsy results come back positive, the forensics lab performs a DNA specimen provenance assignment using genetic microsatellite analysis. This test compares the short tandem repeat profile of the patient's biopsy tissue to the patient's reference sample. The manufacturer explained that  concurrence of these short tandem repeat profiles allows the practitioner to rule out specimen provenance complications. Once a DNA test is complete, the forensics lab issues

an electronic report. If specimen provenance complications are indicated, the appropriate parties are notified to address the error via a defined protocol. Aetna considers the know error system to be part of the laboratory's quality control for specimens and is not separately reimbursed.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes.  Codes requiring a 7th character are represented by "+":

| Code | Code Description |
|------|------------------|
| CPT codes covered if selection criteria are met: | |
| 55706 | Biopsies, prostate, needle, transperineal, stereotactic template guided saturation sampling, including imaging guidance |
| Other CPT codes related to the CPB: | |
| 55700 | Biopsy, prostate; needle or punch, single or multiple, any approach |
| 84152 | Prostate specific antigen (PSA); complexed (direct measurement) |
| 84153 | total |
| 84154 | free |
| HCPCS codes covered if selection criteria are met: | |
| G0416 | Surgical pathology, gross and microscopic examinations, for prostate needle biopsy, any method |
| Other HCPCS codes related to the CPB: | |
| G0102 | Prostate cancer screening; digital rectal examination |
| G0103 | Prostate cancer screening; prostate specific antigen test (PSA) |
| ICD-10 codes covered if selection criteria are met: | |
| D07.5 | Carcinoma in situ of prostate [PIN III] |
| N42.30 - N42.39 | Dysplasia of prostate [PIN I or II] |

**The above policy is based on the following  references:**

1. Cookson MM. Prostate cancer: Screening and early detection. Cancer Control. 2001;8(2):133-140.

2.  Stewart CS, Leibovich BC, Weaver AL, Lieber MM. Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. J Urol. 2001;166(1):86-92.

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# Amendment to
# Aetna Clinical Policy Bulletin Number: 0698 Prostate
# Saturation Biopsy

There are no amendments for Medicaid.