



# CIGNA MEDICAL COVERAGE POLICY

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Subject Prostate Saturation Biopsy

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## Hyperlink to Related Coverage Policies

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Screening, Detection and Disease  
Monitoring  
Prostate-Specific Antigen (PSA) Screening  
for Prostate Cancer  
Transrectal Ultrasound (TRUS)

### INSTRUCTIONS FOR USE

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## Coverage Policy

**CIGNA does not cover prostate saturation biopsy because it is considered experimental, investigational or unproven.**

## General Background

Prostate cancer is the most common cancer diagnosed in North American men, excluding skin cancers. It is estimated that in 2008, approximately 186,320 new cases and 28,660 prostate cancer-related deaths will occur in the United States (National Cancer Institute [NCI], 2008a). Prostate cancer is the second leading cause of cancer death in men, exceeded only by lung cancer. It accounts for 29% of all male cancers and 9% of male cancer-related deaths. Prostate cancer is rare in men younger than age 50, and incidence rises rapidly with each subsequent decade. The age-adjusted incidence rate is higher in African-American men compared to white males. Mortality from the disease is higher in African-American males, even after adjusting for access-to-care factors. Risk factors for prostate cancer include family history, as well as age and race. Other possible risk factors include alcohol consumption, vitamin or mineral interactions, and other dietary habits (NCI, 2008a).

Screening of asymptomatic men for prostate cancer has become a widespread practice in the United States. Screening procedures used for prostate cancer screening include digital rectal examination (DRE) and prostate-specific antigen (PSA). Although there is extensive PSA testing performed there is controversy regarding the evidence that PSA-based screening reduces prostate cancer mortality. In addition, PSA-based

screening is associated with risks of overdiagnosis and overtreatment. Results of two large, randomized studies published recently illustrate this controversy—Andriole et al. (2009) reported on results of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and Schröder et al. (2009) who reported on the European Randomized Study of Screening for Prostate Cancer [ERSPC]). Both studies are on-going with further follow-up and results expected in the future.

In situations of an abnormal DRE and/or elevated PSA, a transrectal ultrasound (TRUS)-guided prostate biopsy is usually performed. Prostate biopsy is used to diagnose prostate cancer, as well as in staging of the condition. In general, prostate biopsies are considered safe and are usually performed in an outpatient setting. The more common complications from prostate biopsies include hematuria, hematospermia, and hematochezia. Other complications are rare and are more severe, including: severe bleeding, prostatitis, sepsis, urinary retention, and vasovagal reactions.

The prostate biopsy samples the areas of the prostate gland where tumors are most frequent, in a systematic manner. The biopsy is not lesion-directed. The ultrasound is used to guide the biopsy needle into different areas of the gland rather than identifying lesions. The traditional prostate biopsy was the sextant biopsy, which involves taking six biopsies in a parasagittal line drawn halfway between the lateral border and midline bilaterally, from the base, mid-gland, and apex, with a 20–25% positive biopsy rate (Raja, et al., 2005). It was thought that the sextant technique was inaccurate mainly because it under-sampled the peripheral zone of the prostate. Modifications of the sextant biopsy have been developed and reported on in the literature. The modified sextant biopsy protocol involves moving the middle biopsies of the standard sextant laterally and the biopsy trajectories angled anterolaterally so that mainly the peripheral zone is sampled. This method appeared to improve the cancer detection rate (Raja, et al., 2005). Extended biopsy techniques that utilized additional cores directed to the peripheral zone have been developed. It has been noted that the sensitivity of prostate cancer screening may be improved by taking 10–12 cores rather than six cores. Taking 10 to 12 tissue cores has become the standard of care (Wilson and Crawford, 2004). Sextant and extended biopsy with 10–12 cores is generally performed with local anesthesia. It has been estimated that up to 31% of all non-palpable prostate cancers diagnosed with needle biopsy and treated with radical prostatectomy are potentially insignificant tumors, with volumes less than 0.5 cm<sup>3</sup> (Djavan et al., 2003).

In some situations, there may be a continuing suspicion of prostate cancer even with repeated negative prostate biopsies. The prostate saturation biopsy has been proposed for circumstances where the patient is considered high-risk for prostate cancer, but biopsies have been negative. The saturation biopsy involves taking between 20 to 40 core biopsies. Additional cores may be taken for larger prostates. It is theorized that the saturation biopsy may detect cancer that was not detected with a prior biopsy. The technique is similar to the sextant or the extended biopsy in that it is performed during a TRUS, utilizing the core needle biopsy device. Some type of regional or general anesthesia or intravenous sedation is typically used. Another method of performing saturation biopsy involves utilizing a transperineal, grid-based method using a brachytherapy template. This method is theorized to be more systematic and allows for improved sampling of the area immediately anterior to the urethra (Raja, et al., 2006).

The saturation biopsy is based on the assumption that the cancer is small and/or located in one of the deeper reaches of the gland (Raja, et al., 2006). The whole gland is sampled without following any particular zonal pattern. It is thought that the larger number of evenly distributed samples increases the probability of detecting an underlying cancer, regardless of the tumor size or location. Increased bleeding is generally noted with an increased amount of core biopsies (Routh and Leibovich, 2005). A concern with this type of biopsy approach is the possibility of an increased risk of detecting clinically insignificant cancers which may lead to unnecessary treatment.

Saturation or mapping biopsy is also proposed to be used for staging of prostate cancer and determination of treatment. It has been proposed that in patients who have been diagnosed with prostate cancer, that saturation biopsy may provide information for staging and management (Sartor, et al., 2008). In particular it is proposed that this test may identify candidates for focal therapy. Focal therapy is a more localized treatment that is directed at the cancerous foci within the gland, rather than at removing or destroying the entire prostate. It is theorized that a mapping biopsy obtained using a grid that samples the entire gland will provide information that may be utilized in characterizing the tumor and treatment planning. While it appears that more information regarding the tumor may be obtained with a mapping biopsy more studies are needed that compare the

accuracy of transperineal mapping and standard transrectal systematic biopsies with reference to the actual size, location, extent, and grade of cancer in the specimen (Sartor, et al., 2008).

It has been noted in the literature that controversy exists regarding which zones of the prostate to sample during a biopsy and how many cores to obtain that will minimize the diagnosis of clinically insignificant cancers. Various interrelated factors are involved in the decisions of when to biopsy and when to perform a repeat biopsy. These factors include: the PSA level, age of patient, family history, size of prostate, and the location and type of prior biopsies. It has been noted in the literature that, although prostate needle biopsy is considered the gold standard for cancer diagnosis, it is impossible to verify the absence of cancer in the prostate in vivo; as a result, the true false-negative rate remains unknown (Chrouser and Lieber, 2004). It appears that increasing the number of biopsies may be associated with increased risk due to an increase in complications (Raja, et al., 2005). Review of the literature does not indicate that the prostate saturation biopsy is more effective than an extended prostate biopsy for the detection of clinically significant prostate cancer or that use of this test will lead to an increase in survival or prognostic yield.

### **Literature Review—Saturation Biopsy for Diagnosis of Prostate Cancer**

Stewart et al. (2001) conducted a study based on the hypothesis that markedly increasing the number of cores obtained during prostate needle biopsy may improve the cancer detection rate in men with persistent indications for repeat biopsy. Saturation TRUS-guided biopsy was performed in 224 men. The mean number of previous sextant biopsy sessions was 1.8 (range one to seven). The median years from the first biopsy until the saturation biopsy was performed were 2.4 years. A mean of 23 saturation biopsy cores (range 14–45) were distributed throughout the whole prostate including the peripheral, medial and anterior regions. Indications for repeat biopsy included persistently elevated PSA levels in 108 cases and persistently elevated PSA and abnormal rectal exam in 27 patients, and persistently abnormal rectal examination in four patients, high grade prostatic intraepithelial neoplasia (PIN) in the previous biopsy in 64 patients, and atypia in the previous biopsy in 21 patients. In 112 of the 224 men (50%), it was noted that they had only a single set of negative biopsies before undergoing the saturation biopsy. It was noted that cancer was detected in 77 of the 224 patients (34%). Of the 77 patients in whom cancer was detected, 52 underwent radical prostatectomy. The location where the cancer was detected with the saturation biopsy was not reported. The complication rate for saturation biopsy was 12% and hematuria requiring hospital admission was the most common event.

Fleshner and Klotz (2002) conducted a study to determine the role of saturation prostate biopsy among selected men with unexplained worrisome PSA parameters. The study involved 37 men who underwent saturation biopsy. This involved obtaining 24 peripheral zone cores, six to 12 transition zone cores and two lateral lobe transurethral samples. All of the men had previously undergone at least three prior sets of TRUS prostate biopsies. The median PSA level and the percent-free PSA level was 22.4 ng/ml (range 7.8–73.8) and 0.11 (range 0.04–0.17), respectively. The specimens were sent for pathologic examination in sets of six in order to determine the marginal benefit of additional sampling. After pathologic examination, it was noted that five patients (13.5%) had detectable carcinoma. In these cases, the carcinoma was detected in the 18 peripheral zone cores. Acute prostatitis was noted in 19% of the specimens. The study concluded that most men with multiple previous biopsies and increasingly worrisome PSA parameters do not have cancer and that the marginal utility of the saturation biopsy is low. It was noted that although rare additional cases may be detected using this technique, 18-core peripheral sampling is recommended for those difficult diagnostic cases.

Sur et al. (2004) conducted a prospective randomized study to compare standard prostate biopsy to extensive biopsy utilizing intravenous conscious sedation (IVCS). Initial biopsy patients (n=197) were randomized to either standard biopsy (i.e., 6–12 biopsies, mean 10.1) using intrarectal lidocaine gel, or extensive biopsy (i.e., 20 biopsies) using IVCS. The objective was to determine if the extensive biopsy technique resulted in a higher rate of cancer detection and/or improved patient tolerance of the biopsy procedure compared to a more standard biopsy technique. Eighty-eight patients (48%), underwent the standard biopsy, and 94 (52%) underwent the 24-core extensive biopsy, with 15 patients withdrawing from the study. The authors note that while the sextant biopsy with six core samples may not be sufficient, the optimal number of biopsies required to maximize cancer detection without over-detection of clinically insignificant cancers is still uncertain. It was noted that the extensive prostate biopsy with 24 cores did not improve cancer detection rates compared to a standard biopsy technique in which an average of 10 cores was obtained. The IVCS technique was well tolerated and associated with significantly less pain and greater patient satisfaction than the rectal lidocaine gel alone. The authors note that the results imply that saturation biopsy is not necessary in patients undergoing initial prostate biopsy so long as extended biopsy that includes 8–12 cores is utilized.

Rabbets et al. (2004) reported on the diagnostic yield of office saturation biopsy in patients at increased risk for prostate cancer and at least one negative prior biopsy. Saturation prostate biopsy was performed on 116 patients with at least one prior negative biopsy and with certain risk factors, including persistently elevated prostate specific antigen, abnormal DRE, or prior atypia or PIN on a prior biopsy. A total of 34 cancers were detected for an overall diagnostic yield of 29%. In this series, only 22% of the patients had undergone prior sextant biopsies. In a small cohort, it was noted that there was a 64% cancer detection rate (seven of 11) in patients who had undergone a previous sextant biopsy.

Epstein et al. (2005) conducted a review of 103 men who had been predicted to have insignificant cancer in their radical prostatectomy (RP) specimen. The aim of the study was to determine whether saturation biopsy of the prostate could reliably predict insignificant and significant cancer in men who were candidates for watchful waiting. Candidates were identified based on the preoperative needle biopsy pathologic findings and serum PSA levels. The patients had limited cancer on the routine needle biopsy: no core with more than 50% involvement; Gleason score less than seven; and fewer than three cores involved. Saturation biopsy with an average of 44 cores and an alternate biopsy saturation scheme with one half of the number of cores were performed in the pathology laboratory on the RP sections. Of the tumors, 97% were organ-confined. The RP Gleason score was less than seven in 84% of the cases. Of the cancer specimens, it was noted that 71% were insignificant, and 29% had been incorrectly classified before surgery using standard biopsy schemes. Using the full saturation biopsy scheme, and where significant cancer was predicted, the probability of having insignificant cancer appeared to be 11.5% (i.e., false-positive rate). If the algorithm model predicted insignificant cancer, the significant cancer was also only 11.5% (i.e., using the alternate biopsy sampling scheme, the false-positive rate was 8%, and the false-negative rate was 11.4%). The authors note that the results of the current study need to be prospectively evaluated to determine their validity. In addition, further testing would be required of the algorithm with saturation biopsy of patients in vivo. It was also noted that the classification of insignificant and significant cancer did not necessarily predict the biologic behavior of cancer long-term.

Jones et al. (2006) reported on results of a sequential cohort study that compared office-based saturation prostate biopsy to traditional 10-core sampling as an initial biopsy. A 24-core biopsy was performed on 139 patients undergoing initial prostate biopsy. Indication for the biopsy was an increased PSA of 2.5 ng/dl or greater in all patients. The results were compared to 87 patients who had undergone 10-core initial biopsies. Cancer was detected in 62 of the 139 patients (44.6%) who underwent the saturation biopsy and 45 of the 87 patients (51.7%) who underwent 10-core biopsy. The study notes that breakdown by PSA level failed to show benefit to the saturation technique for any degree of PSA increase.

Meng et al. (2006) investigated the impact of the greater number of prostate biopsies on the nature of cancer identified. The authors noted that increasing the number of cores obtained at the time of TRUS-guided biopsy has increased the number of cancers identified; however, there is also increasing recognition that many men with prostate cancer may not benefit from early aggressive intervention and that over-detection of prostate cancer has resulted in over-treatment. The Cancer of the Prostate Strategic Urologic Research Endeavor database, a longitudinal disease registry of men with prostate cancer, was utilized to identify 4072 men with six or more prostate biopsies obtained at initial diagnosis. Of these patients, 30%, 47% and 24% underwent 6, 7 to 11, and more than 12 biopsies, respectively. There was a significant correlation noted between the biopsies and numerous sociodemographic and clinical variables, including PSA, comorbidities and income. It did not appear that there was a difference in disease characteristics as assessed by Kattan and Caner of the Prostate Risk Assessment scores among men with a biopsy number between six and 17. In a subset of 1548 men who underwent radical prostatectomy, no differences were observed regarding biochemical-free survival at a follow-up of 2.2 years.

Bott et al. (2006) reported on a case series to describe a modified saturation biopsy technique and results of extensive transperineal template prostate biopsies in men with a high risk of prostate cancer for whom repeated transrectal biopsies were not diagnostic. The study included 60 men who had a rising PSA level and had at least two sets of benign sextant biopsies or two or more prior biopsies containing high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation. In a transverse image, the prostate was divided into six regions. Three to five transperineal biopsy cores were taken in each of the six regions with the use of a brachytherapy template. Cancer was detected in 23 (38%) men. Of this group, cancer was detected in the anterior region of the prostate alone in 12 men (60%). One patient required overnight admission for hematuria, two developed urinary retention, and there were no reported cases of sepsis.

Walz et al. (2006) conducted a study of 161 men who underwent saturation biopsies to explore the yield of saturation biopsy and develop a nomogram to predict the probability of prostate cancer on the basis of saturation biopsy. The biopsy involved obtaining an average of 24 cores and was performed in men with persistently elevated PSA levels. All had at least two previously negative, eight-core biopsies. Prostate cancer was detected in 41% (n=66). Positive cores were found mainly in the far lateral zone (79%), the medio-lateral zone (36%) and the transition zone (18%). It was reported that the rate of insignificant cancers was 15.6%, or five of the 32 men treated with radical prostatectomy; however, the assessment of clinical significance could only be assessed for those who underwent prostatectomy and could not be assessed for the remaining 34 patients. The complication rate was noted to be 2.5% and included two acute urinary retentions, one acute prostatitis and one reactive syncope episode. Two hospitalizations for intravenous antibiotics were required. The results indicated that PSA density and transition zone volume were the most significant predictors of prostate cancer.

Merrick et al. (2006) reported on a study of 102 patients to determine the prostate cancer incidence, anatomic distribution, Gleason score profile, and tumor burden in patients diagnosed by transperineal template-guided saturation biopsy. All but one of the patients had undergone at least one prior negative TRUS biopsy. On average, patients had undergone 2.1 prior negative TRUS biopsies with a mean of 22.4 core biopsies. The prostate gland was divided into 24 regions for the biopsy, and the median number of cores taken was 50. Prostate cancer was diagnosed in 43 patients (42.2%). It appeared that there was considerable anatomic variability in prostate cancer distribution, with no anatomic region of the prostate without cancer. Complications included urinary retention in 38% of the patients who required a urinary catheter overnight, six for two days, and three for six days. Hematuria was noted in one patient who required overnight hospitalization. In their analysis, the authors noted that transperineal template-guided saturation biopsy "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."

Eichler et al. (2006) conducted a systematic review to compare the cancer detection rates and complications of different extended prostate biopsy schemes. Eighty-seven studies were analyzed with a total of 20,698 patients. Data was pooled from 68 studies that compared a total of 94 extended schemes with the standard sextant scheme. Reports were selected that applied a sequential sampling design in the same patients or a randomized design. Studies were excluded that did not compare the 2 schemes in the same population, and those with nonsystematic biopsy schemes (e.g., lesion directed biopsies and computer simulation studies). The studies included participants of all age groups with suspected prostate cancer scheduled for prostate biopsy with increased PSA and/or positive digital rectal examination. Reports of men with already proven prostate cancer were excluded. The authors noted that the quality of reporting in these studies was often poor. Of 87 studies 45 (52%) supplied sufficient information to conclude that the patient spectrum was representative of patients who undergo the test in practice, while 8 of the 45 involved a screening population. twenty-eight studies (32%) clearly described their selection criteria. Information regarding the men undergoing first or repeat biopsy was only partly provided: 10 studies had a first time biopsy population, 11 had a repeat biopsy population, 13 had a mixed population, and no information was available in 53. A total of 18 studies (21%) provided description of the biopsy schemes in sufficient detail to meet the predefined criteria for the systematic review. Only 1 study specified that the pathologist was blinded to the test sequence. Of the seven randomized studies, only three described a suitable method for generating the random sequence and only two mentioned that the allocation to the groups was concealed.

It was noted that increasing the number of cores was significantly associated with the cancer yield. Laterally directed cores appeared to increase the yield significantly, whereas centrally directed cores did not appear to. Biopsy schemes with 12 cores that took additional laterally directed cores detected 31% more cancers than the sextant scheme. Biopsy 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 and that taking more than 12 cores does not add significant benefit.

Pepe and Aragona (2007) reported on a retrospective study that evaluated the incidence of prostate cancer in patients who underwent a saturation prostate biopsy as a primary biopsy or as a rebiopsy. The study included 189 patients. In 98 of these men the biopsy was performed as the primary biopsy procedure, in 75 as the

second procedure, and in 16 as the third biopsy procedure. The prostate cancer detection using an saturation prostate biopsy as initial biopsy was compared retrospectively with that found in 256 and 116 patients who underwent 12- and 18-core biopsy, respectively, according to the same protocol. The results obtained in 75 patients submitted to a saturation prostate biopsy as the second biopsy set were compared retrospectively with those found in 73 men who underwent an 18-core re-biopsy. It was noted that among 189 patients who underwent saturation prostate biopsy, the incidence of prostate cancer was 46.9% (46 cases), 22.6% (17 cases), and 6.2% (1 case) at first, second, and third set of biopsy, respectively. The prostate cancer detection rate, obtained using saturation biopsy as the primary biopsy, was greater than that found using a 12-core biopsy (46.9% versus 39.8%;  $P=0.3$ ) but lower than that observed when using an 18-core biopsy (46.9% versus 49.1%;  $P=0.6$ ). In the saturation biopsy group there was a greater incidence of acute urinary retention and hemospermia compared with the 12- and 18-core sets: 11.6% versus 4.3% ( $p=0.03$ ) and 13.2% versus 6.2% ( $p=0.15$ ) and 7.8% ( $p=0.25$ ), respectively. Limitations of the study include that it was a retrospective evaluation and patients were not randomized among 12- or 18- or 24-core biopsies.

Li et al. (2007) conducted a prospective study to assess prostate cancer detection rate and safety of transperineal ultrasound-guided saturation biopsy of the prostate using an 11-region template of the gland. The study included 303 patients. The inclusion criteria included a prostate-specific antigen level of 4.0 ng/ml or greater, suspicious findings on the DRE, or abnormal prostate gland findings on ultrasonography, computed tomography, or magnetic resonance imaging. A mean of 23.7 cores (range of 11–44 cores) were obtained, with more cores performed in larger prostates than in smaller ones. The overall prostate cancer detection rate was 37.6% (114 of 303). The cancer detection rate in the groups with a prostate-specific antigen level of 0–4.0, 4.1–10.0, 10.1–20.0, 20.1–30.0, 30.1–70.0, and greater than 70.1 ng/ml was 22.2% (4 of 18), 8.2% (6 of 73), 21.6% (22 of 102), 48.4% (15 of 31), 68.4% (26 of 38), and 100% (41 of 41), respectively. No serious complications were noted. Drawbacks of this method include that it is time-consuming, requires brachytherapy equipment and does not appear to be able to replace the transrectal ultrasound guided biopsy technique used today.

Ashley et al. (2007) conducted a nonrandomized cohort study of a consecutive series of prostate biopsies to determine whether saturation biopsy ( $\geq 24$  cores) detects more prostate cancer than a standard 12–18 core office biopsy technique. The primary outcome assessed by both univariate and multivariate analysis was the detection of prostate cancer, with secondary outcomes including analysis of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP). The study included 469 patients undergoing prostate biopsy. A standard office prostate biopsy was performed in 301 men, while 168 men underwent a saturation biopsy. The age, body mass index, prostate volume, and family history of prostate cancer were similar in the two groups. However, patients in the saturation biopsy cohort were more likely to have had prior biopsies, higher prebiopsy PSA, longer PSA doubling times, and to carry more frequent diagnoses of HGPIN or ASAP (all  $p < 0.05$ ). After adjustment for covariates, the saturation biopsy did not detect more abnormal pathology than standard office prostate biopsy, including prostate cancer ( $p = 0.339$ ), HGPIN ( $p = 0.368$ ), or ASAP ( $p = 0.201$ ).

Stav et al. (2008) conducted a study to evaluate 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. The study included 27 patients who underwent saturation biopsy with use of transrectal approach under general or regional anesthesia. The mean number of cores obtained per patient was  $61 \pm 9.5$  (range 41–76). Prostate cancer was found in three patients (11.1%). All three of these patients had minimal disease affecting less than 1% of a single core sampled from the peripheral zone. Two of these patients were chosen for watchful waiting. One of these patients underwent radical prostatectomy—pathologic specimen contained carcinoma of prostate (Gleason 3+3) in less than 1% of total prostate volume.

Lane et al. (2008) reported on a study of men who underwent initial prostate saturation biopsy at a median of 3.2 years. Saturation biopsy was used as an initial biopsy on 257 men, including 139 that had been previously reported on (Jones, et al., 2006). Cancer was initially detected in 43% of these patients. In 147 of the men with negative initial saturation biopsy, the follow-up included DRE and repeat PSA measurement recommended at least annually. Persistently increased prostate specific antigen or an increase in prostate specific antigen was seen as an indication for repeat saturation prostate biopsy. During the follow-up of 3.2 years after the negative initial saturation biopsy, 121 men (82%) underwent subsequent evaluation with prostate specific antigen and digital rectal examination. The median PSA remained 4.0 ng/ml or greater in 57% of the men and increased by 1 ng/ml or greater in 23%. Prostate cancer was detected in 14 of 59 men (24%) who underwent repeat prostate biopsy for persistent clinical suspicion of prostate cancer. There was no significant association found between

cancer detection and initial or follow-up prostate specific antigen, nor findings of atypia and high grade prostatic intraepithelial neoplasia on the initial saturation prostate biopsy. Cancers detected on repeat prostate biopsy were more likely to be Gleason 6 and organ confined at prostatectomy than those that were diagnosed with initial saturation prostate biopsy.

Simon et al. (2008) reported on results using an extensive saturation biopsy in men with negative prostate biopsies but in whom there is a clinical suspicion of cancer. Forty patients underwent an extensive saturation biopsy. A median number of cores taken was 64 (range 39–139) and was adjusted to the size of the prostate. Of the 40 patients, 18 (45%) were found to have carcinoma in at least one core; 16 had radical prostatectomy. Twenty-two (55%) had no malignancy in the specimen. Sixteen patients had marked hematuria after the procedure.

### **Literature Review—Saturation Biopsy for Staging and Treatment Planning**

Baccon-Gibod et al. (2006) evaluated the ability of an extended, 32-core repeat transrectal ultrasound prostate biopsy protocol to improve the characterization of low volume, well differentiated disease in men with a diagnosis of potentially insignificant microfocal prostate cancer, as defined by a single focus positive core of 10 with less than 5mm of Gleason score 6 or less tumor on primary biopsy. The study included 35 consecutive patients. They had a median serum prostate specific antigen of 8 ng/ml (range 0.5 to 14) and a diagnosis of minimal prostate cancer. They were willing to consider observation with delayed treatment at progression. Repeat saturation prostate biopsy with a median of 32 cores (range 18 to 36) was performed under local anesthesia. The purpose of the biopsy was to determine whether more extensive prostate sampling would confirm or disprove the initial diagnosis of microfocal, well differentiated prostate cancer. In one patient the procedure was aborted due to massive rectal hemorrhage. Acute prostatitis with gram-negative sepsis was noted in another patient. Of the 34 evaluable biopsy sets, 11 (32%) were found to be negative for cancer, suggesting that tumor detected at the primary biopsy was probably of low volume and amenable to observation with delayed treatment. Of the biopsies, 23 (68%) were positive, 17 were at multiple sites and seven were upgraded to Gleason score 7 or greater. These patients were then considered to have significant tumors and were offered active treatment.

Barzell and Melamed (2007) studied transperineal mapping biopsy of the prostate as a staging procedure in the appropriate selection of patients for treatment with focal ablation. The study included 80 patients who underwent extensive template-guided transperineal pathologic mapping of the prostate (3-DPM), in conjunction with repeat TRUS-guided biopsies. The results of 3-DPM were compared with those of TRUS-guided biopsies in order to determine patient suitability for focal cryoablation. Of the 80 patients, 43 (54%) were deemed unsuitable for focal cryoablation. When compared with 3-DPM in assessing patient suitability for focal cryoablation, the TRUS-guided biopsies yielded a false-negative rate of 47%, a sensitivity of 54%, and a negative predictive value of 49%. There was no significant correlation noted of the pre-3-DPM variables with patient suitability for focal ablation.

Onik et al. (2008) reported on a study of transperineal 3D mapping biopsy used as an additional staging procedure prior to focal prostate cancer therapy. The study included 110 patients. Transperineal biopsy was performed under transrectal ultrasound guidance. Samples were obtained every 5 mm throughout the volume of the prostate using a brachytherapy grid. The median number of cores taken was 46 (SD±19). Bilateral cancer was seen in 60 patients (55%), all of whom had only unilateral cancer shown on TRUS biopsy. The Gleason score was increased in 25 patients (23%) over the score with the TRUS biopsy. Complications included nine patients (8%) who required short-term indwelling catheter drainage and two with hematuria.

### **Professional Societies/Organizations**

**National Comprehensive Cancer Network (NCCN):** The NCCN published clinical practice guidelines for early detection of prostate cancer. The guidelines include an algorithm for follow-up of TRUS-guided biopsies. This algorithm includes recommendations for when extended-pattern biopsy, defined as 12 cores, is to be performed for initial and repeat biopsies. The recommendations include the following (NCCN, 2007):

- The number of cores in extended pattern biopsy includes:
  - Sextant (6 cores)
  - Lateral peripheral zone (6 cores)
  - Lesion-directed at palpable nodule or suspicious image

- Transition zone biopsy is not supported in routine biopsy. However, the addition of a transition zone biopsy to an extended biopsy protocol may be considered in a repeat biopsy if PSA is persistently elevated.
- After two negative extended TRUS biopsies, prostate cancer is not commonly found at repeat biopsy.
- For high-risk men with multiple negative biopsies, consideration can be given to a saturation biopsy strategy.

**U.S. Preventive Services Task Force (USPSTF):** In 2008, the USPSTF published updated clinical guidelines for screening for prostate cancer (USPSTF, 2008). The guidelines do not include recommendations for biopsies, but include the following statement, “Biopsy detection rates vary according to the number of biopsies performed during a single procedure: The more biopsies performed, the more cancer cases detected. More cancer cases detected with a “saturation” biopsy procedure tend to increase the apparent specificity of an elevated PSA level; however, many additional cancer cases detected this way are likely to be clinically unimportant. Thus, the accuracy of the PSA test for detecting clinically important prostate cancer cases cannot be determined with precision.”

### Summary

The role of prostate saturation biopsy in the detection, staging and/or treatment planning of prostate cancer has not yet been established. It is not known whether this method improves the health outcomes of individuals. There is a concern that with this type of biopsy there is an increased risk of detecting clinically insignificant cancers which may lead to unnecessary treatment. There is no consensus regarding which zones of the prostate to sample during a biopsy and how many cores to obtain that will minimize the diagnosis of clinically insignificant cancers. It has not been demonstrated in the published peer-reviewed literature that the prostate saturation biopsy is comparable to an extended prostate biopsy for the detection of clinically significant prostate cancer, or that use of this test will lead to an increase in survival or prognostic yield.

### Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

#### Experimental/Investigational/Unproven/Not Covered:

CPT <sup>®</sup> * Codes	Description
55706	Biopsies, prostate, needle, transperineal, stereotactic template guided saturation sampling, including imaging guidance (new code effective 1/1/09; replaces 0137T)
0137T	Biopsy, prostate, needle, saturation sampling for prostate mapping (deleted code effective 12/31/08; replaced by 55706)

HCPCS Codes	Description
G0416	Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, 1-20 specimens
G0417	Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, 21-40 specimens
G0418	Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, 41-60 specimens
G0419	Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, greater than 60 specimens

ICD-9-CM Diagnosis Codes	Description
	All codes

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## Policy History

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<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	5/15/2008	0450	Prostate Saturation Biopsy

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.