CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date 5/15/2011
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Coverage Policy Number 0450

Subject **Prostate Saturation Biopsy**

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Gene-Based Testing for Prostate Cancer Screening, Detection and Disease Monitoring
Prostate-Specific Antigen (PSA) Screening for Prostate Cancer
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INSTRUCTIONS FOR USE

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Coverage Policy

Following two successive, extended prostate biopsies negative for invasive cancer, CIGNA covers a transperineal stereotactic template-guided saturation prostate biopsy as medically necessary for the evaluation of an unexplained persistently rising prostate specific antigen (PSA).

CIGNA does not cover prostate saturation biopsy for any other indication because it is considered experimental, investigational or unproven.

General Background

Screening procedures used for prostate cancer screening include digital rectal examination (DRE) and prostate-specific antigen (PSA). In situations of an abnormal DRE and/or elevated PSA, a transrectal ultrasound (TRUS)-guided prostate biopsy is usually performed. A prostate biopsy is used to diagnose prostate cancer, as well as in estimating the aggressive potential of the tumor based on the Gleason score. 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 less common 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 ultrasound is used to guide the biopsy needle into different areas of the gland. 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.

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 biopsy involves a transperineal, grid-based method using a brachytherapy template. This method is thought 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 increased risk of detecting clinically insignificant cancers which may lead to unnecessary treatment.

Saturation or mapping biopsy is also proposed to be used for guiding treatment. It has been proposed that in patients who have been diagnosed with prostate cancer, that saturation biopsy may provide information for management of the disease (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 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). Increasing the number of biopsies may be associated with increased risk due to an increase in complications (Raja, et al., 2005). It appears that for a subset of patients, those with rising PSA and prior negative biopsies, that a prostate saturation biopsy may be an appropriate action to be considered.

Literature Review—Saturation Biopsy for Diagnosis of Prostate Cancer

There have been several studies, mainly prospective and retrospective case series that evaluated saturation prostate biopsy in patients who have undergone previous biopsies. These studies varied in the number of cores and type of biopsies that were previously performed. The studies indicated that the greater number of cores taken during the biopsy did lead to the greater cancer detection. In some of the studies the previous biopsy was the sextant biopsy, or biopsy with 6-8 cores, therefore it is unknown if the extended biopsy with 10-12 cores would have detected cancer. It is unknown if saturation prostate biopsy would lead to the detection of clinically insignificant cancers which may lead to unnecessary treatment.

Systematic review: 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. 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.

Studies: Novara et al. (2010) evaluated 143 patients undergoing transperineal prostate saturation re-biopsy using a 24-core scheme. The number of previous biopsies was one in 59%; two in 26%; and three or more in 15%. Prostate cancer was detected in 26%, atypical small acinar proliferation (ASAP) in 5.6% and high-grade prostatic intraepithelial neoplasia (HGPIN) in 2.1%.

Stav et al. (2008) conducted a study to evaluate the diagnostic value of saturation prostate biopsy in patients with PSA greater than 10ng/ml, PSA velocity greater than 0.75ng/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± 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.

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.

Pepe et al. (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.

Ashley et al. (2007) conducted a nonrandomized cohort study of a consecutive series of prostate biopsies to determine whether saturation biopsy (≥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 ($p = 0.201$).

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 octant 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 syncopal 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.”

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.

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. 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.

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). A mean of 23 saturation biopsy cores (range 14–45) were distributed throughout the whole prostate including the peripheral, medial and anterior regions. 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.

Literature Review—Saturation Biopsy for Focal Treatment
There are few published studies that examine whether saturation prostate biopsy can predict the extent and location of prostate cancer and be used for focal therapy. Falzarano et al. (2010) studied 72 patients who underwent saturation biopsy followed by radical prostectomy (RP) for prostate cancer. Saturation biopsy detected bilateral prostate cancer in 33 and unilateral prostate cancer in 39 men. All cases with bilateral prostate cancer by saturation biopsy had bilateral tumor in RP. Only 4 of 39 patients with unilateral positive saturation biopsy had unilateral cancer in RP. Twelve potentially clinically significant PCA were missed by saturation biopsy in 11 of 35 patients. When patients with unilateral and bilateral positive saturation biopsies were compared with respect to prognostic parameters, biopsy Gleason score (p=.004), number of biopsy cores involved (p<.0001), and highest percentage of core (p=0005) involved by tumor were significantly higher for patients with bilateral positive biopsy. Most (90%) patients with unilateral prostate cancer on saturation biopsy had bilateral cancer in RP; of those 31% had clinically significant undiagnosed prostate cancer. The authors concluded that a negative saturation biopsy does not confirm the absence of cancer in the corresponding side of the gland and cannot be used as single determinant when considering a patient for focal treatment.

Literature Review—Saturation Biopsy for Initial Biopsy
There are case studies that examined the use of saturation biopsy as the initial biopsy (Lane, et al., 2008; Pepe, et al., 2007; Li, et al., 2007; Jones, et al., 2006). The results of these studies indicate that as an initial biopsy technique, saturation biopsy does not improve initial cancer detection.

Professional Societies/Organizations
American Urological Association (AUA): In 2009, the AUA updated their prostate specific antigen best practice statement. The statement included the following regarding prostate biopsies:

- The most common method of obtaining prostate tissue for diagnosis of prostate cancer is by means of a transrectal, ultrasound-guided prostate biopsy, which is usually performed as an outpatient procedure with local anesthesia. A standard biopsy scheme is performed, consisting of at least 8 to 12 cores of tissue targeting the peripheral zone at the apex, midgland, and base, as well as laterally directed cores on each side of the prostate.
- In situation where extended or saturation biopsy schemes are indicated, additional tissue may be taken from the anterior and transition zones of the prostate as well. Saturation biopsy, taking tissue from more than 20 locations, may be considered in men with persistently elevated PSA levels and multiple previous negative prostate biopsies.
- An alternative to the transrectal saturation biopsy method is the transperineal prostate biopsy, which may be performed under local, regional, or general anesthesia utilizing a brachytherapy grid and transrectal ultrasound guidance. Similar to transrectal saturation biopsy, this technique is reserved for patients with elevated and/or rising PSA values and prior negative transrectal prostate biopsies.

European Association of Urology (EAU): In 2010, the EAU published Guidelines on Prostate Cancer. The guidelines note the following regarding saturation biopsies:

- The incidence of prostate cancer detected by saturation repeat biopsy is between 30% and 43% and depends on the number of cores sampled during earlier biopsies (level of evidence: 2a*).
- In special situations, saturation biopsy may be performed with the transperineal technique. This will detect an additional 38% of prostate cancer. The high rate of urinary retention (10%) is a drawback (3D-stereotactic biopsy) (level of evidence: 2b*).

*2a Evidence obtained from one well-designed controlled study without randomization; 2b Evidence obtained from at least one other type of well-designed quasi-experimental study

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, 2010a):

- 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.

In addition, the NCCN guidelines note that, ”in patients with two negative extended biopsies, yet persistently rising PSA values, a saturation biopsy may be considered.”

National Institute for Health and Clinical Excellence (NICE) (United Kingdom): In 2010, NICE published guidance for transperineal template biopsy and mapping of the prostate. The guidelines include the following:

- 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. 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.
- 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.

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

There is no consensus in the published literature regarding which zones of the prostate to sample during a biopsy or the number of core samples needed to minimize the diagnosis of clinically insignificant cancers. While the evidence in the published peer-reviewed literature supporting the clinical utility of prostate saturation biopsy is not robust, it can be considered an accepted standard of care for a carefully selected subset of men with persistently rising prostate-specific antigen (PSA) and prior negative transrectal prostate biopsies. Transperineal

stereotactic template-guided saturation prostate biopsy is an appropriate next step for patients with rising PSA and at least two negative prostate biopsies.

Coding/Billing Information

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

Covered when medically necessary:

CPT®* Codes	Description
55706	Biopsies, prostate, needle, transperineal, stereotactic template guided saturation sampling, including imaging guidance

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
790.93	Elevated prostate specific antigen, (PSA)

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
185	Malignant neoplasm of prostate
233.4	Carcinoma in situ of breast and genitourinary system; prostate
	All other codes

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Policy History

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