Name of Policy:
Saturation Biopsy for Diagnosis and Staging of Prostate Cancer

Policy #: 396 Latest Review Date: February 2014
Category: Surgery Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Saturation biopsy involves obtaining at least 20 biopsy tissue cores from the prostate in a systematic manner. Use of saturation biopsy has been proposed for use in the diagnosis (for initial or repeat biopsy), staging, and management of patients with prostate cancer.

Prostate cancer is a common cancer in men and is the second leading cause of cancer-related deaths in men in the US. The diagnosis of prostate cancer is made by biopsy of the prostate gland. The approach to biopsy has changed over time, especially with the advent of PSA (prostate-specific antigen) screening programs that identify cancer in prostates that are normal to palpation and to trans-rectal ultrasound. For patients with an elevated PSA-level but with a normal biopsy, questions exist about subsequent evaluation since repeat biopsy specimens may be positive for cancer in a substantial percentage of patients.

In the early 1990’s, use of sextant biopsies involving six random, evenly distributed biopsies became the standard approach to the diagnosis of prostate cancer. In the late 1990’s as studies showed high false-negative rates for this strategy (missed cancers), approaches were developed to increase the total number of biopsies and to change the location of the biopsies. While there is disagreement about the optimal strategy, most would agree that initial prostate biopsy strategies should include at least 10 to 14 cores. Additional concerns have been raised about drawing conclusions about the stage (grade) of prostate cancer based on limited biopsy material. Use of multiple biopsies has also been discussed as an approach to identify tumors that may be eligible for sub-total cryoablation therapy.

At present, many practitioners use a 12 to 14 core “extended” biopsy strategy for patients undergoing initial biopsy. This extended biopsy is done in office setting and allows for more extensive sampling of the lateral peripheral zone; sampling of the lateral horn may increase the cancer detection rate by approximately 25%.

Another approach to increase the number of biopsy tissue cores is use of the “saturation” biopsy. In general, saturation biopsy is considered as a minimum of 20 cores taken from the prostate with improved sampling of the anterior zones of the gland, which may be under-sampled in standard peripheral zone biopsy strategies and may lead to 17% of cancers being missed, according to one study. Saturation biopsy may be performed transrectally or with a transperineal approach; the transperineal approach is generally performed as a stereotactic template-guided procedure with general anesthesia.

**Policy:**
Saturation biopsy, taking 20 or more core tissue samples at one time, **does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** in the diagnosis, staging, and management of prostate cancer.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and*
his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
In reviewing the studies, it is important to note that the studies all reflect diagnostic yields (finding cancer) or changes in tumor stage/grade. No studies were identified that link the use of saturation biopsy to clinical outcomes. In addition, the majority of studies were case series of patients who underwent saturation biopsy, rather than a comparative study of various biopsy techniques.

Initial Biopsy
In 2013, Jiang et al published a systematic review and meta-analysis of studies evaluating the utility of an initial transrectal saturation biopsy compared with an extended biopsy strategy. A total of eight studies with 11,997 participants met eligibility criteria (i.e., compared the two biopsy strategies on initial biopsy). Two of the studies were randomized controlled trials (RCTs), one used a paired design, and five were non-RCTs. Overall, prostate cancer was diagnosed in 2328 of 5486 men (42.4%) who underwent saturation biopsy compared with 2562 of 6511 men (39.3%) who had extended biopsy. The detection rate was statistically significantly higher in the saturation biopsy group (risk difference [RD], 0.004; 95% confidence interval [CI], 0.01 to 0.008; p=0.002). When only the higher quality studies were included in the meta-analysis (i.e., the RCTs and prospective paired design), the detection rate was statistically significantly higher with saturation biopsy (RD=0.03; 95% CI, 0.01 to 0.05; p=0.01). For the analysis limited to higher quality studies, the authors did not report the proportion of men in each group diagnosed with prostate cancer. Although the authors found statistically significantly higher rates of diagnosis in their overall pooled analyses, the degree of difference in diagnosis rates may not be clinically significant.

In a subgroup analysis, in patients with prostate-specific antigen (PSA) less than 10 ng/mL, prostate cancer was diagnosed in 998 of 2597 men (38%) in the saturation biopsy group and 1135 of 3322 men (34%) in the extended biopsy group. The diagnosis rate was significantly higher in men receiving the saturation biopsy protocol (RD=0.04; 95% CI, 0.01 to 0.07; p=0.002). As in the overall analysis, the clinical significance of this degree of difference is unclear. There was not a statistically significant difference between groups in the diagnostic yield for men with PSA greater than 10 ng/mL (RD=0.03; 95% CI, -0.01 to 0.08; p=0.15).

As a recent example, a 2013 retrospective nonrandomized study by Li et al reviewed data on 438 men who received an initial saturation biopsy and 3338 men who had an initial extended prostate biopsy. In an analysis stratified by PSA values, there was a statistically significantly higher rate of prostate cancer detection using a saturation biopsy strategy in men with a PSA less than 10 ng/mL. Detection rates among men with PSA less than 4 ng/mL were 47.1% with saturation biopsy (40/85) and 32.8% with extended biopsy (288/878) (p=0.008). Rates among men with PSA between 4 and 9.9 ng/mL were 50.9% with saturation biopsy (144/283) and 42.9% with extended biopsy (867/2022) (p=0.011). There was not a statistically significant difference in
detection rates between groups when PSA was greater than 10 ng/mL. Detection rates in men with PSA greater than 10/ng/mL were 60% with saturation biopsy (42/70) and 61% with extended biopsy (267/438) (p=0.879).

A general limitation of the data on saturation biopsy as an initial prostate biopsy strategy is that they do not address the impact on health outcomes of increased diagnosis rate at initial biopsy.

**Repeat Biopsy**

Mabjeesh et al reported on a high-risk group of men with at least two previous negative transrectal biopsies who then underwent transperineal template-guided saturation biopsy. Prostate cancer was detected in 26% of the 92 patients, predominantly in the anterior zones. A median of 30 cores was taken in the saturation biopsies. Gleason score of 7 or higher was detected in 46% of the diagnosed men. Most of the tumors (83.3%) were found in the anterior zones of the gland, with a significantly higher number of positive cores versus the posterior zones (mean 4.9 vs 1.5, p= 0.015).

A study cited by the National Comprehensive Cancer Network (NCCN) 2012 prostate cancer guidelines was published in 2001 by Stewart et al. The study included 224 men with previous negative biopsies who underwent saturation biopsy. With saturation biopsy, cancer was detected in 77 of 224 patients (34%). However, the study was retrospective, did not compare saturation biopsy with a repeat standard biopsy, and did not report health outcomes.

Lee et al evaluated the role of transrectal saturation biopsy for cancer detection in men with high-grade prostatic intraepithelial neoplasia (HGPIN) diagnosed by extended biopsy. From 1999 to 2009, 314 men had at least one or more repeat biopsies due to the presence of exclusive HGPIN (without any other pathologic finding) in a previous extended biopsy. They were divided into two groups according to the initial follow-up biopsy scheme; 178 men were followed up using a second standard extended biopsy scheme, and 136 were followed up using the saturation biopsy scheme. In the standard repeat biopsy group, 35 of 178 (19.7%) men had cancer on initial repeat biopsy. In the saturation biopsy group, 42 of 136 (30.9%) had cancer on initial repeat biopsy (overall, p=0.04). Multivariate analysis demonstrated that the biopsy scheme on repeat biopsy was an independent predictor of prostate cancer detection (odds ratio [OR], 1.85; CI, 1.03 to 3.29), exclusive of age, PSA-level, days from initial biopsy, digital rectal exam (DRE) status, and multifocal prostatic epithelial neoplasia (PIN). Pathologic findings on repeat biopsies demonstrated similar Gleason grades, regardless of biopsy technique: Gleason 6 was present in 74.3% and 73.1% of specimens in the standard and saturation schemes, respectively. The presence of a Gleason score of 8 or higher was 8.6% and 9.5%, respectively.

Giulianelli et al evaluated whether or not the saturation biopsy technique increased the cancer detection rate in patients with PSA less than 10 ng/mL, after a first negative biopsy. From January 2004 to January 2006, 780 patients underwent prostate ultrasound-guided transrectal core biopsies: 186 (23.8%) were diagnosed with prostate cancer, while 594 (76.2%) had negative biopsies. For one year, all of the patients with no evidence of cancer were observed according to a follow-up schedule including PSA check every three months and DRE every six months. During this period, 140 patients showed an increase of PSA (<10 ng/mL) or a low PSA free/total. This group underwent a second ultrasound-guided transrectal core biopsy with
saturation technique under general anesthesia. Of the 140 patients, 50 (35.7%) had prostate cancer showing a Gleason score of 4 or 5 in 26%, 6 or 7 in 75%, and 8 to 10 in 9%, respectively. Apical biopsies carried out in the anterior horn of peripheral zone tissue showed cancer in 35 patients (70% of those rebiopsied), versus 24% in lateral zones, and 5% for parasagittal. Cancer in the patients who underwent the saturation biopsy was considered clinically significant (defined as Gleason score of ≥7 and tumor volume > 0.5 cc) in 47 patients (94%). Forty-eight of the 50 underwent a radical prostatectomy and two underwent external beam radiation therapy. The authors concluded that the saturation biopsy technique increased the cancer detection rate by 36% in patients with PSA less than 10 ng/mL, after a first negative biopsy, and showed a higher positivity (70% prostate cancer detection rate) if the saturation biopsy included the anterior horn of peripheral zone tissue. No significant pain or side effects were observed.

Zaytoun et al reported the results of a prospective, nonrandomized comparative study of extended biopsy versus office-based transrectal saturation biopsy in a repeat biopsy population. After an initially negative biopsy, 1056 men underwent either a repeat 12- to 14-core biopsy (n=393) or a 20- to 24-core repeat biopsy (n=663) at the discretion of the attending urologist’s practice pattern. Indications for second biopsy included a previous suspicious pathologic finding and/or clinical indications such as abnormal DRE, persistently increased PSA, and PSA increasing greater than 0.75 ng/mL annually. Prostate cancer was detected in 29.8% (n=315) of repeat biopsies. The saturation biopsy group had a detection rate of 32.7% versus 24.9% in the extended biopsy group (p=0.008). Of the 315 positive biopsies, 119 (37.8%) revealed clinically insignificant cancer (defined as Gleason sum <7, a total of three or fewer positive cores, and a maximum of 50% or less of cancer in any positive core). There was a trend toward increased detection of clinically insignificant cancer detection in the saturation versus the extended biopsy cases, 40.1% versus 32.6%, respectively (p=0.02).

Simon et al reported on the results of using an extensive saturation biopsy in 40 men with a clinical suspicion of prostate cancer after previous negative prostate biopsies. The median number of cores taken was 64 (range, 39-139) and was adjusted to the size of the prostate. Of the 40 men, 18 (45%) had cancer in at least one core. Sixteen men had marked hematuria after the biopsy procedure. The investigators concluded there was no significant increase in the cancer detection rate with this extensive saturation biopsy regimen compared with published series with fewer cores, but there was increased morbidity.

Eichler et al conducted a systematic review of cancer detection rates and complications of various prostate biopsy schemes. They pooled data that compared various extended biopsy schemes in studies involving 20,698 patients. The authors concluded that prostate biopsy schemes consisting of 12 cores that add laterally directed cores to the standard sextant scheme seem to have the right balance between the cancer detection rate and adverse events and that taking more than 12 cores added no significant benefit.

Localized Disease
There also are discussions of using saturation biopsy as a technique to identify a localized area of prostate cancer that could be treated with subtotal cryoablation. However, given the limited data on the efficacy of this treatment approach, using saturation biopsy to determine if localized disease is present would be considered investigational.
Active Surveillance
While some have suggested that saturation biopsy could be a part of active surveillance (a treatment approach for men with prostate cancer that involves surveillance with PSA, DRE, and routine prostate biopsies, in men whose cancers are small and expected to behave indolently) in terms of being able to possibly and more accurately assess tumor volume and/or tumor grade, there are no studies that link this potential use to improved outcomes.

Ayres et al evaluated the role of transperineal template prostate biopsies in 101 men on active surveillance for prostate cancer. The men underwent restaging transperineal template prostate biopsies at a single center. The criteria for active surveillance were: age 75 years or younger, Gleason at least 3+3, PSA at least ng/mL, clinical stage T1-2a, and at least 50% ultrasound-guided transrectal biopsy cores positive for cancer, with at least 10 mm of disease in a single core. The number of men with an increase in disease volume or Gleason grade on transperineal template biopsy and the number of men who later underwent radical treatment were assessed. The role of PSA and PSA kinetics were studied. In all, 34% of men had more significant prostate cancer on restaging transperineal template biopsies compared with their transrectal biopsies. Of these men, 44% had disease predominantly in the anterior part of the gland, an area often undersampled by transrectal biopsies. In the group of men who had their restaging transperineal template biopsies within six months of commencing active surveillance, 38% had more significant disease. There was no correlation with PSA velocity or PSA doubling time. In total, 33% of men stopped active surveillance and had radical treatment. The study concluded that around one-third of men have more significant prostate cancer on transperineal template biopsies and that this probably reflects undersampling by initial transrectal biopsies rather than disease progression.

In 2012, Linder et al reviewed data on 500 consecutive patients who underwent standard template prostate biopsy (12 cores) or saturation biopsy (at least 18 cores) before radical prostatectomy. The authors identified 218 patients who would have been candidates for active surveillance. Criteria were Gleason score no greater than 6, clinical stage T1 or T2a, PSA <10 ng/mL, and involvement of no more than 33% of cores. Among these 218 patients, 124 had undergone standard biopsy and 94 underwent saturation biopsy. In a multivariate analysis, biopsy method was not a significant predictor of upstaging upon analysis of pathologic findings (p=0.26). In addition, the five-year biochemical failure-free survival rates (defined as PSA at least 0.4 ng/mL) were not significantly different in the two groups: rates were 97% for standard biopsy and 95% for saturation biopsy (p=0.11). The authors concluded that standard biopsy and saturation biopsy are equally effective for identifying candidates for active surveillance.

Improving Correlation between Biopsy and Operative Stage
Similarly, data are lacking on a potential use of saturation biopsy to assist in more accurately assessing tumor grade/stage when the treatment regimen is determined through biopsy rather than through surgical removal of the prostate. Evaluation of such an approach would require either a randomized trial or determining treatment plans for a group of patients based on use of varying numbers of their biopsy specimens.
Clinical Input Received Through Physician Medical Societies and Academic Medical Centers

In response to requests, input was received through three physician specialty societies and three academic medical centers while this policy was under review in 2014. There were five responses from one specialty society, four responses from another, and one from the third for a total of 10 specialty society responses. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Most reviewers stated that saturation biopsy is considered investigational and did not think that saturation biopsy in patients with two prior negative biopsies and persistently rising PSA level is considered medically necessary. Clinicians proposed various options that could be used in the situation of prior negative biopsies and a rising PSA: there was no consensus on the best alternative approach. Suggestions included magnetic resonance imaging (MRI) with transrectal ultrasound, multiparametric MRI, and 3T pelvic MRI. There was near consensus that there is insufficient evidence to support use of any of these techniques in the situation being considered.

Summary

Studies showing improved initial detection of prostate cancer using saturation biopsy compared to the use of extended biopsies are lacking. The use of saturation biopsy as a repeat biopsy after prior negative biopsies in men with persistent clinical suspicion of prostate cancer appears to increase the detection rate of cancer, particularly in the anterior zones. However, evidence is lacking as to whether this leads to improved health outcomes, including the possibility of detecting clinically insignificant cancers, which could lead to unnecessary treatment. Few studies show improvement in clinical outcomes with the use of saturation biopsy as part of active surveillance. Thus, the technique of saturation biopsy, taking 20 or more core tissue samples, is considered investigational.

National Comprehensive Cancer Network (NCCN) Guidelines

NCCN guidelines (V2 2012) on prostate cancer early detection state that in patients with two negative extended biopsies, yet persistently rising PSA values, a saturation biopsy may be considered (category 2A). The guidelines cite a study by Stewart et al, published in 2001, of men with previous negative biopsies who underwent saturation biopsy. (The study is discussed earlier, in the Rationale section.) NCCN guidelines do not state the reasoning behind this 2A recommendation.

Key Words:
Biopsy, Prostate, Saturation

Approved by Governing Bodies:
Not applicable
**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.
Pre-certification requirements: Not applicable

**Coding:**
CPT Codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>55706</td>
<td>Biopsies, prostate, needle, transperineal, stereotactic template guided saturation sampling, including imaging guidance</td>
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<td>G0416</td>
<td>Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, 1-20 specimens</td>
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<td>Screening cytopathology smears, cervical or vaginal, performed by automated system under physician supervision, 21 – 40 specimens</td>
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<td>Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, 41-60 specimens</td>
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<td>G0419</td>
<td>Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, greater than 60 specimens</td>
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**References:**

Policy History:
Medical Policy Group, December 2009 (3)
Medical Policy Administration Committee, January 2010
Available for comment January 26-March 11, 2010
Medical Policy Group October 2010 (3)
Medical Policy Group, October 2011 (1): Update to Key Points and References related to MPP update; no change in policy statement
Medical Policy Panel, October 2012
Medical Policy Group, November 2012 (1): 2012 Updates to Key Points and References
Medical Policy Group, November 2012: Added 2013 HCPCS Code updates
Medical Policy Panel February 2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.