

Subject: Prostate Saturation Biopsy**Document #:** SURG.00107**Status:** Reviewed**Publish Date:** 09/27/2023**Last Review Date:** 08/10/2023

Description/Scope

This document addresses prostate saturation biopsy, also called prostate saturation needle biopsy, which involves taking numerous samples of prostate tissue in order to increase the likelihood of detecting prostate cancer in a subgroup of high-risk individuals in whom previous conventional prostate biopsies have been negative.

Note: Please see the following related documents for additional information:

- [CG-MED-45 Transrectal Ultrasonography](#)
- [CG-SURG-98 Prostate Biopsy using MRI Fusion Techniques](#)

Position Statement

Investigational and Not Medically Necessary:

Transrectal ultrasound-guided prostate saturation biopsy is considered **investigational and not medically necessary**.

Transperineal stereotactic template-guided prostate saturation biopsy is considered **investigational and not medically necessary**.

Rationale

Background

In the past, an elevated prostate specific antigen (PSA) level, or possibly a suspicious digital rectal examination (DRE) finding, would prompt a prostate biopsy. Multi-parametric magnetic resonance imaging (mpMRI), when available, is now recommended prior to obtaining a prostate biopsy as it has been shown to significantly increase the detection of clinically significant, higher risk disease while lowering the detection of lower-risk disease (National Comprehensive Cancer Network® [NCCN®], V1.2023). A transrectal or transperineal ultrasound guided biopsy can be performed in lieu of, or following, mpMRI evaluation. Typically, the initial biopsy consists of a 12-14 core biopsy of the prostate in an extended pattern, sextant medial and lateral peripheral zone and lesion directed. Based on concerns about false-negative biopsies and misclassification of a tumor as low grade due to under-sampling, prostate saturation biopsy, with 20 to 40 biopsy cores sampled, was developed.

An American Urological Association (AUA, 2018) guideline states that early detection of prostate cancer is driven by PSA-based screening followed by prostate biopsy for diagnostic confirmation. The AUA Panel recommends:

...that the urologist should consider factors that lead to an increased PSA including prostate volume, age, and inflammation rather than using an absolute level to determine the need for a prostate biopsy - keeping in mind that PSA is not a dichotomous test but rather a test that indicates the risk of a harmful cancer over a continuum. The Panel believes that postponing and/or avoiding a prostate biopsy 1) in a man with a large prostate, 2) in the older male especially if in less than excellent health, and 3) in the setting of a suspicion of prostatic inflammation, would be acceptable even at PSA levels exceeding 3-4 ng/mL.

A 2015 AUA white paper, *AUA/Optimal Techniques of Prostate Biopsy and Specimen Handling*, addresses concerns regarding the use of saturation biopsy noting:

As the number of cores increases, the diagnostic yield becomes more marginal. Only limited evidence supports the use of initial biopsy schemes involving more than 12 cores or saturation...The differences in populations studied makes comparing the results from the studies of protocols involving different numbers of cores challenging. Patient age, serum PSA, ethnicity, and family history all influence cancer detection rate (CDR) for any biopsy strategy. What can be concluded from the literature is that increasing core number increases CDR and sextant biopsy results in an unacceptably high likelihood of false-negative results, leading to under detection of clinically significant cancers. Increasing core numbers using saturation techniques might identify cancers missed on extended core sampling but this strategy also increases the risk of over detection of indolent cancers without significantly improving CDR or pathology concordance.

Transperineal versus transrectal

In a meta-analysis and sequential analysis, Xue and associates (2017) compared transrectal and transperineal approaches in the detection of prostate cancer. There were no significant differences between the approaches in terms of efficiency or complications. The transperineal approach was reported as preferable in terms of pain relief and the need for additional anesthesia.

The NCCN Clinical Practice Guideline (CPG) for prostate cancer early surveillance (V1.2023) states:

Saturation biopsies can be performed via transrectal or transperineal approaches, the latter of which is often image-guided. The transrectal and transperineal saturation approaches seem to have similar rates of cancer detection...The transperineal approach may have a lower risk of infection, may allow for better saturation of the gland, and may be more acceptable to patients compared with the transrectal approach... Another possible benefit of transperineal versus transrectal approach is more accurate risk assessment (cancer volume and stage). However, the transperineal approach may be associated with a higher rate of urinary retention. The transrectal approach can be performed routinely in the office whereas transperineal biopsy often requires more extensive local or systemic analgesia.

Initial Biopsy

The NCCN recommends the use of a transrectal or transperineal systematic prostate biopsy under transrectal ultrasound (TRUS) guidance with or without the targeting lesions identified with pre-biopsy MRI. The recommendation is expanded by noting that an extended pattern, sextant medial and lateral peripheral zone, lesion directed, with at least 12 cores should be used. The use of targeted biopsy techniques, cognitive or visual targeting, along with a systematic sampling might result in better improved sensitivity (V1.2023). Early literature evaluated the use of saturation biopsy in obtaining the initial biopsy cores. Cancer detection rates of saturation biopsies were compared to those of standard systematic approaches. The use of saturation biopsies did not improve the detection of cancer or abnormal prostate pathology and may be associated with increased morbidity (Chun, 2011; Jones, 2006; Lane, 2008; Sur, 2004).

Jiang and colleagues (2013) published a systematic review and meta-analysis of studies evaluating the utility of an initial transrectal saturation biopsy compared to an extended biopsy strategy. Eight studies with 11,997 participants who underwent TRUS-guided biopsies for the first time and met other eligibility criteria were included in the analysis. Two of the studies were randomized controlled trials (RCTs), one study used a prospective paired design, and five were nonrandomized controlled studies. Prostate cancer was diagnosed in 42% (2328/5486) of participants who underwent saturation biopsy, compared to 39% (2562/6511) of participants 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 ($n=3$) were included in the meta-analysis, the two 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 individuals with PSA less than 10 ng/mL, prostate cancer was diagnosed in 38% (998/2597) of participants in the saturation biopsy group and 34% (1135/3322) of participants in the extended biopsy group. The diagnosis rate was significantly higher in those 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 individuals with PSA > 10 ng/mL (RD 0.03; 95% CI, -0.01 to 0.08; $p=0.15$).

Whether the increased detection rate by more extensive saturation biopsy is due to the additional biopsy cores or the location from which the cores are taken is still unknown. The *AUA/Optimal Techniques of Prostate Biopsy and Specimen Handling* white paper (2015) on saturation biopsy performed using the transrectal approach concludes that "...the results of biopsy schemes involving more than 12 cores or saturation biopsies appear to have a higher concordance rate with results from prostatectomy, but they also appear to increase the rate of insignificant cancer detection." A potential disadvantage of an initial saturation biopsy strategy is that taking an increased number of cores could escalate the risk of detection of clinically insignificant cancer and lead to over-diagnosis and overtreatment. While the data suggests an increase in the rate of diagnosis of prostate cancer using saturation techniques, there is no peer-reviewed literature which conclusively demonstrates that this approach results in reduced mortality or other clinically significant outcomes when compared to standard biopsy protocols.

Repeat Prostate Biopsy

The NCCN CPG for early detection of prostate cancer (V1.2023) recommends an MRI or the use of refined prostate biopsy techniques for individuals with at least one prior negative prostate biopsy and high suspicion for cancer. NCCN further notes:

Multiparametric MRI followed by lesion targeting increases the detection of clinically significant, higher-risk disease while lowering the detection of lower-risk disease. Although some advocate for excluding systematic biopsy in those undergoing MRI targeting, most advocate for a combined approach as some high-grade cancers are uniquely detected using the systematic approach.

Prior to the use of mpMRI and targeted biopsies, a number of studies were published comparing saturation biopsy techniques with other biopsy techniques. The results were conflicting, showing no additional benefit in a saturation biopsy (Eichler, 2006; Simon, 2008; Stay, 2008) or improved sensitivity at the expense of an increased complication rate or an increased detection of indolent cancers (Bittner, 2013; Zaytoun, 2011).

Scattoni and colleagues (2014) performed an analysis of the peer-reviewed literature to identify the optimal approach for a repeat prostate biopsy scheme. The authors state the recommended approach in a repeat biopsy setting is a 12-core, extended scheme biopsy technique; a sampling with more than 12 cores may optimize cancer detection in individuals with specific clinical characteristics. A saturation biopsy strategy of 20 or greater cores "...clearly improves cancer detection if clinical suspicion persists after previous negative biopsy." However, "...international guidelines do not strongly recommend a saturation biopsy in all situations of repeated setting." At present, an extended prostate biopsy "is still the gold standard" even if saturation biopsy seems to be necessary in many cases. This analysis was performed prior to the widespread use of mpMRI testing.

In a retrospective study involving 103 individuals undergoing repeat biopsy using transperineal template-guided saturation biopsy, Nakai and colleagues (2017) evaluated the cancer detection rate. Participants included those with previous negative TRUS-guided biopsy undergoing a repeat biopsy with one of the following risk factors: increased PSA levels; abnormal digital rectal examination, TRUS or MRI findings or previous biopsy showing high-grade prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation (ASAP). A total of 53 individuals (51.5%) were diagnosed with prostate cancer and 42 of these individuals (79.2%) were diagnosed with clinically significant prostate cancer. While the authors noted the high cancer detection rate along with a high detection rate of clinically significant disease, the study did not include a comparator group with the current recommended biopsy technique.

Drost and associates (2019) compared the diagnostic accuracy of index tests (MRI only, MRI-targeted biopsy, the MRI pathway, and systematic biopsy) against template-guided biopsies including template-guided saturation biopsy. For the purpose of this review, the MRI pathway is defined as MRI with or without MRI-targeted biopsy. A total of 18 studies, which included both initial and repeat biopsy studies were evaluated. The authors concluded that, compared to systematic biopsies, the MRI pathway is associated with the most favorable diagnostic accuracy. The current NCCN CPG for prostate cancer early detection (V1.2023) does not include a saturation biopsy in the algorithm pathway. The use of MRI to obtain targeted biopsies, either immediately preceding or direct MRI guidance, resulted in improved detection of clinically significant prostate cancer. A combined approach using both image-guided biopsy and systematic sampling can be used, as some high-grade cancers can be detected by systematic sampling of up to 12 cores. These high-grade cancers may be missed using only image guidance (Rouvière, 2019; Siddiqui, 2015). While there is some evidence that a saturation biopsy, when compared to an extended biopsy, may detect more cancers in individuals with at least one previous negative biopsy, the NCCN panel notes the following:

Despite this emerging evidence, the panel does not recommend a saturation biopsy strategy for all men with previous negative biopsies at this time given the benefits seen for MRI and MRI-targeted biopsy in this patient population.

In a prospective study, Pepe and colleagues (2020) evaluated the use of saturation biopsy combined with mpMRI targeted biopsy.

The studied population included individuals with a history of a negative DRE and biopsy who were undergoing repeat biopsy for a suspicion of cancer due to a rising or persistently elevated PSA (n=875). All individuals underwent mpMRI prior to biopsies. Lesions categorized as 3 or greater underwent targeted biopsies in addition to saturation biopsies in which 30 cores were sampled. The authors noted that a maximum of 20 systematic transperineal cores detected all cases of clinically significant prostate cancers. The authors concluded that for individuals undergoing repeat evaluations, systematic biopsies should be combined with targeted biopsy rather than be replaced by targeted biopsies. There were a number of limitations associated with the study including not using MRI guidance during the biopsy and evaluating the results based only on the biopsy specimens. The study did not include a comparison to the NCCN referenced combined approach of image guided biopsy and systematic biopsy of up to 12 cores. Further studies using the current recommended diagnostic approaches as a control are needed.

Use of transrectal ultrasound-guided prostate saturation biopsy in individuals with a rising PSA, and with both previous negative biopsies and MRI has not been specifically studied. Further studies are needed to evaluate the value of saturation biopsy in the age of mpMRI and combined systematic biopsies.

High-grade Prostatic Intraepithelial Neoplasia (HGPIN) and Atypical Small Acinar Proliferation (ASAP)

HGPIN and ASAP are non-malignant but pathologically atypical findings on a prostate biopsy. In approximately 10% of prostate biopsies, HGPIN will be detected and 5% of prostate biopsies will detect ASAP (NCCN, V1.2023; Totaro, 2021). In the case of individuals with an initial ASAP biopsy, approximately 50% will be diagnosed with cancer on repeat biopsy, typically in the area of the prostate which demonstrated atypia in the initial biopsy (NCCN, V1.2023). The prevalence of cancer diagnosed on repeat biopsy following an initial HGPIN is approximately 10-20%. In HGPIN, cancers detected on repeat biopsies tend to be low-grade (NCCN, V1.2023).

The current NCCN CPG for prostate cancer early detection (V1.2023) recommends a repeat PSA and DRE at 6-to-24-month intervals followed by a potential repeat biopsy with refined techniques, based on risk, for either HGPIN and ASAP. Saturation biopsy is not included as a considered or recommended diagnostic technique for managing individuals with HGPIN or ASAP. The AUA guideline on the early detection of prostate cancer (2018) does not address the use of saturation biopsy in the further evaluation of HGPIN or ASAP.

Early studies evaluated the potential role of saturation biopsy in cancer detection in individuals with ASAP or HGPIN (Ashley, 2008; Lee, 2011). With the advent of mpMRI and extended biopsies (12-14 cores), there have been limited retrospective studies addressing saturation biopsy in HGPIN or ASAP (Nakai, 2017; Totaro, 2021).

Active Surveillance

The NCCN CPG on prostate cancer (V1.2023) recommends that active surveillance can be undertaken following careful consideration of the individual's prostate cancer risk profile, age and health. Active surveillance consists of monitoring not more often than every 6 months, and possibly surveillance prostate biopsies. The NCCN CPG recommends that a needle biopsy should be repeated within 6 months of diagnosis if the initial biopsy was less than 10 cores or there were discordant findings. The NCCN summarizes biopsy protocols in active surveillance noting:

Early experience supports the utilization of mpMRI in biopsy protocols to better risk stratify men under active surveillance. However, more recent studies have shown that a significant proportion of high-grade cancers are detected with systemic biopsy and not targeted biopsy in men on active surveillance.

The NCCN CPG does not specifically address saturation biopsy in the active surveillance algorithm. The evidence supporting the above summary regarding systematic biopsy did not include studies which used saturation biopsy techniques.

Linder and colleagues (2013) reviewed data on 500 consecutive individuals who underwent TRUS-guided biopsy by a standard template (12 cores) or saturation template (≥ 18 cores, median 27 cores) with subsequent radical prostatectomy. The authors examined the ability of standard and saturation transrectal prostate biopsy techniques to predict appropriate candidates for active surveillance. A total of 218 individuals were identified who were potential candidates for active surveillance using the criteria of Gleason score of greater than 6, clinical stage T1 or T2a, PSA < 10 ng/mL, and involvement of no more than 33% of cores. A standard biopsy was performed in 124 individuals and saturation biopsy in 94 individuals. In a multivariate analysis, the biopsy method was not a significant predictor of upstaging on analysis of pathological findings ($p=0.26$). The 5-year biochemical failure-free survival estimates, defined as PSA at least 0.4 ng/mL, were not significantly different in the standard biopsy group compared to the saturation biopsy group, 97% versus 95% ($p=0.11$), respectively. A conclusion drawn from this review is that in men with prostate cancer, standard and saturation transrectal prostate biopsies techniques may be equally predictive of candidates for active surveillance.

In summary, the role of prostate saturation biopsy in the detection of prostate cancer is unclear. While there is some promising, but limited evidence supporting saturation biopsies, additional well-conducted studies are needed to determine the clinical utility of prostate saturation biopsy, showing that it improves health outcomes when used in place of or in addition to, imaging techniques such as mpMRI.

Background/Overview

Prostate cancer is the second most common diagnosed cancer in North American men. In 2023, there will be an estimated 288,300 new cases and 34,700 disease-related deaths from prostate cancer in the United States. Prostate cancer is the second leading cause of cancer death in American men (American Cancer Society [ACS], 2023; National Cancer Institute [NCI], 2023).

The gold standard for diagnosis of prostate cancer is a prostate biopsy. According to the NCI (2023):

Needle biopsy is the most common method used to diagnose prostate cancer. Most urologists now perform a transrectal biopsy using a bioptic gun with ultrasound guidance. Less frequently, a transperineal ultrasound-guided approach can be used in patients who may be at increased risk of complications from a transrectal approach. Over the years, there has been a trend toward taking eight to ten or more biopsy samples from several areas of the prostate with a consequent increased yield of cancer detection after an elevated PSA blood test.

The prostate saturation biopsy procedure is based on the assumption that the cancer is small or located in one of the deeper reaches of the prostate gland. The whole gland is sampled without following any particular zonal pattern. It is theorized that the larger the number of evenly distributed samples increases the probability of detecting an underlying cancer, regardless of the tumor size or location. Saturation sampling typically involves 20- to 40-core biopsies, with additional cores taken for larger prostates. Saturation biopsy technique is similar to the sextant or the extended biopsy performed during the TRUS-guided biopsy procedures. A template or grid identifies the exact location of each biopsy core so the exact location and size of the tumor can be mapped. Either regional or general anesthesia or intravenous sedation is typically used. Another method of performing saturation biopsy involves utilizing a

transperineal template or grid-based method, known as transperineal template-guided saturation biopsy, or TPSB, using a brachytherapy template. This method has been proposed to be more systematic and allows for improved sampling of the area immediately anterior to the urethra (Raja, 2006).

While prostate biopsies are the gold standard in diagnosing prostate cancer, the use of MRI has revised the approach to biopsies. In contrast to systematic biopsies, such as saturation biopsies, targeted biopsies can be performed on clinically significant suspect lesions detected by MRI. MRI techniques have been shown to be able to accurately detect clinically significant prostate cancer while purposefully detecting less indolent prostate cancer (Drost, 2019).

A number of risks and complications are associated with prostate biopsies. These risks include infection (1-8%) or life-threatening infection due to antibiotic resistance (Drost, 2019). Other risks include epididymitis, orchitis, prostatitis, dysuria, hematospermia, hematuria, rectal bleeding, vasovagal episodes and urinary retention (Drost, 2019; Klein, 2010).

Definitions

Active surveillance: Active monitoring of the course of disease with the intent of administering curative therapy in the event the cancer progresses.

Biopsy: The removal of a sample of tissue for examination under a microscope for diagnostic purposes.

Digital rectal examination (DRE): An examination of the lower rectum where the medical practitioner uses a gloved, lubricated finger to check for abnormalities of the prostate.

Gleason Grading System: A prostate cancer grading system based on a number range from one to five; the lower the number, the lower the grade, and the slower the cancer growth.

Gleason score: Represents the sum of the two most common Gleason grades observed by the pathologist on a specimen, the first number is the most frequent grade seen.

Prostate: A walnut-shaped gland in men that extends around the urethra at the neck of the urinary bladder and supplies fluid that goes into semen.

Prostate mapping: A procedure involving a combination of multi-sequence magnetic resonance imaging (MRI) techniques and a template guided biopsy system used to diagnosis prostate cancer.

Prostate-specific antigen (PSA): A blood test that measures the amount of a specific prostate-related protein in blood, used to screen for prostate cancer and other conditions. A high PSA level in the blood has been linked to an increased chance of having prostate cancer.

Radical prostatectomy: Surgical procedure for the removal of the prostate.

Targeted biopsy: Biopsies in which needle placement is guided by potential abnormalities located via imaging.

Transrectal ultrasound (TRUS): An ultrasound test in which the sound waves are produced by a probe inserted into the rectum. In men, the structures most commonly examined with this test are the prostate, bladder, seminal vesicles and ejaculatory ducts.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

CPT

55706	Biopsies, prostate, needle, transperineal, stereotactic template guided saturation sampling, including imaging guidance
55899	Unlisted procedure, male genital system [when specified as transrectal ultrasound-guided saturation biopsy of the prostate]

ICD-10 Diagnosis

All diagnoses

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Index

3D Mapping Biopsy

Transperineal Stereotactic Template-guided Saturation Prostate Biopsy

Transperineal Template-guided Saturation Biopsy (TTSB)

Transrectal Ultrasound-guided (TRUS) Prostate Biopsy

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
Reviewed	08/11/2022	MPTAC review. Updated Rationale, Background, Definitions and References sections.
Reviewed	08/12/2021	MPTAC review. Updated Rationale, Background, References and Websites sections.
Reviewed	02/11/2021	MPTAC review. Updated Description, Rationale, and References sections.
Reviewed	02/20/2020	MPTAC review. Updated Rationale, Background, References and Websites sections.
Reviewed	03/21/2019	MPTAC review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Updated Description, Rationale, Background, References and Websites sections.
Reviewed	05/03/2018	MPTAC review.
Reviewed	05/02/2018	Hematology/Oncology Subcommittee review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale, Background, References, and Websites for Additional Information sections.
Reviewed	05/04/2017	MPTAC review.
Reviewed	05/03/2017	Hematology/Oncology Subcommittee review. Updated Rationale, Background and References sections.
Reviewed	05/05/2016	MPTAC review.
Reviewed	05/04/2016	Hematology/Oncology Subcommittee review. Updated Description, Rationale, Background, References, and Websites for Additional Information sections. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review.
Reviewed	05/06/2015	Hematology/Oncology Subcommittee review. Updated Description, Rationale, References, and Websites for Additional Information sections.
Reviewed	02/05/2015	MPTAC review. Format changes throughout the document. Updated Rationale, Background, References, and Websites for Additional Information sections.
	01/01/2015	Updated Coding section with 01/01/2015 HCPCS changes; removed G0417, G0418, G0419 deleted 12/31/2014 and G0416 (no longer applicable).
Revised	02/13/2014	MPTAC review. Revised investigational and not medically necessary statement, removing number of core samples. Updated Rationale, Background, Coding, References, and Websites for Additional Information sections.
	01/01/2014	Updated Coding section with 01/01/2014 HCPCS descriptor changes.
Reviewed	02/14/2013	MPTAC review. Updated Rationale, Background, References, Websites for Additional Information, and Index.
Revised	02/16/2012	MPTAC review. Revised investigational and not medically necessary statement, separately addressing transrectal and transperineal saturation biopsy techniques. Reformatted and updated the Rationale, Coding, References, and Websites for Additional Information.
Reviewed	11/17/2011	MPTAC review.
Reviewed	11/16/2011	Hematology/Oncology Subcommittee review. Updated Rationale, Background, References, and Websites for Additional Information.
Reviewed	11/18/2010	MPTAC review.
Reviewed	11/17/2010	Hematology/Oncology Subcommittee review. Updated Description, Rationale, Background, Definitions, References, Websites for Additional Information and Index.
Reviewed	11/19/2009	MPTAC review.

Reviewed	11/18/2009	Hematology/Oncology Subcommittee review. Updated Rationale, Background, and References.
New	11/20/2008	MPTAC review.
New	11/19/2008	Hematology/Oncology Subcommittee review. Initial document development.

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