Review Article

Personalized prostate biopsy protocols: enhancing cancer detection through tailored approaches—a narrative review

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Background and Objective: Traditionally, patients with positive magnetic resonance imaging (MRI) results [i.e., Prostate Imaging-Reporting and Data System (PI-RADS) ≥3] would have to undergo both targeted and systematic biopsies. The 2024 European Urology Association guidelines now recommend incorporating perilesional sampling with targeted biopsy; however, these recommendations have not yet been widely adopted. This review aims to examine recent advancements in personalized prostate biopsy techniques to enhance cancer detection through tailored approaches.

Methods: We conducted a narrative review to highlight recent advancements in personalized prostate biopsy techniques, emphasizing the roles of serum prostate-specific antigen (PSA) levels, prostate volume (PV), PSA density (PSAD), region of interest (ROI), and PI-RADS scores.

Key Content and Findings: This review discusses personalized prostate biopsy protocols, integrating PSA levels, PV, PSAD, and PI-RADS scores. Tumor localization can be refined using transrectal or transperineal approaches. For patients with lower PSA levels (4–19.99 ng/mL), smaller PSAD (<0.1 ng/mL/cc), or PI-RADS 3 lesions, a targeted plus systematic biopsy or regional saturation biopsy may be appropriate. For those with medium PSA levels (20–50 ng/mL), PSAD (0.1–0.2 ng/mL/cc), or PI-RADS 4 lesions, regional saturation biopsy is preferred. Targeted biopsy is recommended for higher PSA levels (>50 ng/mL), PSAD (>0.2 ng/mL/cc), or PI-RADS 5 lesions. Variability in cut-off values across studies precludes meta-analysis, limiting our work to a systematic review.

Conclusions: Personalized prostate biopsy protocols considering PSA levels, PV, PSAD, ROI, and PI-RADS scores can improve prostate cancer detection accuracy. Further research and clinical validation are needed to optimize these personalized methods.

Keywords: Prostatic neoplasms; targeted biopsy; systematic biopsy; regional saturation biopsy; perilesional biopsy

Submitted Oct 30, 2024. Accepted for publication Feb 06, 2025. Published online Mar 26, 2025.
doi: 10.21037/tau-24-619
View this article at: https://dx.doi.org/10.21037/tau-24-619

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Introduction

Since Hodge and colleagues introduced prostate biopsy techniques in 1989, significant advancements have been made. Traditional methods, such as transrectal ultrasound (TRUS)-guided sextant biopsies, have limitations and often miss prostate cancer (PCa) on repeat biopsies. While systematic biopsy (SB) approaches like extended or saturation biopsies have improved detection rates, they also identify clinically insignificant cancers and increase infection risks. To address these issues, there is growing interest in multiparametric magnetic resonance imaging (mpMRI)-guided targeted biopsies (TB), which use advanced imaging to localize suspicious lesions (1,2). MRI fusion-guided biopsy, combining mpMRI with real-time ultrasound, has shown promising results (3). Recent studies suggest that regional or focal biopsy techniques, involving multiple cores from suspicious lesions and perilesional sampling, can improve accuracy by addressing potential guidance errors (4). Our recent study indicates that regional saturation biopsy (RSB) is superior to TB and SB in patients with prostate-specific antigen (PSA) levels between 4–20 ng/mL (5). Despite these advancements, biopsy accuracy varies among centers, highlighting the need for optimal biopsy protocols.

The decision to proceed with a biopsy depends on factors such as PSA levels, prostate volume (PV), PSA density (PSAD), digital rectal exam (DRE) findings, and imaging results. Recent developments, particularly in transperineal approaches, have enhanced tumor localization accuracy, especially for anterior tumors, while reducing infection risk (6). Individuals at risk of PCa should consult their healthcare providers to determine the most appropriate biopsy method for their situation (7).

This review aims to explore personalized techniques and protocols for prostate biopsy, considering factors like PSA levels, PV, PSAD, region of interest (ROI), and Prostate Imaging-Reporting and Data System (PI-RADS) score. Incorporating these factors into a tailored biopsy workflow could enhance diagnostic effectiveness, though further research and clinical validation are needed to optimize these methods. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-619/rc).

Highlight box

Key findings

- The review identifies advancements in personalized prostate biopsy protocols that integrate prostate specific antigen (PSA) levels, prostate volume (PV), PSA density (PSAD), and Prostate Imaging-Reporting and Data System (PI-RADS) scores to improve the accuracy of prostate cancer detection. It highlights appropriate biopsy strategies for different PSA levels, PV, PSAD, and PI-RADS scores. Variability in cut-off values across studies limits the ability to perform meta-analysis.

What is known and what is new?

- The combination of targeted and systematic biopsy is the traditional approach for patients with positive magnetic resonance imaging (MRI) results. The 2024 European Urology Association guidelines recommend integrating perilesional sampling with targeted biopsy.
- Recent advancements suggest personalized biopsy techniques that consider individual patient factors such as PSA levels, PV, PSAD, and PI-RADS scores. These tailored approaches can refine biopsy strategies, shifting towards more customized patient care.

What is the implication, and what should change now?

- Personalized approaches to prostate biopsy are promising for enhancing detection accuracy and could lead to better patient outcomes by tailoring biopsy strategies to individual risk profiles.
- Clinical practice should start incorporating personalized protocols based on PSA levels, PV, PSAD, and PI-RADS scores. Ongoing research and validation are essential to optimize these approaches for widespread adoption.

Methods

To compile evidence for this narrative review, we conducted a comprehensive literature search across multiple electronic databases (PubMed, Google Scholar, and Web of Science) from January 1996 to March 2024. Search keywords included “Prostate Biopsy”, “Targeted Biopsy”, “Systematic Biopsy”, and “Focal Biopsy”. We manually reviewed reference lists to identify additional relevant papers and did not limit the search to English, including both Chinese and English publications (*Table 1*).

The screening process consisted of two stages: title/abstract screening and full-text screening. Initially, two independent researchers screened the titles and abstracts to exclude irrelevant documents. Subsequently, two investigators independently evaluated the full texts against predetermined inclusion and exclusion criteria. Inclusion criteria were studies published in peer-reviewed journals focusing on initial prostate biopsies for patients with suspicious findings, particularly those examining the impact of PSA levels, PV, PSAD, ROI, or PI-RADS scores on biopsy procedures. Exclusion criteria included editorials, letters to the editor, and abstracts.

Table 1 The search strategy summary

Items	Specification
Date of search	10 April 2024
Databases and other sources searched	PubMed, Google Scholar, Web of Science
Search terms used	"Prostate Biopsy", "Targeted Biopsy", "Systematic Biopsy", "Focal Biopsy"
Timeframe	January 1996–March 2024
Inclusion and exclusion criteria	Inclusion criteria
	• Studies on the relationship between initial prostate biopsies and clinical parameters (e.g. PSA, PV, PSAD, or PI-RADS)
	• No language limit; includes Chinese and English papers
	Peer-reviewed literature, including review papers
	Exclusion criteria
	• Main topic not related to ininital prostate biopsy
	• Editorials, letters to the editor, and abstracts
	• Papers published before 1996
Selection process	• Title/abstract screening: two independent researchers excluded irrelevant documents
	• Full-text screening: two independent investigators evaluated texts against criteria

PSA, prostate specific antigen; PV, prostate volume; PSAD, PSA density; PI-RADS, Prostate Imaging Reporting and Data System.

We categorized the findings based on how these factors influence the accuracy of PCa detection. We also evaluated the limitations of the reviewed studies, noting potential biases, diverse study designs, and variations in patient populations and sample sizes. This section provides an objective assessment of the current state of personalized techniques and protocols for prostate biopsy, relying on the most robust and relevant literature available.

Results

Personalized prostate biopsy based on serum PSA levels

Serum PSA levels are critical in PCa screening, reflecting tumor burden. Elevated PSA levels typically indicate a higher tumor burden, while lower levels suggest a smaller burden. Personalized biopsy strategies have emerged to tailor diagnostic approaches based on individual PSA levels, aiming to enhance accuracy and minimize complications (8-10). In 2007, Guichard *et al.* suggested that patients with suspected localized PCa should undergo at least 12 biopsies in peripheral and lateral zones. However, for those with abnormal DRE findings or PSA levels ≥20 ng/mL, a 6-core biopsy might suffice (11). Similarly, Philip *et al.* found that a 6-core biopsy focusing on the prostate apex could be adequate for patients with PSA levels above 20 ng/mL, while an 8-core TRUS-guided biopsy may be effective for PSA levels between 10–20 ng/mL (12). Ravery *et al.* observed that a 20-core biopsy protocol provided higher detection rates compared to the traditional 12-core method, particularly for patients with PSA levels between 3–6 ng/mL (13). Our 2013 systematic review and meta-analysis confirmed that a saturation biopsy protocol (more than 18 cores) outperforms an extended protocol (10–14 cores) for detecting PCa in men with PSA levels below 10 ng/mL (10).

In 2019, we recommended a 12-core biopsy for patients with PSA <20 ng/mL or PSAD <0.3. For PSA 20–50 ng/mL or PSA density 0.3–1.0, combine DRE, MRI, and biopsy. For PSA >50 ng/mL or PSA density >1.0, consider a 6- or 4-core biopsy. For PSA >70 ng/mL or PSA density >1.5, a 2-core biopsy may suffice (14). Further research by Ozorak *et al.* suggests that fewer biopsy cores may be sufficient for patients with PSA levels above 20 ng/mL, recommending 2, 4, and 6 core samples for PSA levels of 100 ng/mL or higher, 50–99.99 ng/mL, and 20–49.99 ng/mL, respectively (15). This approach could reduce invasiveness and patient discomfort while effectively diagnosing PCa. For PSA levels below 20 ng/mL, a combination of MRI-directed TB and SB might be optimal (16). Liu *et al.* compared MRI-ultrasound fusion

TB with SB, finding that MRI-directed TB, when combined with SB, could be a standard method for detecting clinically significant prostate cancer (csPCa) in patients with PSA levels between 10–20 ng/mL (17). Our recent study supports these findings, showing that for patients with PSA levels between 4 and 20 ng/mL, a regional saturation biopsy approach improves detection of csPCa and reduces the number of biopsy cores compared to TB and SB (5).

Additionally, the Prostate Health Index (PHI) test, which combines total PSA, free PSA, and proPSA measures, can enhance diagnostic accuracy and reduce unnecessary biopsies. Incorporating the PHI test into the diagnostic process can minimize invasive procedures, healthcare costs, patient anxiety, and discomfort for individuals with specific PSA levels (18,19). When assessing PSA and other blood markers, potential interferences such as urinary tract infections or urinary retention should be considered to avoid overdiagnosis and overtreatment. In summary, adopting a personalized approach based on PSA levels is crucial when designing a prostate biopsy plan. Personalized biopsy protocols are effective for patients with elevated PSA levels, while increasing the number of biopsy cores may improve diagnostic outcomes for those with lower PSA levels.

Personalized prostate biopsy based on PV or PSAD

Various studies indicated that PV and PSAD significantly impact PCa detection. Larger prostates often yield fewer positive biopsies, leading clinicians to increase biopsy cores or adjust their placement, which can cause complications and detect clinically insignificant cancers (10,20). Tailored biopsy approaches for specific PVs have been proposed to address these challenges.

For example, Inahara *et al.* found that a 14-core biopsy protocol significantly improved cancer detection rates compared to an 8-core protocol in patients with a PV between 30 and 40 cm^3. They recommended this approach for larger prostates when the PSAD, adjusted for transition zone volume, exceeds 0.38 ng/mL/cm^3 (21). Similarly, Yao *et al.* proposed a 12-core biopsy technique with transperineal ultrasound guidance for prostates larger than 50 mL, showing better diagnostic yield compared to the conventional 10-core method (22). Kandıralı *et al.* emphasized considering both PV and PSA levels when deciding on biopsy procedures, noting that PV is crucial for diagnosing PCa in patients with PSA levels of 10 ng/mL or lower (23). Additionally, Stone *et al.* introduced biopsy density, the ratio of biopsy cores to PV. They found that a biopsy density greater than 1.5 improved cancer detection rates by 1.5 times compared to lower densities, particularly for transperineal biopsies (24). Understanding the interplay between PV and PCa detection can guide clinicians in selecting appropriate biopsy strategies.

PSAD, calculated by dividing serum PSA levels by PV, provides further insight. PSA levels can rise due to basal membrane damage in PCa, even if PV remains stable. Conversely, prostate hyperplasia, marked by glandular enlargement, increases PSA production. Theoretically, PSAD levels are typically higher in PCa patients than in those with benign prostatic hyperplasia. Frisbie *et al.* found that PSAD complements PI-RADS in detecting csPCa, with a PSAD cutoff of ≥0.1 ng/mL/cc improving detection rates by 7% for PI-RADS 3, 17% for PI-RADS 4, and 15% for PI-RADS 5 (25). PSAD is also a useful for deciding whether MRI-negative patients should undergo a biopsy, offering a higher negative predictive value for those without detectable MRI lesions (26). The optimal number of cores for prostate biopsy remains uncertain. Yusim *et al.* observed that a PSAD between 0.09 and 0.19 ng/mL^2 and a PV less than 33 mL were associated with higher detection rates of csPCa. They concluded that PSAD is a more effective predictor than PSA alone for identifying clinically significant PCa in TRUS-guided biopsy (27). Jeong *et al.* found that increasing the number of biopsy cores from 6 to 12 notably improved cancer detection rates in patients with PSAD values between 0.1 and 0.2 (28). Ploussard *et al.* identified a PSAD cutoff of 0.20 ng/mL per gram, suggesting that an extended 21-core biopsy could improve detection rates without increasing insignificant cancers (29). Our meta-analysis showed that a saturation biopsy protocol was superior to an extended biopsy protocol for detecting PCa in men with PVs over 40 mL or PSAD below 0.25 ng/mL per gram (10). Similarly, PHI density (PHID) is an effective predictor of csPCa. Restricting biopsies to men with a PHID ≥0.56 may prevent unnecessary procedures, though it risks missing 9.3% of PCa cases and 2.1% of csPCa (19). While personalized biopsy strategies aim to improve cancer detection, they also carry the risk of overdiagnosis and overtreatment. Clinicians should carefully consider the necessity of biopsies, especially in patients with low-risk features such as low PSA levels, small prostate volume, and low prostate density. Future prospective studies are needed to validate these thresholds and integrate them into optimal biopsy strategies.

Personalized prostate biopsy based on tumor location

PCa primarily affects the peripheral zone, accounting for 70–

80% of cases. DRE is commonly used for screening but may miss cancers outside the peripheral zone (30). Combining DRE with imaging tests like TRUS or mpMRI and advanced biopsy techniques improves accuracy. Traditional transrectal biopsies are effective for the peripheral zone but have limitations in detecting cancers in the anterior and transition zones. In contrast, transperineal biopsies offer more comprehensive sampling with lower infection risk but require specialized skills and equipment (31). Tailoring the biopsy approach to the suspected tumor location enhances diagnostic accuracy and reduces complications.

A 2019 systematic review by Xiang *et al.* found that transperineal and transrectal biopsies have similar diagnostic accuracy, but transperineal biopsy reduces the risk of fever and rectal bleeding (32). Another meta-analysis showed comparable sensitivity and specificity for detecting csPCa between MRI/TRUS fusion biopsies, though results varied (33). Cowan *et al.* demonstrated the efficacy of transperineal biopsy in detecting csPCa in the anterior prostate, offering an alternative to transrectal biopsy (34). Rai *et al.*'s meta-analysis found that the transperineal approach had a higher detection rate for csPCa, particularly in anterior tumors, and fewer infection complications (6). A systematic review indicated that MRI-guided transperineal biopsy outperformed transrectal biopsy in detecting clinically significant cancer, especially in anterior tumors, with fewer complications (35). In 2023, Kaneko *et al.* concluded that transperineal MRI/TRUS fusion biopsy provided similar detection rates for csPCa as transrectal biopsy, with advantages in core length and involvement percentage (36). Uleri *et al.* noted the transperineal approach's superior detection in anterior and apical tumors, recommending its use for these lesions. Subgroup analysis showed that transperineal biopsy was associated with higher detection rates for clinically significant cancer in PI-RADS 4 lesions (37). These findings should be interpreted cautiously due to study limitations and heterogeneity.

Overall, evidence supports the advantages of transperineal biopsy for detecting csPCa, particularly in the anterior and apical regions. Advances in local anesthesia have enabled the procedure to be performed in an office setting, reducing costs (38). With lower rates of infectious and bleeding complications, some patients have opted to forgo peri-procedural antibiotics without increased risk of infection (39). Recent improvements have made transperineal biopsy a well-tolerated office procedure. However, the choice of biopsy method should consider factors such as expertise and individual circumstances. Personalized prostate biopsy, tailored to tumor location, ensures accurate diagnosis and aids in effective treatment planning.

Personalized prostate biopsy based on PI-RADS score

The PI-RADS scoring system categorizes lesions on a scale from 1 to 5 based on MRI findings to assess the likelihood of csPCa, with higher scores indicating a higher probability of cancer. Ideally, prostate biopsies should correspond to the PI-RADS score, involving targeted sampling of suspicious lesions identified on mpMRI scans. However, MRI often underestimates tumor size and extent, which is crucial for accurate biopsy planning (40-42). The 2024 European Urology Association guidelines recommend combining targeted and perilesional sampling as standard practice.

In 2022, Brisbane *et al.* did a retrospective study on perilesional biopsies for csPCa detection. They found 90% of significant cancer cores were within 10 mm of the nearest lesion. The penumbra size, covering 90% of significant cancer, varied by MRI grade: 5 mm for grade 5, 12 mm for grade 4, and 16 mm for grade 3. This shows biopsies from both inside and around MRI-detected lesions are more sensitive than from lesions alone (4). Besides, Droghetti *et al.* studied the impact of SB cores in patients doing both TB and SB for suspected PCa. They found that while TB can identify most high-grade PCa, many patients are upgraded by SB cores, even from overlapping areas. Omitting these cores can lead to suboptimal patient care (43). Subsequent studies aims to optimize the number of biopsy cores per lesion for personalized approaches. Sonmez *et al.* suggested 2–3 cores for PI-RADS 4 and 5 lesions, and at least 4 for PI-RADS 3 (44). Given that TB frequently fails to detect clinically significant cancers on the same side as the primary lesion (45), combining TB with ipsilateral SB enhances the detection rate and decreases the risk of overdiagnosing insignificant tumors (46,47). Alternative strategies like focal saturation biopsy, perilesional biopsy, and regional biopsy have been explored. Hansen *et al.* [2020] compared transperineal MR/TRUS fusion-guided biopsy templates. Saturation targeted biopsy detected Gleason score 7–10 cancers in 25% more cases than a two-core targeted approach and 91% as many as the 20–26-core TB plus SB approach, but needed only 10–20 cores. For large, suspicious anterior lesions in small prostates, a four-core extended TB may be enough (48). Lee *et al.* saw that intensive sampling of the umbra and penumbra improved cancer detection and reduced grade-group upgrading risks during radical prostatectomy (49). A regional targeted biopsy with a 2-cm ROI margin had much higher detection rates (over 95%, depending on PI-RADS) than conventional TB

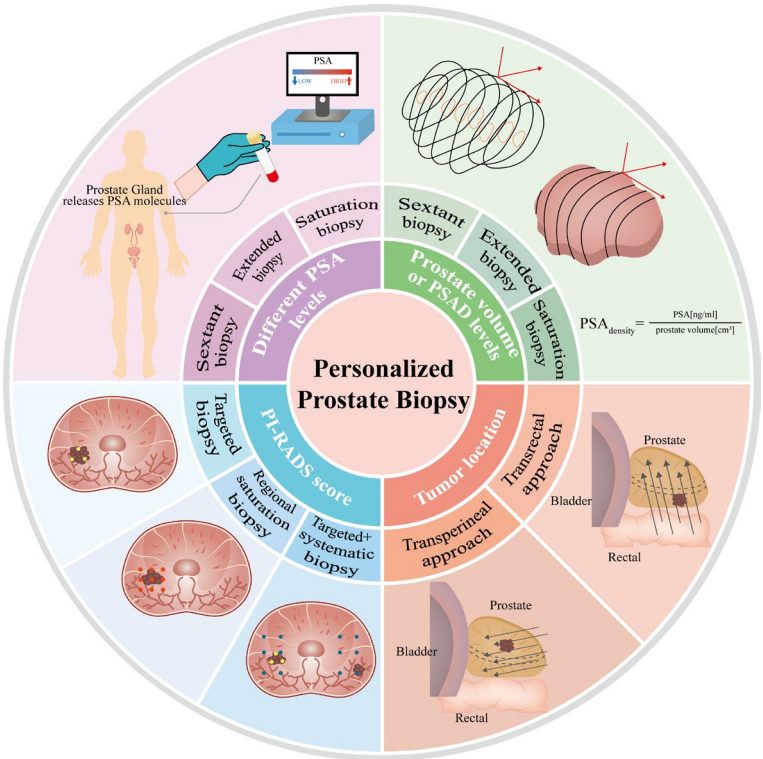

Figure 1 Tailoring prostate biopsies: unleashing precision with personalized approaches. PSA, prostate specific antigen.

(75–93%) (50). Hagens *et al.*'s meta-analysis compared MRI-directed targeted plus regional biopsy with MRI-directed TB alone and TB plus SB for detecting grade group ≥2 PCa. The detection rates for grade group ≥2 cancer were similar between MRI-directed targeted plus regional biopsy and TB plus SB, but different from targeted biopsy alone (51). Note that there's no consensus on regional sampling for MRI-directed targeted plus regional biopsy, affecting generalizability. Saner *et al.* showed a 100% detection rate with targeted saturation biopsy (9 cores) *vs.* 92% with TB, though not statistically significant. This approach relies on TB, requiring high expertise. The study had more PI-RADS 4 and 5 lesions (90.6% *vs.* 78.8%), with no significant differences in csPCa rates (52). Our study evaluated RSB with 9 cores in biopsy-naïve patients with PSA levels of 4–19.99 ng/mL. RSB achieved a 44.09% csPCa detection rate, higher than TB (31.76%) and SB (34.11%). RSB's advantage was notable for PI-RADS 3 and 4 lesions and ROIs <1.5 cm^2, but not for PI-RADS 5 lesions or ROIs >1.5 cm^2 (5). For high-risk PCa patients with PI-RADS ≥4, combining PHI and PSMA PET/CT in nomograms can enable a biopsy-free approach (53). Optimizing biopsy core numbers addresses overdiagnosis and overtreatment, aiming to accurately detect csPCa through mpMRI-ROI and targeted-core correlation. Research focuses on finding the optimal number of cores per lesion for an accurate, minimally invasive method, key to better personalized prostate biopsies.

However, realizing the full potential of personalized biopsy techniques in PCa detection and patient care presents several challenges. Variability in cut-off values and PI-RADS grading across studies limits the effectiveness of meta-analyses and systematic reviews. Additionally, reliance on the quality of mpMRI and operator expertise complicates widespread implementation (54,55). To address these issues, standardization and advanced imaging technologies are crucial. Meanwhile, age is an important factor in biopsy outcomes, with older patients typically having higher detection rates, while younger patients have lower detection rates but higher malignancy (56,57). Further research is needed to refine and validate these approaches, which hold promise for improving cancer detection and patient care.

Conclusions

This narrative review shows how personalized prostate biopsy techniques, using PSA, PV, PSAD, ROI, and PI-

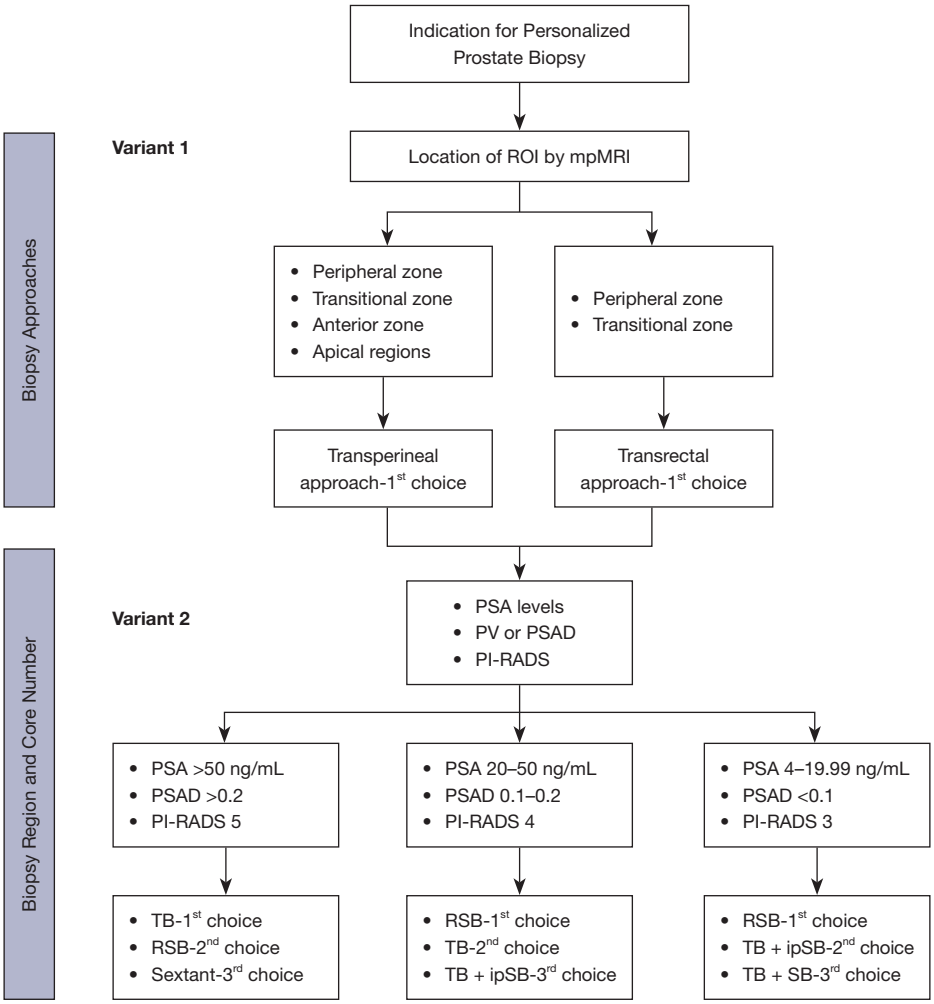

Figure 2 Personalized prostate biopsy workflow that takes into account various factors, including serum PSA levels, PSAD, ROI, and PI-RADS score. ipSB, ipsilateral systematic biopsy; mpMRI, multiparametric magnetic resonance imaging; PSA, prostate specific antigen; PSAD, PSA density; PI-RADS, Prostate Imaging Reporting and Data System; RSB, regional saturation biopsy; ROI, region of interest; SB, systematic biopsy; TB, targeted biopsy.

RADS, boost cancer detection accuracy (*Figures 1,2*). It suggests customizing biopsy strategies by using fewer cores for high PSA levels and integrating PV or PSAD for risk assessment. Advanced imaging like mpMRI with PI-RADS improves lesion localization, enabling more effective biopsies. Combining these factors into a custom biopsy workflow may enhance diagnosis, but more research and clinical validation are needed to optimize the methods.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-619/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-619/prf

Funding: This work was supported by the National Natural Science Foundation (No. 82174174), the Tianjin Science and Technology Project (Nos. KJ20169 and 24JCYBJC01040), and The Second Hospital of

Tianjin Medical University (Nos. MNRC202312 and MYSRC202306).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-619/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Guo S, Jiang X. Personalized prostate biopsy protocols: enhancing cancer detection through tailored approaches—a narrative review. Transl Androl Urol 2025;14(3):831-840. doi: 10.21037/tau-24-619