Study Protocol and Statistical Analysis Plan

ProsBiT – Multicenter Prospective Prostate Biopsy Study in Turkey

Item	Details
Official title	ProsBiT – Multicenter Prospective Prostate Biopsy Study in Turkey
Original (Turkish) title	ProsBiT – Türkiye Çok Merkezli Prospektif Prostat Biyopsi Çalışması
Acronym	ProsBiT
ClinicalTrials.gov identifier	
Study protocol	Version 1.0, 31 October 2025 (English translation of the ethics-approved Turkish protocol)
Statistical analysis plan	Version 1.0, 31 October 2026
Document date	31 October 2026
Ethics committee	Ethics Committee of the Ministry of Health Göztepe Prof. Dr. Süleyman Yalçın City Hospital — approval number: **[2025/0327]**
Study design	Prospective, multicenter, observational cohort study
Study period	Enrollment from 30 December 2025 to October 2026; complication follow-up 30 days after biopsy
Coordinating investigator	Assoc Prof H.Ozgur Kazan, Department of Urology, İstanbul Medeniyet University, İstanbul, Turkey
Funding	None (investigator-initiated; no sponsor)
SAP prepared and approved by	ProsBiT Collaborative Group

PART 1 — STUDY PROTOCOL

A. Study Information

A.1. Full title of the study: ProsBiT – Türkiye Çok Merkezli Prospektif Prostat Biyopsi Çalışması

A.2. English title of the study: ProsBiT – Multicenter Prospective Prostate Biopsy Study in Turkey

B. Study Characteristics

- **B.1. Retrospective:** No
- **B.2. Prospective:** Yes
- **B.3. Status of the study:** Individual research project (not a master's, doctoral, or specialty thesis)

C. Sponsor

- **C.1. Does the study have a sponsor?** No
- **C.1.8. Costs covered by the investigators:** Yes — stationery costs will be covered by the investigators.

D. General Information on the Study

D.1.1. Background

According to the 2020 World Health Organization Global Cancer Observatory data, prostate cancer is the fourth most commonly diagnosed cancer across both sexes; in 2020, 1,414,259 new cases and 375,304 prostate cancer deaths were recorded worldwide.[1] For many years, transrectal prostate biopsy has been the gold standard for the diagnosis of prostate cancer. This standard method, which involves transrectal ultrasound-guided biopsy, consists of 12-core random sampling of the prostate gland (systematic biopsy).[2] It continues to be widely used in many centers. With the increasing availability of imaging, MRI- and ultrasound-cognitive biopsy (multiple samples taken from suspicious lesions in addition to systematic biopsy) has recently emerged as the preferred biopsy method. In recent years, the dramatic worldwide increase in multidrug-resistant uropathogens has called the use of the transrectal procedure into question and has led to a shift toward transperineal prostate biopsy.[3,4] Although both biopsy approaches remain valid for the diagnosis of prostate cancer, studies comparing them in terms of the pain experienced by the patient during the procedure, complication rates, and cancer detection rates have become increasingly common in recent years.

References

- 1. Thomson A, Li M, Grummet J, Sengupta S. Transperineal prostate biopsy: a review of technique.
- 2. Chang DTS, Challacombe B, Lawrentschuk N. Transperineal biopsy of the prostate—is this the future? Nat Rev Urol. 2013;10:690–702.
- 3. Miller J, Perumalla C, Heap G. Complications of transrectal versus transperineal prostate biopsy. ANZ J Surg. 2005;75(1-2).
- 4. Xiang J, Yan H, Li J, Wang X, Chen H, Zheng X. Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. World J Surg Oncol. 2019;17:31.

D.1.2. Contribution of the study to the literature

To date, no study in Turkey has examined prostate biopsies at the national level, including biopsies performed via the transperineal route. In this multicenter study, biopsies performed for suspected prostate cancer will be compared in terms of the biopsy method used, local anesthesia methods, antibiotic prophylaxis

administered, pre- and post-procedural practices, and patient and imaging characteristics, with respect to complications, pain scores, and diagnostic rates, thereby providing additional information to the existing literature.

D.1.3. Is any of the conditions studied a rare disease?

No.

D.1.5. Aims and objectives

The main aim of this study is to comparatively evaluate the transrectal and transperineal approaches in prostate biopsies performed for suspected prostate cancer across Turkey in terms of diagnostic performance, complication profile, pain level, and clinical feasibility. Accordingly, the study aims to examine the clinical and imaging-based factors that influence the choice of biopsy method, and to describe the variation in local anesthesia practices, antibiotic prophylaxis protocols, and pre- and post-procedural follow-up processes across centers in the country.

The primary objective of the study is to compare the effect of transrectal and transperineal prostate biopsy on cancer detection rates (particularly clinically significant prostate cancer). The secondary objectives are to evaluate the pain level during and after the procedure; complication rates, primarily infection; the diagnostic contribution of MRI-guided targeted biopsy; and the effect of the anesthesia and antibiotic practices used at different centers on outcomes.

The hypothesis of this study is that the transperineal biopsy approach will reduce infectious complications compared with transrectal biopsy while showing equal or superior performance in the detection of clinically significant prostate cancer. In addition, MRI-based targeted biopsies are expected to increase diagnostic accuracy compared with the systematic biopsy method.

The literature shows a clear trend toward the transperineal approach, particularly with the increase in antibiotic resistance. However, there are no multicenter national data from Turkey comparing the two methods. By providing a current and comprehensive analysis of the prostate biopsy techniques used in our country, this study aims to contribute to the standardization of clinical practice, to provide a scientific basis for strategic changes that may reduce complications, and to contribute new data to the international literature.

D.1.6. Approach and methods

Within the scope of this study, prostate biopsies performed via the transrectal or transperineal approach in patients with suspected prostate cancer at the participating centers across Turkey will be evaluated prospectively from 30 December 2025 onward. During and after the biopsies, which will be performed under local anesthesia in line with routine clinical indications, patients' pain levels will be measured with the visual analog scale (VAS), and complications that may occur in the early and late post-procedural periods will be recorded systematically. Patients' demographic characteristics, clinical findings, MRI results, biopsy method and number of cores, development of complications (primarily infection), and pathology results will be collected through face-to-face outpatient follow-up visits and the electronic data capture system. Patients included in the study will be divided into two groups according to the biopsy method: the transperineal biopsy group and the transrectal biopsy group. For the statistical comparison of pain scores, complication rates, and diagnostic performance between the two methods, Student's t-test or the Mann–Whitney U test will be used for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Written informed consent will be obtained from all participants before biopsy, and data will be evaluated in an anonymized manner in accordance with confidentiality principles.

D.1.7. Eligibility criteria

Inclusion criteria:

- Patients undergoing transrectal or transperineal prostate biopsy
- Patients aged 18 years or older
- Patients with suspected prostate cancer on physical examination, laboratory tests (PSA), or MRI

Exclusion criteria:

- Patients who do not agree to participate in the study
- Patients for whom sufficient data cannot be obtained during post-study follow-up
- Patients who do not wish to complete the questionnaire form

D.2. Endpoints

D.2.1. Primary endpoint: Comparison of the detection rate of clinically significant prostate cancer (Grade Group ≥2) between the transrectal and transperineal biopsy methods.

D.2.2. Secondary endpoints:

- Comparison of patients' pain levels during and after the procedure using VAS scores
- Evaluation of complications, primarily infection
- Analysis of the diagnostic contribution of MRI-guided targeted biopsy
- Investigation of the effect of the local anesthesia and antibiotic protocols used on biopsy outcomes

E. Risks and Benefits of the Study

- **E.1. Potential risks:** No risk identified (E.1.9). None of the listed potential risks (psychological or social effects, presentation of sensitive material, detection of abuse, injury or bodily harm, examination of personal or sensitive data in surveys or interviews, breach of privacy, use of private records, or other risks) was selected. All biopsies are performed for routine clinical indications.
- **E.2. Scope of the study:** Other — prospective.
- **E.3. Type of study:** Other — prospective (not a study of a new surgical technique, stem cell, tissue, or organ transplantation).
- **E.6. Study centers:** Multicenter — Yes.

E.6.3. Planned number and names of centers in Turkey: The study is planned to be conducted at 22 (twenty-two) centers: Adana City Hospital; Ankara Bilkent City Hospital; Ankara Oncology Training and Research Hospital; Bağcılar Training and Research Hospital; Bakırköy Dr. Sadi Konuk Training and Research Hospital; Etlik City Hospital; Gaziantep University; Giresun University; Harran University; İstanbul Başakşehir Çam and Sakura City Hospital; İstanbul Haseki Training and Research Hospital; İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital; İzmir Democracy University; İzmir Katip Çelebi University; İzmir City Hospital; İzmir Tepecik Training and Research Hospital; Kartal Dr. Lütfi Kırdar City Hospital; Kütahya Training and Research Hospital; Mersin University; Okmeydanı Prof. Dr. Cemil Taşcıoğlu City Hospital; Samsun Training and Research Hospital; and Trabzon Kanuni Training and Research Hospital.

E.7. Study duration: Start date: 30 December 2025. End date: 2028.

F. Study Population

- **F.1.2. Participants younger than 18 years:** No
- **F.1.4–F.1.5. Participants older than 18 years:** Yes — age range 40–80 years; 150 patients
- **F.2. Sex:** Male
- **F.3. Participant group:** Patients

G. Participating Centers and Investigators

G.1. Coordinating investigator: Prof. Dr. Asıf Yıldırım, Urology, İstanbul Medeniyet University.

G.2. Co-investigators (specialist physicians)

#	Name	Specialty	Institution
1	Mehmet Çağlar Çakıcı	Urology	—
2	Yiğit Akın	Urology	İzmir Katip Çelebi University
3	Alper Bitkin	Urology	Bakırköy Dr. Sadi Konuk Training and Research Hospital
4	Ural Oğuz	Urology	Giresun University
5	İsmail Engin Kandıralı	Urology	İstanbul Bağcılar Training and Research Hospital
6	Bilal Eryıldırım	Urology	Kartal Dr. Lütfi Kırdar Training and Research Hospital
7	Cüneyt Özden	Urology	Ankara Bilkent City Hospital
8	Eyyüp Sabri Pelit	Urology	Harran University
9	Alper Ötünçtemur	Urology	Okmeydanı Prof. Dr. Cemil Taşcıoğlu Training and Research Hospital
10	Murat Bozlu	Urology	Mersin University
11	Halil Lütfü Canat	Urology	İstanbul Başakşehir Çam and Sakura City Hospital
12	Turgay Turan	Urology	İzmir Democracy University
13	Hasan Rıza Aydın	Urology	Trabzon Kanuni Training and Research Hospital
14	İlker Seçkiner	Urology	Gaziantep University
15	Ömer Sarılar	Urology	İstanbul Haseki Training and Research Hospital
16	Muhammet Abdürrahim İmamoğlu	Urology	Etlik City Hospital
17	Hakan Erçil	Urology	Adana City Hospital
18	İbrahim Halil Bozkurt	Urology	İzmir City Hospital
19	Yusuf Arıkan	Urology	İzmir Tepecik Training and Research Hospital
20	Bekir Aras	Urology	Kütahya Training and Research Hospital
21	Mustafa Kemal Atilla	Urology	Samsun University Health Application and Research Center
22	Muhammed cicek	Urology	Malatya Research and Training Hospital
23	Bilal Hamarat	Urology	Konya City Hospital

Confidentiality

Within the scope of this study, the consent/permission document obtained from the volunteer has been added to the file, and it has been stated that the data will be presented for scientific purposes. I undertake that no information revealing the identity of the individual or violating privacy and the confidentiality of private life will be included.

H. Declaration of the Applicant

With this application form, on my own behalf / on behalf of the applicant, I undertake that:

- the information provided in the application is correct;
- the study will be conducted in accordance with the protocol, the relevant legislation, the current Declaration of Helsinki, and the principles of Good Clinical Practice;
- I have informed the study team (including laboratory staff, research nurses, etc.) about the study;
- the proposed clinical study is feasible;
- the application has not been submitted simultaneously to more than one ethics committee established under the relevant regulation;
- I will submit reports on serious adverse events/reactions and safety reports; and
- I will submit a copy of the final report to the relevant unit within a maximum of 1 (one) year after the study has ended in all countries/in our country.

PART 2 — STATISTICAL ANALYSIS PLAN

1. Objectives

Primary objective: to compare the detection rate of clinically significant prostate cancer (csPCa; ISUP grade group ≥2) between transperineal (TP) and transrectal (TR) prostate biopsy.

Secondary objectives (consistent with the protocol), including the prespecified sub-studies:

- S1. Compare procedural pain (VAS), patient acceptability, and complications (primarily infection) between TP and TR biopsy, including the effect of local anesthesia and antibiotic prophylaxis.
- S2. Evaluate the diagnostic contribution of MRI: PI-RADS and PSA density (PSAD) as predictors of csPCa, and external validation of the Schoots–Padhani risk-adapted biopsy matrix (BJU Int 2021;127:175–178).
- S3. Describe between-center variation in biopsy practice (route, MRI use, targeting, antibiotic prophylaxis, anesthesia, number of cores) and benchmark case-mix-adjusted csPCa detection.
- S4. Assess the association between antithrombotic therapy and bleeding complications, overall and by biopsy route.
- S5. Assess concordance between the MRI index-lesion location and biopsy-positive zones, and compare it between TP and TR biopsy.
- S6. Describe the institutional learning curve of TP biopsy (cancer detection, complications, pain, and core length).

2. Study Population and Analysis Sets

- **Full analysis set (FAS):** all enrolled men with a recorded biopsy route. Used for baseline description, pain, acceptability, and complications.
- **Detection set:** FAS men with a biopsy pathology result. Used for any-cancer detection.
- **csPCa set:** detection set excluding men with adenocarcinoma but no recorded ISUP grade group. Used for csPCa endpoints.
- **MRI validation set (S2):** biopsy-naive men in the csPCa set with pre-biopsy MRI, a reported index-lesion PI-RADS score, PSAD available, and PSA <100 ng/mL. Men with a prior negative biopsy form a separate secondary set.
- **Concordance set (S5):** cancers with at least one marked index-lesion zone and at least one marked malignant-core zone; primary analysis restricted to PI-RADS ≥3.
- **TP learning-curve set (S6):** TP biopsies from centers with at least 30 TP procedures.
- **Data-quality exclusion:** a center in which more than 20% of detected cancers lack an ISUP grade group, or more than 20% of MRIs lack a PI-RADS score, after resolution of data queries will be excluded from csPCa and MRI-based analyses and included in sensitivity analyses.

3. Endpoint Definitions

Endpoint	Definition
csPCa (primary)	Adenocarcinoma with ISUP grade group ≥2 on biopsy pathology
Any prostate cancer	Adenocarcinoma of any grade on biopsy pathology
Clinically insignificant cancer	ISUP grade group 1
Procedural pain	VAS 0–10 at digital rectal examination, probe insertion, local anesthetic injection, right-lobe sampling, left-lobe sampling, and end of procedure; maximum VAS from probe insertion onward; moderate-to-severe pain = VAS ≥4 at any step
Acceptability	Patient would choose the same biopsy method again (yes/no)

Endpoint	Definition
Infectious complications	Post-biopsy infection, cystitis, urethritis, epididymitis/orchitis; sepsis analyzed separately within 30 days after biopsy
Bleeding complications	Hematuria, urethrorrhagia, or perineal hematoma within 30 days after biopsy
Serious events	Hospitalization, intensive care admission, biopsy-related death within 30 days after biopsy
PSA density (PSAD)	Serum PSA (ng/mL) divided by prostate volume (mL)
Index-zone concordance	At least one malignant core in a zone marked for the MRI index lesion on the 24-zone map (1–12 peripheral zone, 13–24 transition zone; apex 1–4/13–16, mid-gland 5–8/17–20, base 9–12/21–24; odd numbers anterior, even numbers posterior)
Core length	Total, longest, and shortest core length (mm); mean core length = total core length / number of cores

Complications are those recorded during the post-biopsy follow-up defined in the protocol (early and late period) (30 days after biopsy).

4. Sample Size

The study is a national multicenter cohort, and the sample size is determined by the number of consecutive eligible biopsies at participating centers during the enrollment period rather than by a formal calculation. Assuming a csPCa prevalence of about 23% and a TR:TP ratio of 3:1 (about 6,000 TR and 2,000 TP biopsies), the study has 88% power to detect an absolute difference of 3.5 percentage points and 77% power for a difference of 3.0 percentage points in csPCa detection (two-sided $\alpha = 0.05$), before accounting for clustering by center. For the MRI validation set, about 1,600 men in whom biopsy would be avoided give a 95% confidence interval half-width of about ±1.1% around an expected negative predictive value of 94–95%. The anticipated total enrollment was approximately 8,000 men; 8,310 men had been enrolled by the end of enrollment (export of 31 October 2026). The ethics application stated a planned sample of 150 patients; the inclusion of all consecutive eligible patients at participating centers resulted in a larger cohort.

5. Data Handling

- **Data source:** REDCap electronic case report form with one data access group per center. Analyses use locked data exports; the export date is reported with each analysis.
- **Data cleaning:** decimal commas and unit suffixes are harmonized. Values outside plausible ranges are set to missing: age <40 or >95 years, BMI <15 or >60 kg/m², PSA ≤0.05 or >5,000 ng/mL, prostate volume <5 or >500 mL, number of cores <2 or >60, and core length >30 mm. Inconsistencies (e.g., "no complication" ticked together with a complication, or more malignant than total cores) are queried with the centers before database lock.
- **Data queries and source verification:** range and consistency checks generate record-level queries to each center; a random sample of records at centers with anomalous patterns undergoes source-data verification.
- **Missing data:** analyses are complete-case. The proportion of missing data is reported for each variable. Sensitivity analyses code cancers with a missing ISUP grade group as csPCa and as non-csPCa. Multiple imputation by chained equations may be used for covariates with >5% missing data as a sensitivity analysis.
- **Chronological order (S6):** procedures are ordered by biopsy date; if biopsy date is unavailable, by the sequential registry record number within each center, which will be stated as a limitation.

6. General Statistical Methods

Continuous variables will be summarized as mean ± standard deviation or median (interquartile range) and compared with Student's t-test or the Mann–Whitney U test, as appropriate. Categorical variables will be summarized as counts and percentages and compared with the χ^2 test or Fisher's exact test (when any

expected cell count is <5). Baseline balance between biopsy routes will be described with standardized mean differences (SMD >0.10 indicating imbalance). Proportions will be reported with Wilson 95% confidence intervals.

Because patients are clustered within centers and the biopsy route is largely determined by the center, regression analyses will account for clustering using (i) logistic or linear regression with cluster-robust standard errors by center; (ii) random-intercept generalized linear mixed models; and (iii) center fixed effects restricted to centers performing both biopsy routes (within-center comparison). All tests are two-sided with $\alpha = 0.05$.

7. Analysis of the Primary Endpoint

csPCa detection will be compared between TP and TR biopsy in the csPCa set. The primary estimate is the adjusted odds ratio (TP vs TR) from multivariable logistic regression with cluster-robust standard errors, adjusted for age, log-transformed PSA, log-transformed prostate volume, MRI/PI-RADS category (no MRI, PI-RADS 1–2, 3, 4, 5, MRI with PI-RADS not reported), prior negative biopsy, family history, targeting technique (systematic only, cognitive, software fusion/in-bore), and number of cores. Supportive analyses: (a) unadjusted comparison; (b) within-center comparison with center fixed effects in centers with ≥20 biopsies by each route; and (c) inverse probability of treatment weighting using a propensity score for TP biopsy estimated from the same covariates (stabilized weights truncated at the 1st and 99th percentiles).

Prespecified subgroups: biopsy-naive vs prior negative biopsy; no MRI and each PI-RADS category; systematic, cognitive, and fusion biopsy. Any-cancer and ISUP 1 detection and the ISUP grade distribution will be analyzed in the same way.

8. Analysis of Secondary Endpoints

8.1 Pain, acceptability, and complications (S1)

VAS scores at each procedural step will be compared with linear regression (mean difference TP − TR) adjusted for age, log prostate volume, number of cores, prior biopsy, local anesthesia technique (periprostatic nerve block, periapical triangle block, prostatic apex block), and anesthetic agent. Acceptability and moderate-to-severe pain will be analyzed with logistic regression using the same covariates. Infection and hospitalization will be modeled with adjustment for age, diabetes mellitus, Charlson comorbidity index, history of urinary tract infection, prior biopsy, antibiotic prophylaxis, and number of cores; sepsis, if fewer than 50 events, with a reduced model (diabetes, UTI history, antibiotic prophylaxis). Within-center effects will be summarized with center fixed effects and Mantel–Haenszel odds ratios. Results will be stratified by antibiotic prophylaxis and antibiotic agent. Sensitivity: exclusion of centers with outlying infection rates.

8.2 MRI and PSA density; Schoots–Padhani validation (S2)

Logistic regression models for csPCa: PSA alone; PI-RADS alone; ln(PSAD) alone; PI-RADS + ln(PSAD); and an extended model adding age, prior biopsy, and family history. Discrimination: AUC with DeLong 95% CIs and DeLong tests between nested models; likelihood-ratio tests. Calibration: calibration intercept and slope and decile calibration plots; Brier score. Internal validation: 200 bootstrap resamples (optimism-corrected AUC and calibration slope). Transportability: leave-one-center-out validation in centers with ≥10 events and ≥10 non-events, with random-effects pooling of center AUCs (I^2 and 95% prediction interval). Clinical utility: decision curve analysis (threshold probabilities 2–40%).

Schoots–Padhani matrix: men are assigned to 12 cells (PI-RADS 1–2, 3, 4–5 × PSAD <0.10, 0.10–0.14, 0.15–0.19, ≥0.20 ng/mL²). Low-risk threshold strategy: biopsy omitted for PI-RADS 1–2 with PSAD <0.20 and PI-RADS 3 with PSAD <0.10. High-risk threshold strategy: biopsy omitted for all PI-RADS 1–2 and PI-RADS 3 with

PSAD <0.20. Comparators: biopsy all; MRI-only (PI-RADS ≥3); PI-RADS 4–5 or PI-RADS 3 with PSAD ≥0.15. For each strategy: biopsies avoided, csPCa missed (proportion of csPCa and of all men), ISUP 1 diagnoses avoided, sensitivity, specificity, NPV, PPV (Wilson 95% CIs); exact McNemar tests vs MRI-only; net benefit; center-level NPV and sensitivity pooled by random-effects meta-analysis. Cell-level csPCa prevalence with trend tests. Subgroups/sensitivity: biopsy route, targeting, PSA ≤10 and 4–10 ng/mL, age, prostate volume, multiparametric MRI only, csPCa redefined as ISUP ≥3, prior negative biopsy set.

8.3 Center-level practice variation (S3)

For each practice and outcome indicator: overall proportion, center median, IQR, and range, with χ^2 tests of heterogeneity. Random-intercept logistic models will estimate the between-center variance, latent-scale intraclass correlation, and median odds ratio; case-mix adjustment for csPCa (age, log PSA, log volume, MRI/PI-RADS category, prior biopsy) and infection (route, antibiotic prophylaxis, diabetes, UTI history, age). Observed-to-expected csPCa ratios will be displayed in a funnel plot with 95% and 99.8% control limits. Center-level correlations (Spearman) are exploratory.

8.4 Antithrombotic therapy and bleeding (S4)

Antithrombotic exposure: any agent; class (single antiplatelet, dual antiplatelet, anticoagulant, anticoagulant + antiplatelet). Primary model: logistic regression for any bleeding complication with center fixed effects, adjusted for biopsy route, age, log prostate volume, number of cores, diabetes, and targeted biopsy; secondary: cluster-robust population-averaged model. Effect modification by route: antithrombotic × route interaction and route-stratified models. Hematuria and urethrorrhagia analyzed separately.

8.5 MRI–biopsy concordance (S5)

Primary outcome: index-zone miss (no malignant core in any marked index-lesion zone). Miss rates compared between routes overall and by PI-RADS, targeting technique, ISUP grade, and lesion location (peripheral/transition zone, anterior/posterior, apex/base). Multivariable logistic regression with cluster-robust standard errors adjusted for PI-RADS, number of marked zones, targeting technique, number of cores, and transition-zone, anterior, and apical involvement; random-intercept and within-center models; sensitivity analysis restricted to centers with ≥10 TP cancers with complete zone data. Documentation bias: completeness of zone data compared between routes. Zone-level hit rates by region with clustered logistic models; region comparisons Bonferroni-corrected.

8.6 TP learning curve (S6)

Within each center with ≥30 TP biopsies, procedures are ordered chronologically and divided into quartiles (Q1 earliest to Q4 latest). Trends are tested with logistic or linear regression with quartile as an ordinal variable and center fixed effects. Adjustment: detection — age, log PSAD, MRI/PI-RADS category, prior biopsy, targeted sampling; complications — antibiotic prophylaxis, diabetes, age; VAS — age, log prostate volume, number of cores, anesthesia technique; core length — log prostate volume. VAS during digital rectal examination serves as a negative-control outcome. Detection is also analyzed by PI-RADS stratum and by absolute center case number (1–50, 51–100, 101–200, >200). Heterogeneity between centers: quartile × center interaction. Sensitivity: excluding the largest center, centers with <100 TP biopsies, and biopsy-naive or MRI-only subsets.

9. Multiplicity

There is one primary endpoint; no adjustment for multiplicity is applied to it. Secondary endpoints and sub-study analyses are considered supportive or exploratory and will be interpreted with emphasis on effect sizes and confidence intervals; where multiple regions or subgroups are tested for the same hypothesis (e.g., zone-level analyses), a Bonferroni correction will be applied.

10. Reporting and Software

Reports will follow the STROBE statement (cohort analyses), TRIPOD (prediction-model validation), and STARD (diagnostic strategy performance), as applicable. Analyses will be performed in Python (pandas, SciPy, statsmodels, scikit-learn) and/or R; software versions will be reported. Any deviation from this plan will be documented with its rationale in the final report.