Supplementary Material. Clinical algorithm. Interpreting PSA elevations when inflammation is present or suspected

A. Initial clinical screen (symptoms & context)

1. Are there symptoms/signs of febrile UTI or acute bacterial prostatitis? (fever, dysuria/urgency, perineal/pelvic pain, systemic illness)

- Yes → Defer PSA testing until after clinical resolution. If a PSA was already obtained during the acute phase, do not act on it; repeat after recovery (pragmatically ≥6–8 weeks, recognizing that normalization can be slow and occasionally prolonged).
- If infection is uncertain, a PSA may aid differential diagnosis, provided results are interpreted cautiously and the test is repeated after recovery before proceeding to imaging or biopsy.
- No → proceed to B.

2. Exclude transient confounders before interpreting/ordering PSA: recent ejaculation, instrumentation, urinary retention (manage first), active UTI. Document pre-analytical conditions.

B. Confirm (standardize & repeat PSA)

3. Asymptomatic men with PSA 3–10 ng/mL and a nonsuspicious DRE: repeat PSA in ~4 weeks under standardized conditions (same lab/assay; avoid ejaculation/manipulation; UTI excluded).

- Normalizes → return to routine/annual monitoring as appropriate.
- Remains elevated → proceed to C.

C. Image (MRI-first) & quantify PSAD

4. Obtain prebiopsy multiparametric MRI.
5. Calculate PSA density (PSAD=PSA/prostate volume)

D. Refine (integrate MRI + PSAD ± biomarkers; decide biopsy vs. observe)

6. MRI negative (PI-RADS ≤2)

- PSAD ⟨0.20 ng/mL/cc with low clinical suspicion → defer biopsy; structured monitoring.
  (More conservative local thresholds (e.g., ⟨0.15 or ⟨0.10) may further reduce post-test risk; select with regard to MRI quality and pretest risk.)
- PSAD 0.15–0.20 (borderline) → consider secondary biomarkers (PHI, 4Kscore, IsoPSA, Stockholm3, Proclarix, SelectMDx, ExoDx, MPS/MPS2) to reduce unnecessary biopsy without missing csPCa.
- PSAD ≥0.20 or rising risk → consider biopsy despite negative MRI.

7. MRI indeterminate (PI-RADS 3)

- PSAD ⟨0.10 → observation with PSA monitoring (± biomarker if uncertainty persists).
- PSAD ≥0.10 → consider targeted (±systematic) biopsy, or apply a validated biomarker if decision remains borderline.

8. MRI positive (PI-RADS ≥4) → targeted biopsy (±systematic).

E. Antibiotic stewardship (balanced statement)

9. In asymptomatic men with an unexplained PSA rise, empiric antibiotics "then retest" remains controversial but is increasingly discouraged by contemporary evidence: some cohorts (e.g., Serretta 2008) reported PSA declines, but randomized trials failed to show diagnostic benefit. Treat symptomatic infection, not the number; otherwise retest,

image, and refine.

F. Programmed follow-up when biopsy is deferred

10. Monitoring cadence: PSA every 6–12 months (document pre-analytical conditions each time); DRE as indicated. This interval is illustrative and should follow institutional protocols and shared decision making; current guidelines do not prescribe a fixed cadence.
11. Re-image (MRI) if:

- PSA or PSAD rises meaningfully (e.g., PSAD crossing locally chosen thresholds such as 0.15–0.20),
- New clinical suspicion arises, or
- Prior MRI quality was suboptimal.

PSA, prostate-specific antigen; UTI, urinary tract infection; DRE, digital rectal examination; MRI, magnetic resonance imaging; PSAD, PSA density; PHI, Prostate Health Index; IsoPSA, isoform PSA; SelectMDx, select molecular diagnostics; ExoDx, exosome diagnostics; MPS/MPS2, MyProstateScore/MyProstateScore 2.0; csPCa, clinically significant prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; EAU, European Association of Urology; AUA/SUO, American Urological Association/Society of Urologic Oncology; NICE, National Institute for Health and Care Excellence.

Do not use PSA velocity alone as the sole trigger for biopsy; interpret in context with PSAD/MRI and overall risk. This algorithm aligns with EAU 2025 (repeat PSA; MRI-first; PSAD-integrated biopsy decisions), AUA/SUO 2023 (retest newly elevated PSA; avoid PSA velocity as a sole trigger; empiric antibiotics discouraged in asymptomatic PSA elevation), and NICE NG131 (consider biopsy omission after negative MRI with shared decision-making). Monitoring intervals should follow local protocols (e.g., 6–12 months) and shared decision-making.