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Beyond the Number: Interpreting Prostate-Specific Antigen Elevation in the Context of Prostate Inflammation

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Prostate-specific antigen (PSA) is indispensable but not cancer specific; inflammation, benign prostatic hyperplasia, urinary retention, ejaculation, and instrumentation can all elevate PSA and complicate cancer risk assessment. This review synthesizes current evidence and guidelines to support clinicians in interpreting PSA elevations when inflammation is present or suspected. Acute febrile urinary tract infection and acute bacterial prostatitis may produce very high PSA values, sometimes exceeding 100 ng/mL, and normalization can be slow; therefore, PSA testing during active infection is discouraged. When PSA is only mildly to moderately elevated, standardized repeat testing is essential because a meaningful proportion of results normalize on retesting. A magnetic resonance imaging (MRI)-first pathway improves detection of clinically significant prostate cancer while reducing overdiagnosis and enables biopsy deferral after a negative MRI under structured monitoring. PSA density (PSAD) further refines triage alongside MRI, with practical working thresholds of roughly 0.10–0.20 ng/mL/cm^3 calibrated to MRI quality and pretest risk. However, asymptomatic histologic prostatitis (National Institutes of Health category IV) is common and may raise PSA without reliably altering PSAD, which means that PSAD alone cannot confirm that an elevation is attributable solely to inflammation. Validated secondary biomarkers (e.g., Prostate Health Index, 4Kscore, IsoPSA [isoform PSA], Stockholm3, Proclarix, PCA3 [prostate cancer gene 3], SelectMDx [select molecular diagnostics], ExoDx [exosome diagnostics], MPS/MPS2 [MyProstateScore/MyProstateScore 2.0]) are best used selectively when MRI is negative or equivocal and clinical risk remains uncertain. A pragmatic sequence—confirm, image, and refine—helps minimize missed clinically significant cancer while reducing unnecessary antibiotics and biopsies when inflammation is the predominant driver of PSA elevation.

Keywords: Prostate-specific antigen, Prostatitis, Prostatic neoplasms, Prostate-specific antigen density

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HIGHLIGHTS

• Prostate-specific antigen (PSA) should not be measured during febrile urinary tract infections or acute prostatitis; levels can exceed 100 ng/mL and normalize slowly.
• Approximately 25%–40% of newly elevated PSA readings normalize on standardized retesting. MRI-first and PSA density (PSAD)-guided pathways improve clinically significant prostate cancer detection, while reducing unnecessary biopsies.
• Asymptomatic histologic prostatitis (National Institutes of Health category IV) is common, but PSAD alone cannot determine whether the elevation is due solely to inflammation.
• Avoid empiric antibiotics for unexplained PSA elevation; treat symptomatic infection, not the number.

INTRODUCTION

Prostate-specific antigen (PSA) remains the most widely used blood test for detecting and monitoring prostate disease. But PSA is sensitive but not specific: it rises not only with cancer but also with benign conditions such as prostatic inflammation, benign prostatic hyperplasia (BPH), urinary retention, recent ejaculation, or instrumentation [1]. PSA rises with both malignant and benign conditions, which lowers specificity. When PSA is elevated, balance vigilance for clinically significant prostate cancer (csPCa) with avoiding unnecessary testing in likely inflammation-driven cases.

Inflammation is a particularly common and consequential confounder. Febrile urinary tract infection (UTI) and acute bacterial prostatitis can produce marked PSA elevations (sometimes 〉100 ng/mL), and normalization may be slow, occasionally taking months and, in rare cases, up to a year. Accordingly, major guidelines advise deferring PSA measurement until the infection has resolved [2-4]. When PSA lies in the diagnostic 'gray zone'—approximately 3–10 ng/mL per EAU guidance—biological and analytical variation further blur interpretation [2]. A substantial share of newly elevated results normalize on retesting even without intervention [5,6].

To manage this uncertainty, contemporary guidance emphasizes standardization and repetition. The European Association of Urology (EAU) Prostate Cancer Guidelines 2025 recommends that in men with PSA 3–10 ng/mL and no suspicious digital rectal examination (DRE), clinicians should repeat PSA after ~4 weeks, in the same laboratory and under standardized conditions (no ejaculation, no recent manipulation, and UTI excluded). If the repeat value normalizes, PSA can be rechecked at 1 year. The same document notes that febrile UTI can greatly inflate PSA and that testing should be postponed in that setting.

The American Urological Association/Society of Urologic Oncology (AUA/SUO) guideline on the Early Detection of Prostate Cancer (2023) aligns with this direction: for a newly elevated PSA, clinicians should confirm with retesting before moving on to a secondary biomarker, imaging, or biopsy; moreover, PSA velocity should not be used as the sole indication for further steps. Importantly, 25%–40% of newly elevated PSAs may normalize on repeat testing, underscoring the value of confirmation before escalation [5].

Randomized and systematic studies have not shown a clinical benefit to empiric antibiotics in asymptomatic men; PSA often falls, but the decline does not exclude cancer [7,8]. PSA may fall after antibiotics, but a decline does not exclude cancer and should not be used to avoid indicated imaging or biopsy.

This review addresses the gray zone where PSA is mildly to moderately elevated and inflammation is present or suspected. We synthesize current evidence and guidelines to propose a risk-adapted, stepwise approach: (1) standardize and repeat PSA; (2) use Multiparametric MRI (mpMRI) and PSA density (PSAD) to triage; (3) deploy validated biomarkers selectively; and (4) treat symptomatic infection, not the number. Our goal is to help clinicians minimize missed clinically significant cancer while reducing unnecessary antibiotics and biopsies in inflammation driven PSA elevations.

PSA BIOLOGY: DISCOVERY, SOURCE, METABOLISM, AND ROLE

The antigen we now call PSA emerged from converging lines of work on semen and prostate tissue. Proteins such as gamma-seminoprotein and p30 were characterized in seminal fluid, while Wang et al. purified PSA from prostate tissue in 1979 and Papsidero et al. later quantified it in serum, enabling clinical translation in the 1980s–1990s [9,10]

PSA is kallikrein related peptidase 3 (KLK3), a secreted serine protease regulated by the androgen receptor (AR) and produced mainly by luminal (secretory) epithelial cells of the prostate. AR signaling drives KLK3 transcription, making PSA abundant in prostatic secretions but present at much lower concentrations in the blood [11,12]. PSA cleaves semenogelin-1 and -2 in seminal

fluid, liquefying the postejaculatory coagulum; human studies support this central role in semen liquefaction [13]. Under normal conditions, epithelial tight junctions, the basal cell layer, basement membrane, and stromal microvasculature limit PSA leakage from ducts into the circulation. Inflammation, benign hyperplasia, instrumentation, or cancer can disrupt these barriers, increasing serum PSA despite benign pathology [14,15].

Once in the circulation, PSA exists in several molecular forms: the predominant immunodetectable species is the complex with α1-antichymotrypsin (PSA-ACT), a smaller fraction circulates as unbound free PSA (fPSA), and a portion binds α2-macroglobulin (PSA-A2M), which sequesters enzymatically active PSA but masks epitopes and is therefore not measured by conventional immunoassays while also clearing more rapidly [16,17]. These biochemical distinctions clarify the clinical significance of percent free PSA (%fPSA) and indicate that most "total PSA (tPSA)" assays predominantly quantify fPSA and PSA-ACT rather than PSA-A2M. Accurate interpretation of borderline PSA values therefore requires careful assay selection and strict preanalytical standardization [15]. Total PSA has a terminal half-life of approximately 2–3 days, whereas free PSA clears more rapidly - within several hours to about one day. Differences in hepatic and renal clearance, as well as inhibitor binding, account for this behavior and provide practical guidance for determining retesting intervals and defining an undetectable nadir [18-20]. Circulating free PSA is heterogeneous, comprising precursor forms such as proPSA—particularly [−2]proPSA—and nicked isoforms like benign PSA associated with BPH. This biochemical diversity underlies why markers such as the percentage of [−2]proPSA (%[−2]proPSA) and the composite Prostate Health Index (PHI) provide diagnostic information beyond tPSA and %fPSA [21,22].

PROSTATITIS RAISES PSA – MAGNITUDE, DURATION, MECHANISMS

Inflammation of the prostate is a frequent, clinically important cause of PSA elevation [23,24]. In acute febrile UTI or acute bacterial prostatitis, serum PSA can rise markedly—occasionally to very high values—and the return to baseline can be slow [4,25,26]. The EAU 2025 guideline explicitly lists febrile UTI as a source of very high PSA values (〉100 ng/mL) and notes that normalization may take up to a year; it therefore recommends deferring PSA testing until the infection has resolved and repeating the test under standardized conditions (no ejaculation, no manipulation, UTI excluded) before moving to imaging or biopsy [2]. Prospective human data are consistent with this time course: in men with febrile UTI, free, complexed, and tPSA values decline over months, with some patients showing protracted recovery despite appropriate antibiotics [4,23-25]. Rare case reports illustrate the extreme: PSA values 〉1,000 ng/mL have been described in acute prostatitis without cancer, underscoring the magnitude of inflammation driven PSA spikes and the potential for diagnostic confusion [26].

Experimental evidence supports these clinical observations. In a well-established nonhuman primate model of bacterial prostatitis [27,28], serum PSA levels rose rapidly, reaching their peak 5 to 7 days after infection, and then gradually declined back to baseline by around 8 weeks. This timeline offers a biologically reasonable framework for how quickly PSA may rise and fall during and after an acute prostate infection. Mechanistically, inflammation disrupts the epithelial–basement membrane–vascular barriers that normally confine PSA to the glandular lumen, facilitating leakage into the circulation; this concept, emphasized in foundational urologic reviews, explains why benign processes like infection, BPH, or instrumentation can raise serum PSA [23,24]. In parallel, inflammatory signaling can modulate KLK3 (PSA) expression: cytokines such as interleukin 6 activate AR pathways and increase PSA gene expression in prostate epithelial and cancer cell models [29-31]. On a broader scale, chronic inflammatory lesions such as proliferative inflammatory atrophy have been proposed as part of an inflammation–carcinogenesis continuum, helping to frame why inflammation may both elevate PSA and in-

tersect with cancer biology [32-34].

For day-to-day decision making, 2 cautions follow. First, a single PSA value cannot rule in or rule out cancer in the setting of inflammation. Contemporary guidelines therefore prioritize confirmation and context. The AUA/SUO 2023 guideline advises that a newly elevated PSA should be repeated before ordering secondary biomarkers, imaging, or biopsy; it also cautions not to use PSA velocity as the sole trigger for escalation [5]. Notably, 25%–40% of newly elevated PSAs normalize on retesting, reflecting biological and analytical variability as well as resolution of transient contributors like inflammation [5,6]. The EAU 2025 guideline offers practical timing: in men with PSA 3–10 ng/mL and a nonsuspicious DRE, repeat PSA after ~4 weeks under standardized pre analytical conditions; if PSA normalizes, retest at one year [2]. Second, PSA testing should be deferred during active infection: febrile UTI can inflate PSA dramatically and delay normalization; testing at that time is more likely to mislead than to help [2,4,5]. These points underpin a risk-adapted pathway in which clinicians repeat and standardize PSA, treat symptomatic infection, and then interpret the trend alongside mpMRI, PSAD, and biomarkers as needed.

PSA TESTING DURING ACTIVE INFECTION AND THE 'ANTIBIOTICS THEN RETEST' PITFALL

When infection is clinically active–especially febrile UTI or acute bacterial prostatitis–PSA testing should be deferred, because infection can inflate PSA dramatically and normalize only slowly. The 2025 EAU guideline notes that febrile UTI can produce 〉100-ng/mL PSA and that normalization may be slow (up to a year) [2]. Defer PSA until recovery and repeat under standardized conditions (same lab/assay; no ejaculation/manipulation; UTI excluded). However, in real world practice, acute infection may be clinically uncertain—imaging is often nondiagnostic and urinalysis can be normal. In such scenarios, obtaining a PSA for differential diagnosis can be reasonable, provided that results are interpreted cautiously and the test is repeated after clinical recovery before proceeding to imaging or biopsy. Clinical data echo this: in men with febrile UTI, 83% have an elevated PSA at presentation (median, ~14 ng/mL; range, 0.54–140 ng/mL), with a rapid fall over the first month but protracted decline thereafter in a subset—behavior that can easily mislead if PSA is checked during the acute phase [4]. Prospective studies measuring free, complexed, and tPSA show that complexed PSA and tPSA can remain elevated for months after a febrile UTI, a pattern that may be mistaken for cancer if timing and clinical context are ignored [3].

Against this background, the once common approach—empiric antibiotics for an unexplained, asymptomatic PSA rise followed by retesting—remains controversial but is increasingly discouraged by contemporary evidence. Although a few observational cohorts, such as Serretta et al. [35], reported PSA declines and proposed selective clinical utility, randomized trials [7,36] failed to confirm a meaningful diagnostic advantage, leading major guidelines to recommend against routine use. The EAU guideline explicitly advises against empiric antibiotics in an asymptomatic man to lower PSA before decision making [2]. In the prospective clinical trial by Stopiglia et al. [36], PSA decreases occurred in both the ciprofloxacin and placebo arms, and a PSA fall did not exclude cancer on subsequent biopsy. In the multi-institutional RCT [7], 2 weeks of ciprofloxacin did not produce a statistically significant change in PSA level compared with controls and did not improve cancer detection outcomes. A systematic review focused on National Institutes of Health (NIH) category IV (asymptomatic) prostatitis similarly found no advantage of antibiotics over observation in the 2 available randomized trials, despite PSA declines reported in uncontrolled series [8].

Observational studies and some meta-analyses have reported short term PSA reductions after antibiotics in selected cohorts, but these signals do not validate biopsy avoidance and may reflect regression to the mean, selection, or timing effects rather than a causal antibiotic

effect. For example, in a prospective series, PSA often decreased after empiric therapy without lowering the likelihood of cancer; cancer detection was not reduced [7,36]—and was higher in men whose PSA fell ("responders") in one study [37]. Earlier uncontrolled work [35] suggested that large PSA drops might identify men who could defer biopsy, but the nonrandomized design and inconsistent oncologic outcomes limit generalizability. Taken together, these data, plus antimicrobial resistance concerns, support an antibiotic stewardship stance: treat symptomatic infection, not the PSA number. In men with active infection, manage the infection first and delay PSA; in men with an asymptomatic, mildly to moderately elevated PSA, standardize and repeat the test EAU Prostate Cancer Guidelines suggests ~4 weeks for PSA 3–10 ng/mL) and then use mpMRI, PSAD, and selective biomarkers to triage rather than prescribing empiric antibiotics [2].

ASYMPTOMATIC HISTOLOGIC PROSTATITIS (NIH CATEGORY IV): PREVALENCE AND LIMITATIONS OF PSAD

Asymptomatic, histologically defined prostatic inflammation (NIH category IV) is common and can increase tPSA, but its effect on PSAD is inconsistent across cohorts. In several benign cohorts, PSAD does not differ meaningfully by histologic inflammation, likely because prostate volume increases alongside PSA in benign disease [23,38]. By contrast, when inflammation is epithelium disruptive or "aggressive," both tPSA and PSAD tend to be higher and %fPSA lower [23,39-41]. Mixed histology series from different settings also document high background rates of histologic prostatitis (mostly chronic), underscoring the ubiquity of inflammation in noncancer tissue [42,43]. We therefore emphasize PSAD here because it is central to MRI-based triage in contemporary practice, but PSAD alone cannot prove that an elevated PSA is "just inflammation"; clinicians should integrate MRI findings and, when needed, validated biomarkers [44].

Asymptomatic histologic prostatitis (NIH category IV) can increase tPSA; however, the mere presence or extent of inflammation does not consistently correlate with PSA or PSAD across cohorts. Associations are more evident when inflammation is epithelium disruptive ("aggressive"), which tends to raise PSA and PSAD and lower %fPSA; conversely, in benign enlargement prostate volume may offset inflammation-related PSA increases, resulting in similar PSAD [23,38-42,45,46]. Therefore, PSAD should be interpreted together with MRI findings rather than used alone to assume that a high PSA is caused only by inflammation [44]. In one biopsy-based study, the mere extent of inflammation showed no association with PSA or PSAD, but more aggressive inflammation - characterized by dense leukocytic infiltration and epithelial disruption—was significantly correlated with higher PSA and PSAD values (PSA, $p=0.0028$; PSAD, $p=0.033$) [23]. Yaman et al. [47] similarly found no correlation with extent, but significant correlations between aggressiveness and tPSA/PSAD (both $p<0.001$). Kandirali et al. [39] reported positive correlations of both extent and aggressiveness with PSA and PSAD, and a negative correlation with %fPSA, suggesting that more disruptive inflammation reduces free PSA fractions. Complementing this, Stimac et al. [40] showed that subclinical inflammation can lower fPSA and %fPSA in men without cancer with tPSA<10 ng/mL, yielding a biomarker pattern similar to prostate cancer - namely a reduced %fPSA, consistent with a shift toward PSA-ACT bound forms. Other reports highlight context effects: in negative biopsy patients, prostate size may overshadow inflammation as the independent determinant of PSA, with acute inflammatory aggressiveness mattering more in small prostates [41,45]. In summary, the evidence is heterogeneous. Histologic inflammation can raise PSA and sometimes PSAD, especially when the epithelium is disrupted. However, across cohorts, PSAD alone is not a reliable indicator that an elevated PSA is due only to inflammation.

Modern prospective studies suggest that PSAD can

aid in distinguishing inflammation-related PSA elevations from those due to clinically significant prostate cancer, but this distinction should be interpreted with caution. In a large single center study of 1,988 biopsy candidates, Bruno et al. [46] found that PSAD strongly predicted clinically significant cancer and was not associated with intraprostatic inflammation; in men without csPCa, those with inflammation had higher PSA and larger prostates, but similar PSAD to those without inflammation. Proposed PSAD cutoffs to enrich for csPCa while ruling out inflammation driven PSA were 0.10 ng/mL/cm^3 in biopsy naïve men and 0.15 ng/mL/cm^3 after a prior negative biopsy [46]. These findings echo earlier BPH surgery data (no PSAD difference by histology) and help explain why PSAD often outperforms tPSA in the "gray zone," while also cautioning that PSAD should not be used to attribute an elevated PSA to inflammation without clinical context [48]. NIH category IV inflammation is common and can confound PSA-based risk assessment. Use PSAD as part of a multimodal pathway—repeat PSA under standardized conditions, assess mpMRI, and consider biomarkers—rather than assuming that an abnormal PSAD reflects inflammation alone.

BEYOND TPSA – MPMRI, PSAD, AND MODERN BIOMARKERS

Multiparametric MRI before biopsy has reshaped the diagnostic pathway by improving detection of csPCa while lowering detection of indolent disease. In the paired validation PROMIS study, mpMRI used as a triage test showed higher sensitivity (93%) and negative predictive value (89%) for csPCa than standard transrectal ultrasound biopsy, supporting an "MRI first" approach [44]. The randomized PRECISION trial then demonstrated that an MRI-targeted biopsy strategy significantly improved the detection of csPCa compared with systematic biopsy alone (38% vs. 26%), while markedly reducing the diagnosis of clinically insignificant cancer (9% vs. 22%). Notably, about 28 % of men with negative MRI findings were able to avoid biopsy altogether, supporting an 'MRI-first' diagnostic approach [49]. Current guidelines summarize this shift: used as a triage test, MRI provides excellent negative predictive value for ruling out csPCa at biopsy and remains reassuring over multiyear follow-up [2].

Population level screening data further support an MRI directed pathway. In the Swedish STHLM3 MRI randomized trial, a PSA→MRI strategy with targeted biopsy in MRI positive men was noninferior for csPCa detection and reduced detection of clinically insignificant cancer compared with systematic biopsy [50]. In the GÖTEBORG 2 program, a PSA and MRI pathway allowed biopsy omission after a negative MRI with structured monitoring, substantially reducing diagnoses of clinically insignificant cancer while maintaining an extremely low rate of interval or advanced (incurable) cancer during follow-up [51,52]. These trials, together with meta-analyses and prospective cohorts, underpin an MRI first diagnostic workflow that is now widely adopted [53,54].

PSAD refines risk stratification alongside MRI. The EAU 2025 guideline explicitly recommends integrating PSAD with MRI findings and provides practical thresholds: when MRI is negative (Prostate Imaging Reporting and Data System [PI-RADS] ≤2) and PSAD 〈0.20 ng/mL/cm^3 with low clinical suspicion, biopsy can be omitted with PSA monitoring; when MRI is indeterminate (PI-RADS 3) and PSAD〈0.10 ng/mL/cm^3, observation with PSA monitoring is reasonable [2]. Contemporary evidence supports tailoring thresholds between 0.10–0.20 depending on MRI quality and pretest risk: for negative MRI, posttest probabilities of csPCa drop to ~6% at PSAD 〈0.15 and ~4% at PSAD 〈0.10 [55]. In PI-RADS 3 lesions, several studies identify 0.10 as a sensible biopsy trigger, balancing missed csPCa against unnecessary procedures [56]. Other cohorts and reviews corroborate that adding PSAD to the MRI pathway improves triage performance, with some suggesting 0.12–0.15 as alternative cutoffs depending on local prevalence and imaging performance [57,58].

Validated secondary biomarkers can complement MRI/PSAD when risk remains equivocal (e.g., PSA 3–10

Table 1. Practical triage using MRI and PSAD

MRI category	PSAD threshold (ng/mL/cm³)	Suggested action
PI-RADS ≤2	<0.20 (consider <0.15 or <0.10 if high MRI quality/low pretest risk)	Defer biopsy, programmatic PSA monitoring
PI-RADS 3	<0.10	Observation±biomarker if uncertainty
PI-RADS 3	≥0.10	Consider targeted (±systematic) biopsy (or biomarker if borderline)
PI-RADS ≥4	-	Targeted (±systematic) biopsy

MRI, magnetic resonance imaging; PSA, prostate-specific antigen; PSAD, PSA density; PI-RADS, Prostate Imaging Reporting and Data System; NIH, National Institutes of Health.
NIH IV asymptomatic histologic prostatitis is common and may raise PSA without reliably altering PSAD; PSAD alone cannot prove "just inflammation." Use PSAD to contextualize MRI—not to dismiss risk.

ng/mL, negative or indeterminate MRI). The EAU 2025 guideline lists blood-based PHI, 4Kscore, IsoPSA, Stockholm3, Proclarix, and urine-based PCA3, SelectMDx, MyProstateScore (MPS/MPS2), ExoDx as options for selective use [2]. Representative data include: for PHI, a large multicenter trial (PSA, 2–10 ng/mL) showed improved specificity and potential to reduce unnecessary biopsy [59,60]. The 4Kscore has been prospectively validated to predict high grade cancer and shown to influence biopsy decisions in practice [61,62]. IsoPSA, a structure focused assay, demonstrated superior discrimination versus total and %free PSA in multicenter validation [63,64]. Stockholm3 (S3M) improves risk prediction over PSA and has been used within MRI-based screening workflows [50,65]. Proclarix can reduce unnecessary MRI/biopsies while preserving csPCa detection in selected cohorts [66]. For urine markers, PCA3 shows moderate accuracy and is most helpful in repeat biopsy settings [67,68]. SelectMDx adds information for ≥GG2 risk stratification and can be combined with MRI to refine decisions [69,70]. The exosomal RNA assay ExoDx (EPI) has been validated to predict ≥GG2 at initial biopsy and shown clinical utility for biopsy deferral [71,72]. Finally, MyProstateScore (MPS) improves rule out performance over PSA alone, and next generation MPS2 panels are emerging with promising validation [73,74].

Putting it together in practice, a risk-stratified pathway for clinically significant prostate cancer is pragmatic and evidence-based: (1) confirm a newly elevated PSA under standardized conditions; for PSA 3–10 ng/mL and nonsuspicious DRE, repeat in ~4 weeks as per EAU guideline. (2) obtain mpMRI; if MRI is negative and PSAD 〈0.20, consider no biopsy with PSA monitoring; if PI-RADS 3 and PSAD 〈0.10, observation is reasonable; otherwise proceed to targeted (± systematic) biopsy depending on risk. (3) in gray zone cases—especially with negative or equivocal MRI—use validated biomarkers selectively to reduce unnecessary biopsy without sacrificing csPCa detection, choosing tests supported by local availability, cost, and published performance [2]. This combination of MRI, PSAD, and targeted biomarkers helps clinicians avoid both missed csPCa and avoidable procedures—precisely the balance needed when inflammation and other benign factors blur the meaning of a raised PSA (Table 1).

GUIDELINE-BASED FOLLOW-UP STRATEGIES FOR ELEVATED PSA

Across major guidelines, 3 themes are consistent: (1) confirm and standardize a newly elevated PSA before escalation, (2) use an MRI first pathway with PSAD to triage biopsy, and (3) avoid relying on PSA velocity alone. The EAU 2025 guideline states that in men with PSA 3–10 ng/mL and a nonsuspicious DRE, clinicians should repeat PSA after ~4 weeks in the same laboratory and under standardized conditions (no ejaculation or manipulation and UTI excluded), with annual re check if PSA normalizes [2]. In parallel, the AUA/SUO 2023 guideline advises that a newly elevated PSA should be repeated before ordering a secondary biomarker, imaging, or biopsy, and that PSA velocity should not be used as the

sole indication for further testing [5]. The National Institute for Health and Care Excellence (NICE) guideline (NG131) embeds pre biopsy mpMRI into the diagnostic pathway and supports biopsy deferral with structured monitoring after a negative MRI when clinical suspicion is low [75].

The EAU 2025 document also details sources of PSA error that must be controlled when following up an elevation. It explicitly notes that (febrile) UTI can produce very high PSA values (〉100 ng/mL) and that normalization can take up to a year, reinforcing the recommendation not to test during active infection and to delay repeat testing until recovery. Prospective data in febrile UTI show the same pattern: free, complexed, and tPSA fall rapidly at first, but residual elevation can persist for months, which can mislead if timing and context are ignored [2].

What to do after confirmation that PSA remains elevated? Guidelines now anchor decision making on mpMRI plus PSAD. The EAU 2025 recommends that if MRI is negative (PI-RADS ≤2) and clinical suspicion is low (e.g., PSAD 〈0.20 ng/mL/cm^3, negative DRE, no family history), omit biopsy and monitor PSA; if MRI is indeterminate (PI-RADS 3) and suspicion is very low (e.g., PSAD 〈0.10 ng/mL/cm^3 with favorable clinical features), observation is also reasonable [2]. These recommendations are supported by population level trials showing that an MRI directed pathway reduces overdiagnosis and allows biopsy omission after a negative MRI with very low risk of incurable or interval cancer under programmatic monitoring [51,52].

Putting this into a practical follow-up pathway: If the patient has symptomatic acute UTI or acute prostatitis, treat the infection first and defer PSA; a pragmatic window is to wait at least several weeks (often ≥6–8 weeks) after symptom resolution before retesting, recognizing that normalization can be delayed and occasionally prolonged, as noted by EAU and prospective UTI cohorts [2]. In asymptomatic men with PSA 3–10 ng/mL and a normal DRE, repeat PSA in ~4 weeks under standardized conditions; if still elevated, proceed to mpMRI, then use PSAD (and, when needed, validated biomarkers) to triage biopsy versus observation, rather than relying on PSA velocity [2,5]. In men with a negative MRI, shared decision making about biopsy deferral with programmed monitoring is justified by contemporary randomized data and is reflected in UK practice patterns following NICE [51,75].

CONCLUSION

PSA remains indispensable yet imperfect: inflammation, BPH, urinary retention, ejaculation, and instrumentation can all raise levels, making context and confirmation essential. Across guidelines and evidence, 3 principles are consistent: do not measure PSA during active infection, do not “treat the number,” and do not act on a single result. When PSA remains elevated, a risk-adapted, MRI-based pathway reduces overdiagnosis while preserving detection of clinically significant cancer. Integrating MRI, PSAD, and validated biomarkers provides a balanced, evidence-based approach that minimizes missed disease and avoids unnecessary procedures.

A crucial nuance is that asymptomatic histologic prostatitis (NIH category IV) is common and may raise PSA without consistently changing PSAD; therefore, PSAD should be interpreted together with MRI findings, not in isolation. In symptomatic infection, treat first and retest after recovery (typically ≥6–8 weeks). In asymptomatic mild elevations, standardize and repeat PSA, then use MRI and PSAD, adding biomarkers only when uncertainty persists. This simple sequence “confirm → image → refine” captures the essence of contemporary PSA interpretation. A practical clinical algorithm summarizing this approach is provided as Supplementary Material to support real-world implementation. Key research needs include understanding the time course of PSA normalization after inflammation, validating PSAD thresholds across MRI settings, and generating prospective data in diverse populations, especially in Asia. Such evidence will refine our ability to distinguish inflammation-related

PSA increases from those due to prostate cancer, helping clinicians detect significant disease without exposing patients to unnecessary procedures.

NOTES

- **Supplementary Material:** Supplementary Material is available at https://doi.org/10.14777/uti.2550032016.
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