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POSITION PAPER

Prostate cancer diagnostic pathway in men with lower urinary tract symptoms or performing opportunistic screening: The Italian Society of Urology (SIU) position paper

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ABSTRACT

BACKGROUND: Voluntary PCa screening frequently results in excessive use of unnecessary diagnostic tests and an increasing risk of detection of indolent PCa and unaffordable costs for the various national health systems. In this scenario, the Italian Society of Urology (Società Italiana di Urologia, SIU) proposes an organized flow chart guiding physicians to improve early diagnosis of significant PCa avoiding unnecessary diagnostic tests and prostate biopsy.

METHODS: According to available evidence and international guidelines [*i.e.*, European Association of Urology (EAU), American Association of Urology (AUA) and National Comprehensive Cancer Network (NCCN)] on PCa, a Panel of expert urologists selected by Italian Society of Urology (SIU, Società Italiana di Urologia) proposed some indications to develop a stepwise diagnostic pathway based on the diagnostic tests mainly used in the clinical practice. The final document was submitted to six expert urologists for external revision and approval. Moreover, the final document was shared with patient advocacy groups.

RESULTS: In voluntary men and symptomatic patients with elevated PSA value (>3 ng/mL), the Panel strongly discourage the use of antibiotic agents in absence of urinary tract infection confirmed by urine culture. DRE remains a key part of the urologic physical examination helping urologists to correctly interpret PSA elevation and prioritizing the execution of multiparametric Magnetic Resonance Imaging (mpMRI) in presence of suspicious PCa. Men with negative mpMRI and low clinical suspicion of PSA (PSA density < 0.20 ng/mL/cc, negative DRE findings, no family history) can be further

monitored. Men with negative mpMRI and a higher risk of PCa (familial history, suspicious DRE, PSAD>0.20 ng/mL/cc or PSA>20 ng/mL) should be considered for systematic prostate biopsy. While PI-RADS 4-5 lesions represent a strong indication for prostate biopsy, PI-RADS 3 lesions should be further stratified according to PSAD values and prostate biopsy performed when PSAD is higher than 0.20. Accreditation, certification, and quality audits of radiologists and centers performing prostatic mpMRI should be strongly considered. The accessibility and/or the waiting list for MRI examinations should be also evaluated in the diagnostic pathway. The panel suggests performing transperineal or transrectal targeted plus systematic biopsies as standard of care.

CONCLUSIONS: Scientific societies must support the use of shared diagnostic pathway with the aim to increase the early detection of significant PCa reducing a delayed diagnosis of advanced PCa. Moreover, a shared diagnostic pathway can reduce the incorrect use of antibiotic, the number of unnecessary laboratory and radiologic examinations as well as of prostate biopsies.

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KEY WORDS: Prostatic neoplasms; Diagnosis; Lower urinary tract symptoms; Prostate-specific antigen; Digital rectal examination; Magnetic resonance imaging.

In Italy, prostate cancer (PCa) is the most frequent cancer in men representing 19.8% of all sites, with a reported incidence in 2023 of 41,100 new cases. In 2022, an estimated 8,200 deaths were attributed to PCa. Currently, approximately 564,000 men live with a diagnosis of PCa in Italy.[1] In the USA the probability of developing an advanced PCa is 3.9% for men between 50 and 64 years, and 10.4% for those between 65 and 85 years, respectively. Overall, the probability of developing an advanced PCa over the lifetime is 12.9%.[2] Studies on PSA-based screening conducted on invited, asymptomatic men showed conflicting results.[3, 4] At a median follow-up of 21 years, the ERSPC Rotterdam Study Group showed significantly lower PCa mortality in screened individuals as compared with the control group (RR: 0.73-95%CI: 0.61-0.88). The overdetection of indolent PCa and consequent overtreatment are the main disadvantages of population based PCa screening program. Recently, clinical trials demonstrated that the use of pre-biopsy mpMRI can reduce the risk of overdetection of indolent PCa and the risk of underdetection of clinically significant disease.[5, 6]

Waiting for pilot studies testing modern population-based PCa screening programs, early diagnosis of PCa is currently made from non-organized, individual, opportunistic screenings or emerges within the diagnostic pathway for evaluation of lower urinary tract symptoms (LUTS) secondary to prostate enlargement. Patients with urological symptoms often have a higher chance of elevated PSA due to benign prostatic conditions rather than PCa. Voluntary, unorganized PCa screening frequently results in excessive use of unnecessary diagnostic tests and an increasing risk of detection of indolent PCa and unaffordable costs for the various national health systems. Moreover, voluntary screening programs are more achievable in high-income countries, potentially generating social iniquity.

In this scenario, the Italian Society of Urology (Società Italiana di Urologia, SIU) established a dedicated working group to propose an organized flow chart guiding physicians to improve early diagnosis of significant PCa avoiding unnecessary diagnostic tests and prostate biopsy.

Materials and methods

In April 2024, the SIU scientific committee composed a team of urologist's experts in the field of PCa screening and early diagnosis aiming to report the current recommendations of the leading International Guidelines on PCa diagnosis in men who did not undergo an organized screening program. According to available evidence and international guidelines (*i.e.*, European Association of Urology [EAU], American Association of Urology [AUA] and National Comprehensive Cancer Network [NCCN]) on PCa, the Panel proposed some indications to develop a stepwise diagnostic pathway based on the diagnostic tests mainly used in the clinical practice.

The final document was submitted to expert

urologists for external revision and approval. Moreover, the final document was shared with members of scientific committees of patient advocacy groups [EUROPA Uomo Italia and Fondazione Prevenzione Ricerca Oncologia].

The diagnostic pathway

Total PSA is the primary test performed in men presenting for voluntary screening or referred for LUTS. PSA is not a cancer-specific biomarker, and therefore it may be elevated also in conditions including benign prostatic hyperplasia (BPH), prostatitis, and other non-malignant disorders. Moreover, total PSA should be considered as a continuous parameter, with higher values correlating with a greater likelihood of PCa diagnosis, with no "normal" values. Indeed, 23.9% of men with a PSA level ≤3 ng/mL and a normal digital rectal examination (DRE) had a PCa, with 4.6% of them showing even a clinically significant disease. Nevertheless, more than 67% of patients with PSA>10 ng/mL had positive prostate biopsy.[7]

As previously reported, in the most representative PSA-based screening protocols, the cut-off of ≥3 ng/mL was the most frequently used. Although the context in which patients performing the test outside a population-based screening is different from those included in a population-based algorithm, the PSA test keeps its diagnostic value for PCa detection also in asymptomatic men voluntarily performing the test and in patients with LUTS due to prostate enlargement.

In voluntary men and symptomatic patients with elevated PSA value (>3 ng/mL), initial steps should include a repeated confirmatory test to rule out possible laboratory error. Moreover, all confounding factors (recent ejaculation, vigorous exercise, transurethral or transrectal maneuvers) and benign conditions (prostatitis, prostate enlargement due to adenoma) potentially responsible for PSA elevation must be carefully assessed and eventually treated before repeating PSA test itself.

Considering the concerns due to the antimicrobial resistance in the European Union, we strongly discourage the use of antibiotic agents in presence of increased PSA levels and in absence of urinary tract infection confirmed by urine culture.

Suspicious elevation of PSA levels must be further evaluated before proceeding to prostate biopsy. DRE is part of the urologic physical examination, and it can contribute to the interpretation of PSA elevation detecting a suspicion of prostatitis or a significant prostate enlargement. Moreover, DRE can raise the suspicion of cancer showing induration of the prostate with a positive predictive value ranging from 5-30%.[8] A positive DRE is a strong indication to carry out a mpMRI in a relatively short time frame because of the high likelihood of detecting a clinically significant PCa. Considering the issues related to the waiting list, a positive DRE represents a criterion to prioritize access to mpMRI. This should consider the actual availability and accessibility of appropriate mpMRI in the different geographic areas. In cases where the mpMRI cannot be performed in an appropriate time is it advisable to perform directly prostate biopsy. Similar considerations can be made for patients showing a PSA higher than 20 ng/mL and a negative DRE.

DRE remains a key part of the urologic physical examination helping urologists to correctly interpret PSA elevation while excluding prostatitis or better qualifying benign prostate enlargement, thus raising the suspicion of PCa. In the last case, mpMRI should be performed in a short time or, in the alternative skipped in favor of an upfront prostate biopsy.

Men with total PSA ranging between 3-20 ng/mL and a normal DRE must be further investigated with a mpMRI. Besides suggesting the presence of PCa, the mpMRI allows precise calculation of prostate volume (and subsequently PSA density), precise targeting of the index lesion(s), and eventually facilitates the definition of the clinical staging of the disease. Moreover, the application of the Prostate Imaging-Reporting and Data System (PI-RADS) criteria resulted in fewer unnecessary prostate biopsies and detection of clinically insignificant PCa. A recent meta-analysis reported an overall predictive positive value (PPV) for positive mpMRI (PI-RADS≥3) of 40% (95% confidence interval [CI] 36-43%) with an incremental value based on PCa suspicion. Specifically, PPV was 13%, 40%, and 69% for PI-RADS 3, 4, and 5 lesions, respectively.[9] A further meta-analysis reported an average PPVs

for clinically significant PCa with a PI-RADS version 2.1 score of 3, 4 and 5 of 16% (7-27%), 59% (39-78%), and 85% (73-94%), respectively, showing a significant heterogeneity among studies.[10] Moreover, mpMRI showed an excellent NPV for ruling out the presence of clinically significant PCa not only at a subsequent biopsy but also after four years of follow-up.[11, 12] The real radiologist volume coupled with the imaging quality can eventually play a significant role in influencing the diagnostic yield of mpMRI and explain the heterogeneity among available studies. In this context, adequate radiologist training, accreditation, certification, and quality audits are needed.[13, 14] Men with negative mpMRI and low clinical suspicion of PSA (PSA density <0.15 ng/mL/cc, negative DRE findings, no family history) can be further monitored. Men with negative mpMRI and a higher risk of PCa (familial history, suspicious DRE, PSAD>0.15 ng/mL/cc or PSA>10 ng/mL) should be considered for systematic prostate biopsy, since the occurrence of false-negative findings at mpMRI is not negligible. In this scenario, the clinical interpretation of all the available data by the treating Urologist has a paramount importance in the further diagnostic pathway. The need for a mpMRI could be questionable in patients with life-expectancy less than 5 years or aged ≥80 years.

While PI-RADS 4-5 lesions entail a high risk for PCa and represent a strong indication for prostate biopsy, PI-RADS 3 lesions should be carefully considered. The prevalence of PI-RADS 3 lesions is approximately 17.3% with clinically significant PCa identified only in 18.5% of biopsied cases.[15] To avoid unnecessary biopsies, mpMRI examinations reporting PI-RADS 3 lesions should be reviewed by expert radiologists. Then, patients with confirmed PI-RADS 3 lesions could be further stratified according to PSAD values. Available risk-adapted matrix table for biopsy decision management suggested that prostate biopsy should be considered in patients with PI-RADS 3 lesions and PSAD value between 0.10-0.15, highly considered when PSAD ranged between 0.15-0.20 and it must be performed when PSAD is higher than 0.20.[16] The Panel suggests the PSAD cut-off value of 0.15 to discriminate between patients at different risk of PCa. Figure 1 summarizes the proposed diagnostic algorithm for PCa.

Considering the crucial role of pre-biopsy mpMRI, it is strongly recommended that the examination be performed by dedicated, experienced, high-volume radiologists. The quality of prostate imaging is an essential criterion for the appropriateness of the examination report. Accreditation, certification, and quality audits

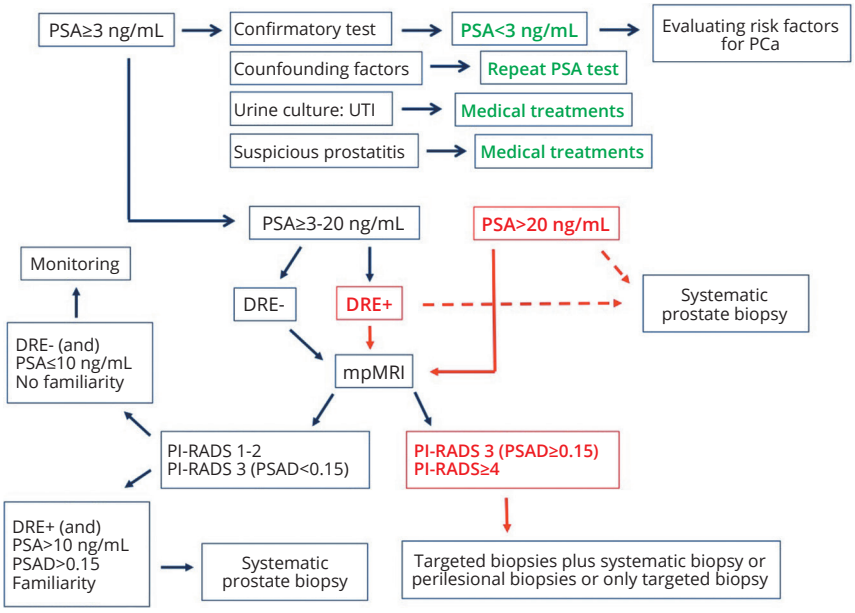

Figure 1.—Italian Society of Urology (SIU) proposed Prostate Cancer diagnostic algorithm for men with Lower Urinary Tract Symptoms (LUTS) or performing opportunistic screening.

of radiologists and centers performing prostatic mpMRI should be strongly considered. The accessibility and/or the waiting list for MRI examinations should be also evaluated in the diagnostic pathway.

Although MRI in-bore prostate biopsy can be performed in some specialized centers, fusion guided prostate biopsy, either performed by transperineal or transrectal US approaches, remains the largest used method. Literature data seems to be in favor of the transperineal approach in terms of higher detection of clinically significant PCa above anteriorly located and a significantly reduced risk of postoperative infections.[17, 18]

Concerning biopsy strategy, systematic and targeted biopsies represent the two options that can be usually combined. Moreover, targeted biopsies can be obtained using cognitive guidance, US/MR fusion software, or direct in-bore guidance, with, apparently, no superiority of one over the other technique.[19] To employ cognitive, fusion, or in-bore guidance for targeted biopsies depends on the available technology and experience. For several years, the combination of targeted and systematic biopsies represented the best strategy for patients' candidates to prostate biopsies. However, a recent meta-analysis showed that targeted biopsy plus peri-lesional/regional systematic sampling had no significant difference in comparison with mpMRI targeted plus systematic biopsies in terms of detection of clinically significant PCa.[20] Therefore, peri-lesional biopsies could be an adequate alternative strategy to an additional systematic sampling to reduce the number of cores taken in patients with positive mpMRI.[21] However, some studies highlighted that perilesional biopsies without systemic sampling can miss 7-10% of clinically significant PCa.[22, 23]

The panel suggests still performing targeted plus systematic biopsies as standard of care Schemes based on targeted biopsies with or without additional perilesional biopsies must be considered under investigation.

Conclusions

Waiting for the implementation of population based, organized PCa screening, scientific societies must support the use of shared diagnostic pathway with the aim to increase the early detection of significant PCa reducing a delayed diagnosis of advanced PCa. Moreover, a shared diagnostic pathway can reduce the incorrect use of antibiotic, the number of unnecessary laboratory and radiologic examinations as well as of prostate biopsies. Therefore, the wide application of the proposed diagnostic pathway can represent a valid tool to reduce the costs of national health system for the diagnosis of PCa.

References

1. Associazione Italiana Oncologi Medici (AIOM): I numeri del cancro in Italia 2023. Orvieto: Intermedia Editore; 2023.

2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12–49.

3. Pinsky PF, Parnes H. Screening for Prostate Cancer. N Engl J Med 2023;388:1405–14.

4. James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, *et al.* The Lancet Commission on prostate cancer: planning for the surge in cases. Lancet 2024;403:1683–722.

5. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, *et al.*; PROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.

6. Kasivisvanathan V, Emberton M, Moore CM. MR-targetedbiopsy for prostate cancer diagnosis. N Engl J Med 2018;379:589–90.

7. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, *et al.* Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004;350:2239–46.

8. Carvalhal GF, Smith DS, Mager DE, Ramos C, Catalona WJ. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. J Urol 1999;161:835–9.

9. Mazzone E, Stabile A, Pellegrino F, Basile G, Cignoli D, Cirulli GO, *et al.* Positive predictive value of prostate imaging reporting and data system version 2 for the detection of clinically significant prostate cancer: a systematic review and meta-analysis. Eur Urol Oncol 2021;4:697–713.

10. Oerther B, Engel H, Bamberg F, Sigle A, Gratzke C, Bendorf M. Cancer detection rates of the PI-RADSv2.1 assessment categories: systematic review and meta-analysis on lesion level and patient level. Prostate Cancer Prostatic Dis 2022;25:256–63.

11. Moldovan PC, Van den Broeck T, Sylvester R, Marconi L, Bellmunt J, van den Bergh RC, *et al.* What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol 2017;72:250–66.

12. Kamal O, Comerford J, Foster BR, Young DJ, Amling C, Coakley FV. Intermediate-term oncological outcomes after a negative endorectal coil multiparametric MRI of the prostate in patients without biopsy proven prostate cancer. Clin Imaging 2022;92:112–6.

13. Padhani AR, Barentsz J, Villeirs G, Rosenkrantz AB, Margolis DJ, Turkbey B, *et al.*; PI-RADS Steering Committee. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. Radiology 2019;292:464–74.

14. Stabile A, Sorce G, Barletta F, Brembilla G, Mazzone E, Pellegrino F, *et al.* Impact of prostate MRI central review over the diagnostic performance of MRI-targeted biopsy: should we routinely ask for an expert second opinion? World J Urol 2023;41:3231–7.

15. Maggi M, Panebianco V, Mosca A, Salciccia S, Gentilucci A, Di Pierro G, *et al.* Prostate Imaging Reporting and Data System 3 Category Cases at Multiparametric Magnetic Resonance for Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus 2020;6:463–78.

16. Schoots IG, Padhani AR. Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation. BJU Int 2021;127:175–8.

17. Tu X, Liu Z, Chang T, Qiu S, Xu H, Bao Y, *et al.* Transperineal Magnetic Resonance Imaging-Targeted Biopsy May Perform Better Than Transrectal Route in the Detection of Clinically Significant Prostate Cancer: Systematic Review and Meta-analysis. Clin Genitourin Cancer 2019;17:e860–70.

18. Pilatz A, Veeratterapillay R, Köves B, Cai T, Bartoletti R, Wagenlehner F, *et al.* Update on Strategies to Reduce Infectious Complications After Prostate Biopsy. Eur Urol Focus 2019;5:20–8.

19. Falagario UG, Pellegrino F, Fanelli A, Guzzi F, Bartoletti R, Cash H, *et al.* Prostate cancer detection and complications of MRI-targeted prostate biopsy using cognitive registration, software-assisted image fusion or in-bore guidance: a systematic review and meta-analysis of comparative studies. Prostate Cancer Prostatic Dis 2024. [Epub ahead of print].

20. Hagens MJ, Noordzij MA, Mazel JW, Jager A, Boellaard TN, Tielbeek JA, *et al.* An Magnetic Resonance Imaging-directed Targeted-plus-perilesional Biopsy Approach for Prostate Cancer Diagnosis: "Less Is More". Eur Urol Open Sci 2022;43:68–73.

21. Cornford P, Tilki D. van den Bergh RCN *et al.* EAU Guidelines on Prostate Cancer 2024 [Internet]. Available from: www.uroweb.org [cited 2024, Sep 11].

22. Duwe G, Schmitteckert M, Haack M, Sparwasser P, Dotzauer R, Thomas A, *et al.* Value of perilesional biopsies in multiparametric magnetic resonance imaging-targeted biopsy and systematic biopsy in detection of prostate cancer: results of a prospective, non-randomized, surgeon-blinded study. World J Urol 2024;42:297.

23. Lombardo R, Tema G, Nacchia A, Mancini E, Franco S, Zammitti F, *et al.* Role of Perilesional Sampling of Patients Undergoing Fusion Prostate Biopsies. Life (Basel) 2023;13:1719.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Protocol/project development Vincenzo Ficarra; data collection or management: all; data analysis: all; manuscript writing/editing: all; supervision: Vincenzo Ficarra; Giuseppe Carrieri. All authors read and approved the final version of the manuscript

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