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LETTER TO EDITOR

The need for novel biomarkers in prostate cancer: A UrOP perspective

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Dear Editor,

Prostate cancer (PCa) remains one of the most common malignancies among men worldwide, representing a major healthcare burden both in terms of morbidity and economic cost (1-5). Over the last two decades, the diagnostic pathway for prostate cancer has been substantially re-evaluated and modelled by the introduction of *multiparametric magnetic resonance imaging* (mpMRI) and targeted biopsies (6-11). While these tools have improved the detection of *clinically significant prostate cancer* (csPCa), they have also contributed to a considerable increase in healthcare costs and patient burden. The *Urologi Ospedalità Gestione Privata* (UROP) scientific association strongly believes that the time has come to shift a substantial part of our research focus towards the development and validation of novel biomarkers that can more effectively stratify patients before they reach the stage of repeated imaging and invasive procedures.

Over the last decades, the widespread use of *prostate-specific antigen* (PSA) as a screening tool has historically led to the overdiagnosis and overtreatment of indolent prostate cancers. In an attempt to overcome these limitations, mpMRI has emerged as diagnostic tool. Randomized trials and real-world data have consistently demonstrated its value in guiding biopsies and improving detection of csPCa, while reducing unnecessary procedures in men with low-risk disease (12).

However, the use of mpMRI and fusion prostate biopsies comes at a high cost. Imaging is resource-intensive, requires specialized expertise among radiologists, and in many healthcare systems is associated with long waiting lists, multiple hospital visits, and expenses also for patients. Moreover, even in experienced centers, mpMRI interpretation suffers from

inter-reader variability, and not all men with suspicious lesions ultimately harbor significant disease. The subsequent need for targeted and systematic biopsies not only further inflates costs but also exposes patients to complications such as infection, bleeding, and urinary retention (13, 14). In the current era of medicine, this diagnostic pathway, while effective, cannot be considered sustainable in the long run without additional refinement.

To address these challenges, in the same line of other cancers such bladder tumors (15), there is an urgent need for biomarkers that can better identify men truly at risk of harboring csPCa before committing them to expensive imaging and invasive testing. These biomarkers should ideally improve risk stratification beyond PSA and clinical parameters, be minimally invasive (preferably blood, urine, or semen-based), be able to reduce unnecessary mpMRI and biopsies, thereby sparing patients from anxiety, morbidity, and repeated hospital visits. Of course, be cost-effective and easy to be used in clinical practice.

Several promising biomarkers and genomic signatures have already been proposed both for diagnosis and targeted therapy, including *Prostate Health Index* (PHI), 4Kscore, PCA3, SelectMDx, ExoDx, and tissue-based genomic panels, but their uptake remains limited, partly due to cost, lack of standardization, and limited integration into clinical guidelines. More importantly, many of these tests have been developed in small or highly selected populations, and their performance in real-world, diverse cohorts is not yet fully established (16-21).

While these commercially available tests have demonstrated utility in refining risk assessment and guiding the decision regarding prostate biopsy, their limitations underscore the need for further progress in this field. In this regard, next-generation approaches such as non-coding RNAs, *circulating tumor DNA* (ctDNA), and analysis of PSA glycosylation patterns are emerging as highly promising tools. These novel biomarkers, currently still under clinical investigation, may allow a better understanding of tumor biology and hold the potential to complement or even surpass existing assays. Recent reviews and translational studies have highlighted their relevance and future role in reshaping the diagnostic landscape of prostate cancer (22-25).

From a health economics perspective, every unnecessary mpMRI or biopsy avoided translates into significant cost savings for healthcare systems. Furthermore, reducing the need for repeated hospital visits, possible complications, and invasive tests would have a profound positive impact on patients' quality of life. Anxiety, physical discomfort, and potential complications associated with biopsies are often underestimated but carry real consequences for men and their families.

Collaborative, multicenter, prospective validation studies are urgently needed. Importantly, these studies should be designed with cost-effectiveness as a primary endpoint, ensuring that the biomarkers developed are not only clinically useful but also economically viable, both for public and private settings. Another crucial element is accessibility. Biomarkers should be developed ensuring they can be applied across different healthcare settings, including those with limited imaging availability. This would not only optimize resource allocation in high-income countries but also improve equity of access to early and accurate prostate cancer diagnosis worldwide.

The UROP hope a future in which the diagnostic pathway for prostate cancer is more personalized, efficient, and sustainable. In this vision, biomarkers serve as the first gatekeeper, filtering men who truly require advanced imaging and biopsy from those who can be safely monitored. Such an approach would substantially reduce healthcare costs, minimize patient morbidity, and improve overall outcomes. UROP strongly calls upon the international research community, funding bodies, and policymakers to prioritize the development of novel biomarkers for prostate cancer. The current reliance on mpMRI and biopsy-heavy strategies, while valuable, may not be sustainable in the long term. Innovative, accessible, and validated biomarkers represent the next frontier in prostate cancer diagnostics. Investing in this direction is not only a scientific necessity but also a moral imperative, as it will ultimately reduce costs, minimize patient burden, and ensure that care is truly focused on those at greatest risk of clinically significant disease.

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