EDITORIAL

Concerns regarding prostate cancer screening guidelines in minority populations

Prostate-Specific Antigen (PSA) is a first-line recommended serum biomarker used for prostate cancer (PCa) screening. However, this test has critical limitations in specificity within the gray zone of PSA from 4–10 ng/ml. The low specificity for clinically significant Gleason grade group 2–5 (GG2-5) PCa leads to unnecessary negative biopsies, over-detection of indolent cancers, and over-treatment, especially in Black men with favorable risk PCa. The urological community relies on secondary screening tools to augment specificity and increase sensitivity for GG2-5 PCa such as multiparametric magnetic resonance imaging of the prostate (MRI). Current National Comprehensive Cancer Network (NCCN) Early Detection guidelines specifically call for biomarkers and MRI tests to improve the specificity of PSA. Urologists rely on the negative predictive value (NPV) of the secondary screening tools for GG2-5 PCa to defer biopsies for men with elevated PSA. However, the NPV of any threshold chosen decreases in populations with a high prevalence of GG2-5 PCa. For most of these popular secondary biomarkers, specificity and NPV have not been assessed in Black men despite their known high risk. It is necessary to focus on other aspects of accuracy like specificity, NPV and the correlation of predicted risk versus observed risk (i.e., calibration) in populations with both high and low PCa risk (e.g., Black and Asian men). The impact of the new NCCN guideline-supported PSA ≥ 3.0 ng/ml threshold and the currently recommended thresholds of the secondary screening tools should be modeled or prospectively evaluated to see if they provide an acceptable risk-benefit ratio. Beyond discrimination/area under the curve, biomarkers should be evaluated for their calibration, specificity at high sensitivity, and their NPV for men with varied prevalence of GG2-5 PCa before being told to forego prostate biopsy.
Clinical, biomarker, and imaging-integrated race stratified risk calculators and statistical modeling can be used to improve screening outcomes in minorities. Guidelines should also involve community providers to better reflect the resource limited settings within the US.

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BACKGROUND

Prostate Cancer (PCa) is the leading malignancy among US men and the second leading cause of cancer-related deaths in the US [1]. Black men have 70% higher PCa incidence and twice the PCa mortality rate of White men [2]. While serum Prostate-Specific Antigen (PSA) remains a widely used biomarker for PCa screening, its specificity in detecting clinically significant PCa remains low [3]. The National Comprehensive Cancer Network (NCCN) and US Preventive Services Task Force (USPSTF) differ in their guidelines regarding the age of PSA screening initiation and frequency of repeat tests, but both guidelines encourage the use of an informed, shared decision-making process and that the decision should respect a patient's values and preferences.

The current standard of care in the NCCN guidelines recommends PSA testing using thresholds of PSA ≥ 3.0 ng/ml as opposed to ≥4.0 ng/ml used by most clinicians. However, a recent publication by Babajide et al. suggests that the specificity of PSA drops by 45% with the lower threshold (4.7%), leading to an increased number of healthy Black men qualifying for urologic referral for biopsy evaluation [4]. This is essentially a *biopsy all* strategy for Black men, and it subjects many Black men to unnecessary biopsies. Other potential concerns include overwhelming community and safety net hospitals, worsening biopsy compliance, over-biopsy/over-detection, and over-treatment. Although the NCCN guidelines are more nuanced and thoughtful because baseline evaluations include family history, digital rectal exams, medications, history of prostate disease and screening, race, and family or personal history of high-risk mutations, the guidelines assume a similar improvement in specificity with our current biomarkers and a similar uptake and safety of active surveillance in Black men and other minority groups. Data on the monitoring intensity for active surveillance in Black men or in safety net hospitals suggests that lost to follow-up is high and repeat surveillance biopsies are not done frequently enough to ensure the safety of a lowered PSA threshold at this point in time [5, 6].

PROBLEMS WITH THE SECONDARY SCREENING TESTS

Biomarkers for biopsy-naive patients include blood tests such as Prostate Health Index (PHI) and 4Kscore, and urine tests such as ExoDx, PCA3, and Select MDx. For prior negative biopsy, 4Kscore, PCA3, ExoDx and the biopsy tissue-based Confirm MDx can help avoid unnecessary biopsies [7]. Currently, a major concern is that available biomarkers used for further evaluation are not well validated in Black men [8]. By our understanding of the literature and two reviews on the topic, current screening biomarkers are mainly validated only for discrimination with no assessment of the specificity or the concordance between predicted and observed risk, i.e., calibration, in Black men. The urine- and blood-based biomarkers on the market have similar discrimination (0.6 to 0.8), and so urologists tend to utilize their favorite or rely on

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multiparametric magnetic resonance imaging (MRI). Reviews of each test demonstrate that other important accuracy measures are rarely reported including calibration, negative predictive values (NPV), and specificity at greater than 90 and 95% sensitivity. Confirm MDx does report a 96% NPV for Black men, but it is limited to men with prior negative biopsy [9].

The PHI is a blood-based assay that uses total PSA, free PSA, and [-2]proPSA in an equation to predict the likelihood of finding any PCa and high-risk PCa upon biopsy. Babajide et al's assessment of PHI assay in 158 Black biopsy-naive patients suggests poor calibration with rates of GG2-5 PCa resembling the predicted risk of GG1-5 PCa on the assay report [4].

Compared to White men, the specificity of PHI is also much lower in Black men in a study from Dr. Moul's lab [10]. Findings from the Babajide et al. study suggest that lowering the PSA threshold from ≥4.0 ng/ml to ≥3.0 ng/ml increases the number of "cancer-free" Black men who would be referred for biopsy by 66% from 6.7% to 11.1% [4]. If we lower the threshold to ≥3.0, we also lower

PSA's specificity by 45% to less than 5% and increase the number of healthy Black men referred to urologists for biopsy evaluation. These urologists have to rely on the specificity and NPV of secondary screening tests which have not been routinely assessed. Several tests have yet to be studied specifically in men with African ancestry. This highlights the need for upfront minority enrollment with subgroup analyses for validation of lab developed tests that gain Medicare coverage.

In addition to secondary screening biomarkers, prostate MRI is guideline recommended, if available. However, the prostate MRI has similar shortcomings in minority populations compared to their White counterparts. While prostate MRI increases sensitivity from 76 to 95% [11] in academic medical centers, this screening tool's efficacy varies. MR fellowship-trained radiologists are not widely available, and the concordance between community versus tertiary-center radiologists is only 60.5% [12]. The sensitivity and NPV of prostate MRI for GG2-5 PCa may not be as high in non-White men nor in safety net hospitals [13, 14]. Prostate MRIs are also underutilized in Black men where they have 40% lower odds of having an MRI before prostate biopsy [15]. Additionally, prostate MRI has a variable 63–100% NPV and a varied positive predictive value (PPV) [11, 13, 16], highlighting the importance of a powered validation in Black men [13, 17]. Despite the wide-ranging NPV, MRI has increased sensitivity since Black men have 60% higher odds of cancer on both targeted and systematic biopsy cores [17]. This suggests that pre-biopsy MRI should be used to augment sensitivity but may not be helpful for deferring biopsy which has a false negative rate of 24% in PROMIS [16].

Although most secondary tests such as ExoDx, Confirm MDx, 4Kscore and PHI are covered by insurance, they are often unavailable at resource-constrained health systems. As a result, these health systems must rely on using PSA density. However, this can be difficult to obtain as PSA density requires a volume estimate from a prostate MRI or a transrectal ultrasound, both of which are additional resources that are also limited. While ExoDx, a urine-based test, sends test kits to patients' homes to help with accessibility, the test is not validated in Black men. NCCN guidelines suggest frequent testing at a less specific PSA threshold, yet availability of secondary screening tests is limited in many health systems.

RISK CALCULATORS AS A POTENTIAL SOLUTION

Risk calculators have higher accuracy than individual biomarkers for PCa detection and represent a promising approach. The use of a combination of clinical information, biomarker data and MRI PIRADS in risk prediction models offers several potential advantages such as personalized risk assessment, improved sensitivity and specificity, reduction in overdiagnosis and overtreatment and they can be re-weighted or include a term to improve prediction in high-risk groups. It is however essential to note that adopting risk calculators as a standard presents its own set of challenges. Risk calculators need calibration to different populations and may need to be updated for changes in clinical practice and biopsy techniques [18]. In some resource-constrained health systems, missing biomarker results and inaccurate imaging data could bias assessments of personalized risk. Other challenges include varied biomarker availability, patient and provider awareness and the relative inaccessibility of the calculators during patient visits. Ultimately, it is essential that risk prediction models validate the discrimination, calibration, and net benefit for GG2-5 PCa detection across ethnic groups to help improve biopsy decisions [19]. Development of a risk calculator that incorporates clinical and imaging data that can be readily updated based on new patient data, is flexible to different biomarkers, includes race-stratified models and are integrated into electronic health records systems should be a priority.

CONCERNS WITH THE GUIDELINES

While urologists may prefer the NCCN guidelines and primary care providers prefer USPSTF guidelines, data in Black men continues to lag, making specific recommendations difficult. Black men are disproportionately affected by PCa with earlier presentation, higher incidence, more aggressive disease, and higher mortality rates versus White men [20]. It is our assertion that the USPSTF guidelines are doing more harm in Black men from age 40–54, whereas the NCCN guidelines are operating under the assumption that the calibration, negative predictive value, and availability of biomarkers are similar between Black and White men despite the fact that the prevalence is so much higher in Black men. Screening's risk-benefit balance is unclear with the lower PSA threshold and the unknown specificity of most risk tools. Further work is needed for inform the guidelines so they can be optimized for use in Black men and other racial/ethnic minorities given these limitations.

POSSIBLE SOLUTIONS TO THE GUIDELINE SHORTCOMINGS

Given that the USPSTF only considers Level 1 data to make their recommendations, there is a critical need for clinical trials that compare different screening strategies. Some of the outcomes of these trials could be shorter term outcomes relative to the performance of the USPSTF guidelines. Examples include indolent or GG1 PCa detected, proportion of GG2-5 detected and missed, unnecessary biopsies performed relative to men screened, proportion of men with metastatic PCa at diagnosis, NCCN risk distributions of cancers detected, and costs.

Comparisons could be stratified by race and age as: 40–54, 55–69, and 70 years or older age groups.

Alternatively, modeling can be used to estimate the benefits of screening on PCa over-detection and mortality and whether these benefits vary by race. A study by Yamoah et al. assessed the differences in PCa mortality in Black and White veterans with PCa based on the frequency of PSA screening in the 5 years before diagnosis. They used incidence-level differences with known PSA screening disparities to inform their models. Results indicated that annual PSA screening versus less frequent PSA testing in the 5 years before diagnosis predicted PCa mortality only for Black men [21]. Because of the long observation time needed for mortality outcomes and the expense of PSA screening randomized control trials, modeling serves as a cost-effective way to assess the impact of annual screening to aid in obtaining actionable data in a shorter timeframe. It is worth mentioning that even though USPSTF does not base their guidelines decisions off modeling, modeling can provide important insights to suggest that the current screening guidelines are not serving Black men well [22, 23].

It should be noted that most Black patients seek medical attention outside of academic medical centers, often without access to prostate MRI-trained radiologists or secondary biomarkers which is determined by often overwhelmed pathology departments. Therefore, community urologists that care for ethnic minorities should be included in developing guidelines since they are aware of the available resources. Another potential way to address the concern of the lower PSA threshold in the guidelines is by conducting full validation of tools with subgroup analyses by race. It should, however, be noted that fixing the problem may not be attainable by a single biomarker alone and may be best achieved with a risk calculator that is validated and calibrated across ethnic groups, EMR-integrated and incorporates clinical, imaging and biomarker data. This would help men choose prostate biopsy in line with their own risk thresholds.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.