Rapid Review – Prostate Cancer

Prostate Cancer Racial Disparities: A Systematic Review by the Prostate Cancer Foundation Panel

Brandon A. Mahal, Travis Gerke, Shivanshu Awasthi, Howard R. Soule, Jonathan W. Simons, Andrea Miyahira, Susan Halabi, Daniel George, Elizabeth A. Platz, Lorelei Mucci, Kosj Yamoah

* Dana-Farber Cancer Institute, Boston, MA, USA; Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; Prostate Cancer Foundation, Santa Monica, CA, USA; Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, USA; * Divisions of Medical Oncology and Urology, Duke University School of Medicine, Durham, NC, USA; Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; Department of Urology and the James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

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Abstract

Context: Prostate cancer (PCa) is a complex disease that disproportionately impacts Black men in the USA. The structural factors that drive heterogeneous outcomes for patients of differing backgrounds are probably the same ones that result in population-level disparities. The relative contribution of drivers along the PCa disease continuum is an active area of investigation and debate.

Objective: To critically synthesize the available evidence on PCa disparities from a population-level perspective in comparison to data from “equal access and equal care settings” and to provide a consensus summary of the state of PCa disparities.

Evidence acquisition: A plenary panel on PCa disparities presented at the Prostate Cancer Foundation meeting on October 24, 2019 and ensuing discussions are reported here. We used a systematic literature review approach and the Preferred Reporting Items for Systematic Reviews and Meta-analyses to select the most relevant publications. A total of 3333 publications between 2011 and 2021 were retrieved, of which 52 were included in the review; an additional 13 articles on screening guidelines, seminal clinical trials, and statistical methodology were used in the evidence synthesis.

Evidence synthesis: Race disparities in PCa are a result of a complex interaction between socioeconomic factors impacting access to care and ancestral/genetic factors that may influence tumor biology. Black men in the USA continue to have a nearly 1.8 times higher population-level incidence rate than White men. Failure to

1 These authors contributed equally and are joint first authors.

* Corresponding author. H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL 33612, USA. Tel. +1 813 7454257, Fax: +813 7457231. E-mail address: kosj.yamoah@moffitt.org (K. Yamoah).

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1. Introduction

Prostate cancer (PCa) is a complex disease, with risk factors and outcomes influenced by a combination of socioeconomic status, access to care (AtC) and quality of care (QoC) delivery, lifestyle factors, variations in inherited genetics and molecular tumor profiles (biology), as well as epigenetics [1–5]. In the USA, Black men are approximately 80% more likely to be diagnosed with and 220% more likely to die from PCa in comparison to White men [6].

The aforementioned factors that drive PCa as a complex disease with heterogeneous outcomes are probably the drivers of PCa population-level disparities, although the field is currently fraught with conflicting interpretations of data on the relative contributions of these factors to disproportionately higher PCa incidence and poor outcomes among Black men [4,7,8]. Thus, the relative contribution of drivers of PCa differences along the disease continuum remains an active area of investigation and debate. A consensus summary of the state of PCa disparities from global experts in the field is warranted, as inaccurate data interpretation or lack of data altogether for Black men can impact policy, potentially in a detrimental way, ultimately affecting millions of individuals of African origin worldwide.

With significant controversy over prostate-specific antigen (PSA) screening, the rapid evolution of PCa prognostic and treatment nomograms and paradigms, and the emergence of precision medicine whereby therapies are developed to specifically target dominant molecular drivers of a patient’s tumor, it is concerning that Black men who experience the highest PCa incidence and mortality are the least represented in studies. In turn, such studies result in guidelines or major advances that are based on data with minimal representation of Black men, who have a disproportionate burden of disease [8–11]. PCa disparities are likely to continue and possibly worsen without a change in the conduct and scope of PCa research practice.

In October 2019, the Prostate Cancer Foundation organized a panel discussion focused on the state of evidence on racial disparities in PCa. In this report from panel members, we summarize the evidence on this complex problem, attempt to reconcile potential conflicting data, and provide guidelines for studies evaluating PCa health disparities. PCa disparities span the disease continuum, including incidence and carcinogenesis, adverse clinical presentation, treatment delivery, and response, and lethal outcomes and mortality [12–14]. To adequately address the issue of PCa racial disparity, the relative contributions of biology and AtC/QoC must be dissected. In this panel report, biologic factors that impact PCa racial disparities are defined as inherited genetic or environmental factors, including but not limited to carcinogens, stress, immunosuppression, diet, adiposity, body composition, and metabolic changes that exert an overall lifetime impact on the genome and result in PCa. AtC/QoC is defined as the ability to readily access the appropriate medical care for timely diagnosis and management of PCa, as well as the ability to obtain quality health care delivery, both of which are known to directly impact disease outcomes.

2. Evidence acquisition

2.1. Study design

This panel report examines the existing evidence on PCa race disparities according to a systematic review framework and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

2.2. Literature review

We performed a systematic literature review following the PRISMA guidelines and used the PubMed database to identify and retrieve publications. We used the Boolean
operators “AND” and “OR” with specific keywords to identify original and review articles published in the area of PCa race disparities between January 2011 and April 2021. The search query was built by combining the first component “prostate cancer/prostatic neoplasm” with keywords using the AND operator. Keywords included “African American men” (including all the keywords specific to African ancestry), “sociodemographic disparities” (including socioeconomic status and AtC), and “racial disparities”.

2.3. Literature inclusion

The systematic literature review identified a total of 3333 publications (Fig. 1). The abstracts of these publications were reviewed, with a focus on race disparity and prostate cancer. This led to identification of 166 articles for review of the full text. A total of 52 articles were then selected for inclusion on the basis of their relevance to the panel discussion. We used an additional 13 publications related to screening guidelines, seminal clinical trials, and statistical methodology papers that were not identified in the systematic review.

3. Evidence synthesis

3.1. Epidemiology of PCa disparities

3.1.1. Disparities in PCa incidence

In comparison to men in other racial groups, PCa has affected Black men at an unmatched rate. The disproportionate impact of PCa among Black men in the USA has persisted over the past two decades (Fig. 2A–C). The most recent age-adjusted PCa incidence rates reported are 179.2 and 101.7 per 100,000 for Black and White men, respectively [15]. The median age for PCa incidence is consistently younger for Black than for White men, with a higher lifetime risk of PCa of 1 in 7 for Black compared to 1 in 9 for White men [15]. Although the incidence rate has declined by approximately 5% annually over the past decade for both race groups, the magnitude of the difference between Black and White men persists, with Black men experiencing a 60% higher incidence rate in comparison to White men [15]. Whether the decrease in overall incidence rates observed is due to the impact of the 2012 US Preventive Services Task Force recommendations against routine PSA testing remains undetermined [16]. Since the only well-established risk factors for overall PCa are older age, African ancestry, and family history of PCa [17], there has been an increase in focus on better understanding the genetic basis of the disease, the interplay of social and environment contexts, and individual behavior that might ultimately result in the development of PCa [18,19]. Collectively, this body of evidence strongly suggests that the higher incidence of PCa among Black men is driven primarily by genomic factors, as defined in Table 1. It is conceivable that elimination of any differences in AtC/QoC may actually favor earlier diagnosis of PCa in Black men by improving screening and detection and will unmask the true excess incidence rate for Black compared to White men.

3.1.2. Disparities in adverse clinical presentation

Epidemiological studies have shown that Black men are more likely to present with adverse clinical features at the time of diagnosis in comparison to White men [12,20–22]. Factors contributing to these findings include well-documented AtC/QoC issues among Black men leading to later stages at disease presentation and diagnosis [21], as well as differences in tumor biology [23,24] and tumor location [20]. Tumor stage, diagnostic PSA, and biopsy Gleason score are clinical factors that have guided prognostication and treatment decisions in PCa since the 1990s [25]. Despite their utility, clinical nomograms cannot accurately identify which patients are more likely to harbor underlying biologically aggressive disease that might benefit from more aggressive management than indicated by clinical features alone [26,27]. Data have shown that Black men with clinically low-grade disease who were eligible for active surveillance but underwent radical prostatectomy had a higher frequency of adverse pathological features compared to White men [28,29]. A fundamentally problematic approach with these models is the use of self-identified race as a surrogate for genetic ancestry. Self-identified race is a complex mixture of behavioral, social, and biologic determinants that can introduce many confounding factors when used as a surrogate to estimate the contribution of genetic ancestry to disease presentation (Table 1) [30]. Contemporary evidence suggests that
individual patient-specific genomics and germline information, which may inherently account for genetic ancestry, can help in differentiating biologically aggressive from indolent PCa [13,27,31–35]. In a later section we address the issue of self-identified race and genetic ancestry and recommend novel strategies to account for this when conducting studies on PCa health disparities.

3.2. Treatment disparities

3.2.1. Disparities in treatment access and delivery

Historically, population data for the USA have shown that Black men with intermediate- to high-risk PCa are at higher risk of dying from PCa when compared to White men; however, Black men receive curative-intent treatment

Fig. 2 – Age-adjusted prostate cancer (A) incidence, (B) mortality, and (C) mortality rate ratio per 100 000 across race groups in the USA. Curves generated on May 15, 2020 from https://wonder.cdc.gov. PI = Pacific Islander.
Table 1 – Integrated model of racial disparities in prostate cancer incidence and mortality

<table>
<thead>
<tr>
<th>Contributor</th>
<th>Incidence</th>
<th>Adverse clinical presentation</th>
<th>Suboptimal treatment delivery</th>
<th>Treatment response</th>
<th>Lethal outcomes/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomics</td>
<td>[13,35]</td>
<td>[18,20]</td>
<td></td>
<td></td>
<td>[7,31]</td>
</tr>
<tr>
<td>Access/QoC</td>
<td>[21]</td>
<td>[14]</td>
<td></td>
<td></td>
<td>[12]</td>
</tr>
<tr>
<td>Cumulative disparity</td>
<td>1.8x</td>
<td></td>
<td></td>
<td></td>
<td>2.2x</td>
</tr>
</tbody>
</table>

QoC = quality of care delivery.

nearly 20% less often than White men, even after adjusting for age and disease features [36]. Such differences are even greater among high-risk patients, as Black men with high-risk disease are estimated to be 40% less likely to receive curative treatment than their White counterparts [36]. Insurance coverage could help to reduce racial disparities in treatment patterns for aggressive cancers, probably by increasing AtC/QoC. For example, the available data suggest that there is a significant interaction between race and insurance status, so increasing insurance coverage for Black men may could in significant reductions in treatment disparities [37]. Specifically, the adjusted odds ratio (AOR) for receipt of definitive treatment for Black versus White men with high-risk PCA is approximately 0.38 (95% confidence interval [CI] 0.27–0.54; p < 0.001) among uninsured men and 0.62 (95% CI 0.57–0.66; p < 0.001) among insured men [37]. Still, even with insurance coverage, Black men are less likely to receive treatment, more likely to experience treatment delays, and less likely to receive high-quality care [2,37–39].

Race-specific differences in treatment quality and receipt remain a highly complicated and problematic issue that has been prevalent for several decades. These disparities are alarmingly worse among men with higher-risk disease and among older men, and are persistent across care settings. Efforts to improve AtC such as enhancing insurance coverage may reduce disparities in receipt of treatment and QoC (Table 1). Ultimately, the underlying reasons for these racial disparities in treatment receipt must be carefully studied and the findings could guide policy-level intervention if they identify potentially correctable contributors to excess PCA mortality among Black men.

3.2.2. Disparities in treatment response and outcomes

A historical and persistent difficulty in the management of PCA is distinguishing indolent from aggressive disease, since both disease conditions can present with adverse clinical features at the time of initial diagnosis. PCA disease progression is a complex, multistep, temporal process that involves inherent genomic predisposing risk factors, molecular alterations in tumor cells, and associated interactions within the tumor microenvironment that cannot be entirely accounted for by baseline clinical risk factors alone before treatment. In addition, given that most of the clinical prognostic tools and treatment guidelines currently available were developed primarily using data for White men, it is debated whether these tools are applicable to Black men [40]. Thus, studies on PCA racial disparities have attempted to determine whether Black men might have a unique disease course and response to treatment. These studies have shown seemingly conflicting findings, depending on the data source (population-level data vs curated stage-for-stage matched data) used in the analyses [4,41–44]. Specifically, studies that evaluated the impact of self-identified race on PCA-specific outcomes within the context of randomized clinical trials and relatively equal-access medical centers demonstrated that although Black men still presented with higher rates of adverse clinical presentation, when appropriately treated stage-for-stage there was no difference in outcomes—a measure of treatment response [4,41,43–45]. In fact, for nearly two decades, data from several clinical trials suggest that Black men may respond better to radiation-based treatment regimens and other therapies when compared head-to-head to their clinically matched White counterparts [4,46,47]. These observations are hampered by the possible selection bias that may arise from studying only Black men who have presented for randomized clinical trials, as these patients may have higher health care-seeking behaviors and trust in the system than the average Black patient in the USA [48]. That being said, this clinical observation is supported by emerging data on racial differences in DNA
Table 2 – Summary of recent clinical studies evaluating outcomes by race among men with similar disease characteristics treated in “equal” access settings

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Study design</th>
<th>Patient population</th>
<th>Endpoint</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sartor [52]</td>
<td>Sipuleucel-T</td>
<td>Retrospective registry study, matched on PSA</td>
<td>mCRPC</td>
<td>OS</td>
<td>0.70 (0.57–0.86)</td>
</tr>
<tr>
<td>Halabi [50]</td>
<td>Docetaxel</td>
<td>Meta-analysis from individual patient data</td>
<td>mCRPC</td>
<td>OS</td>
<td>0.81 (0.72–0.91)</td>
</tr>
<tr>
<td>Dess [4]</td>
<td>RT</td>
<td>Meta-analysis from individual patient data</td>
<td>NO–1M0 (RTOG)</td>
<td>PCSM</td>
<td>0.81 (0.66–0.99)</td>
</tr>
<tr>
<td>McKay [45]</td>
<td>RT</td>
<td>Retrospective cohort study</td>
<td>4569 Black men (30.8%)</td>
<td>PCSM</td>
<td>0.79 (0.69–0.92)</td>
</tr>
</tbody>
</table>

aHR = adjusted hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; mCRPC = metastatic castration-resistant prostate cancer; RTOG, Radiation Therapy Oncology Group; OS = overall survival; PCSM = prostate cancer–specific mortality.

Data shown for the randomized control trial cohort only.

repair and the immunobiology of prostate tumors that may impact disease development, detection, and response to therapy, particularly for lethal or metastatic disease [49–51]. Although it is unclear if racial biomarker differences observed are driven by genetic ancestry–related factors versus epigenetic phenomena, multiple independent sources of genomic and preliminary clinical data suggest that Black men are more likely to respond to radiation therapy and immunotherapy, including sipuleucel-T (Table 2) [50,52,53]. However, it is worth recognizing that the genetic basis for treatment response in selected studies remains hypothesis-driven and is likely to be influenced by sample size. The major issue with the discussion in such studies is the perception that the results are discordant with population-level estimates from the Surveillance, Epidemiology and End Results (SEER) program [7].

Participants in clinical trials represent a highly selected group that tends to be managed more homogeneously than the general population. It is therefore of great interest to understand why Black men with high-risk or advanced disease enrolled in trials do better than would be expected on the basis of SEER data. A comprehensive approach that integrates information from different resources, such as clinical trials, registries, and institutional databases, is critical to understanding the factors that impact the race disparity observed for PCa outcomes.

3.2.3. Cumulative racial disparities in outcomes and mortality

The overall higher PCa mortality among Black compared to White men is the result of a complex interplay between differences in incidence rate, adverse clinical presentation, and treatment delivery, as well as treatment response (Table 1). Therefore, it is imperative to carefully identify which disparities in outcomes the available analytic data can systematically address and to clearly define these outcomes when interpreting the results. The difference is in the denominator used in these analyses: men at risk of PCa and death from PCa (for mortality estimates) versus men with PCa at risk of death from PCa (for survival estimates). SEER reports of PCa disparities are population-level estimates that include incidence and mortality rates. In SEER, the PCa incidence rate is 173.0 for Black men compared to 97.1 for White men, while the mortality rate is 38.7 for Black men compared to 18.0 in White men (all per 100,000 men)—these population-level estimates specifically describe the overall PCa incidence and mortality among all individuals in the population with a denominator that includes healthy men without PCa (Fig. 2A–C) [7]. By contrast, the aforementioned studies report Kaplan-Meier measures in cohorts of men already diagnosed with PCa [4,41,43]. These studies do not use population-epidemiologic methodology and therefore have little impact on and should not be directly compared to SEER population-level estimates.

Furthermore, if the conclusion from these studies is that men with similar disease characteristics at diagnosis/treatment who receive “equal” high–quality treatment have similar PCa-specific outcomes regardless of race, this would not account for a significant proportion of the population-level differences in PCa mortality observed. This is because the excess incidence of PCa among Black men is the major driver of PCa mortality observed in the population. As shown in Figure 3, if we assume an equal 18% risk of dying from PCa for Black and White men after diagnosis, then on the basis of the higher incidence among Black men, there would still be 31.1 Black men (173.0 [incidence of PCa among Black men] × 0.18 [assumed equal 18% PCa-specific mortality]) who die for every 17.5 White men (97.1 [incidence of PCa among White men] × 0.18 [assumed equal 18% PCa-specific mortality]), which would translate to Black men having a 1.8 times higher population-level mortality rate, despite an equal PCa outcome setting. Essentially, the mortality difference is 2.2 and higher incidence among Black men accounts for 1.8, with the remaining 1.22 fold being a residual difference, demonstrating an apparent disparity even after diagnosis. Thus, it is likely that population PCa disparities are largely driven by the different risk of developing PCa, in addition to contributions from differences in the risk of dying from PCa once diagnosed. This additional risk of developing PCa among Black men may be driven by the complex interaction of socioeconomic and biological factors that are often difficult to account for in a single study. Therefore, continuing research is warranted to unravel these interactions that often modify PCa outcomes for Black men.
3.3. **Precision medicine implications**

Advances in the diagnosis and treatment of PCa in the era of precision medicine are expanding at an uneven rate across race groups, whereby Black men and men in minority and underserved populations experience the most systematic genomic disparity [54]. Several biomarker-driven predictive tools have been developed, but these biomarker panels have been mainly derived from data for White patients [34]. A recent study reported that individuals of European descent comprise more than 95% of the participants in genome-wide association studies [55]. This is largely because of insufficient efforts to recruit Black and non-White participants in publicly funded research; hence, not only are biomarkers discovered in White populations but their validation is also limited to predominantly White populations. Large-scale efforts dedicated to creating racially and ancestrally diverse germline and tissue-based databases and generating genomic information from patients with various cancer types are needed. Racial minorities are substantially under-represented in The Cancer Genome Atlas and in the Prostate, Lung, Colorectal and Ovarian screening trial [3,56]. Ultimately, the disparity in precision oncology continues to widen as the knowledge base for specific molecular aspects of cancer grows in population subsets with limited diversity. The discovery of targeted therapies for specific somatic mutations identified in selected patient populations has resulted in effective therapies for some patients with PCa [57]. However, while some of these precision therapies have gained US Food and Drug Administration approval, it is unclear whether they will provide equal benefit for patients from different racial groups. Given the differences in the prevalence of adverse outcomes among racial groups, validation of these tools must also include rigorous analysis of specificity, sensitivity, and positive and negative predictive values in non-White populations, or they may very well exacerbate the issue of PCa disparities.

Over the past decade, most leading-edge clinical trials have been enrolling patients on the basis of molecular profiling of tumors using genomic sequencing data [58]. In addition, matching of genetic variants to treatment selection is important, but this information is largely unavailable for Black men. In the absence of actionable genomic information, Black men with PCa will be unable to enroll in these personalized clinical trials. Furthermore, the recruitment of Black and other non-White populations to clinical trials has been extremely challenging. To exemplify this point, an interim analysis of the NCI-MATCH trial revealed that of 795 patients screened, only 11% were Black, and of these, only one Black man (3%) was assigned to treatment [59]. The reasons behind this insufficient recruitment of Black individuals probably involve a combination of factors, including lower access to clinical trials, insufficient and ineffective efforts to recruit Black patients, patient distrust of research activities, Black patients not meeting health-related eligibility criteria, and patient reluctance to participate in clinical trials because of a limited understanding of their potential benefits, which all further contribute to disparities in generating actionable data [60,61].
3.4. A new framework for studying PCa disparities

What is apparent from our review of the existing research is that there is a clear need for a robust, methodical, and targeted attempt to rectify the extreme paucity of data with regard to PCa disparities, especially among Black men. Appropriate data collection and harmonization of variables and outcomes, study design, study population, and methodological strategies to study PCa disparities depend on the research goal. To create a simple but helpful classification system, research goals may be broadly categorized into description (what is the current form and distribution of PCa disparities?), prognostication (eg, nomograms and prognostic biomarkers), predictors of therapeutic efficacy (testing the effectiveness of novel drugs in clinical trials and predictive biomarkers for treatment response), and causal explanation (eg, the mechanistic origin of disease). In PCa disparities research, the associations observed in Table 1 arise from each of these study types.

Methods and data resources for studies of description are well characterized. These are typically conducted on large-scale registry systems, such as SEER and the National Cancer Data Base and convey information regarding the historical and present distribution of disease burden, treatment patterns, and outcomes according to racial or ethnic profiles. In the modern era, racially stratified descriptions of molecular profiles and abnormalities are also possible, although, as previously mentioned, robust data capture

Fig. 4 – Signed directed acyclic graphs relating genetic ancestry, the social construct of race, and access to and quality of care (QoC) to PCa outcomes. Associational signs across multiple edges are inferred by the following rule: the sign of a path on a causal directed acyclic graph is the product of the signs of the edges that constitute that path. Afr. = African.

from non-White populations is currently lacking. In general, a primary consideration for this type of disparities research concerns representative patient sampling; however, if this cannot be fully achieved, weighted sampling designs with analytic reweighting exist to balance population-level characteristics between groups.

Currently, PCa studies of prediction are most often conducted to identify or validate prognostic nomograms or biomarkers that distinguish lethal from indolent disease. The goal of such studies is solely to establish an accurate tool for the prediction of future events. Machine learning techniques are now commonly used, although penalized regression methods are highly effective as well [40]. In either case, the most pressing need with respect to disparities research is validation of predictive models in non-White populations. Most existing PCa prognostic tools were developed using data for men of European ancestry; these may be acceptably accurate across diverse populations, but without sufficient data capture to permit validation efforts, we cannot be sure that use of such models in non-White populations is not exacerbating disparities [62]. For future studies, biomarker discovery and model training that focuses on or explicitly oversamples from Black and other non-White populations will lead to more equitable and reliable prognostic models across heterogeneous populations.

The area of causal explanation is the most lacking in prevailing methodological robustness across study types. Association-based and correlative studies that take a predictive modeling approach are often conflated with claims of mechanism [63]. An understanding of the drivers of PCa disparities and public health/personalized medicine strategies for reducing them requires careful analysis in the domain of causal inference. For example, a currently debated topic concerns whether access to quality healthcare fully explains the racial disparities in PCa observed [37]; if it does not, one interpretation could be that biologic mechanisms may play a role. Put another way, this is a question of mediation [64]: what proportion of adverse outcomes experienced by Black men are mediated through AtC or QoC? To date, no group has conducted a formal mediation analysis of this question. A mediation analysis framework can estimate whether a direct causal association exists between two variables in the model and quantifies the extent to which it can be modified by the presence of a third variable. Such strategies for this question and others in the literature on disparities may be highly enlightening in the coming years. With respect to drivers of disparities, a framework that is currently lacking in the PCa landscape is that of institutional racism as a fundamental cause in its own right [65]. Appropriate incorporation of social epidemiology innovations will substantially accelerate our understanding and highlight actionable clinical and policy arenas.

Overlaying each of these topics is the construction of the “race” variable itself: self-reported race captures certain societal exposures (eg, institutional racism, dietary and lifestyle habits, and health-seeking behaviors, among others) experienced by individuals, whereas genetic ancestry may correlate with markers of higher or lower genomic risk that are common to some populations. We argue that both may be useful; indeed, when studied together in a mechanistic framework (Fig. 4) they may help in disentangling biologic from AtC/QoC impacts on disparate PCa outcomes. This approach has seen limited success in other disease types; for example, analyses of ancestrally linked variants suggest that ≈5% of cardiovascular disease and type 2 diabetes disparities are genetically driven. However, cancer is a uniquely genomic disease, and similar efforts to disentangle biologic from social determinants of disparities may reveal patterns that differ from those for other chronic diseases.

4. Conclusions

This panel report provides an evidence-based summary focused on the etiologic underpinnings of PCa disparities. We recommend contemporary methods, particularly in the domain of mediation analyses, that can promote scientific rigor in approaching and studying PCa disparities. Our report highlights the need for validation of existing biomarkers and predictive tools routinely used in PCa management within racially diverse clinical studies. Furthermore, we emphasize the urgent need to develop and prioritize an inclusion strategy for Black and other non-White men with PCa in intervention studies and randomized clinical trials to avert the widening gap for PCa disparities in the era of personalized medicine.

Author contributions: Kosj Yamoah had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Mahal, Gerke, Awasthi, Yamoah.
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**References**


