

# Racial Disparity in Utilizing Genetic Testing for Personalized Care of Prostate Cancer

Tu Le<sup>1</sup>, Pilar Soto Rojas<sup>2</sup>, Mary Fakunle<sup>1</sup>, and Franklin Huang<sup>1</sup>

<sup>1</sup>UCSF

<sup>2</sup>Hospital Universitario Virgen Macarena

February 14, 2023

## Abstract

Significant racial disparities in prostate cancer incidence and mortality have been reported between African American Men (AAM) who are at increased risk for prostate cancer, and European American Men (EAM). In most of the studies carried out on prostate cancer, this population is underrepresented. With the advancement of genome-wide association studies (GWAS), several genetic predictor models of prostate cancer risk have been elaborated, as well as numerous studies that identify both germline and somatic mutations with clinical utility. Despite significant advances, the AAM population continues to be underrepresented in genomic studies, which can limit their generalizability and potentially widen disparities. Here we outline racial disparities in currently available genomic applications that are used to estimate the risk of individuals developing prostate cancer and to identify personalized oncology treatment strategies. While the incidence and mortality of prostate cancer are different between AAM and EAM, the biological features and differences of prostate tumors in AAM and EAM are still being described. Samples from AAM remain to be unrepresented in different studies. This disparity impacts the available genomic data on prostate cancer. As a result, the disparity can limit the predictive utility of the genomic applications that have been developed and may lead to widening disparities. More studies with substantially higher recruitment and engagement of African American patients are necessary to overcome this disparity.

## Introduction

Prostate cancer (PCa) is the second most common solid tumor and the fifth leading cause of cancer death in men. In 2020, there were over 1,414,000 estimated new cases of PCa worldwide<sup>1</sup>. It is well established that significant racial disparities exist regarding PCa incidence and mortality. African American Men (AAM) are 1.8 times more likely to be diagnosed with PCa than men of European ancestry and they also have 2.4 times higher mortality rate<sup>2</sup>. These differences in the course of the disease and survival of patients with PCa are frequently attributed to socioeconomic status and access to medical care, but the cause of this increased PCa risk for AA men is unclear<sup>3 4</sup>. Even if we adjust for biases attributable to these racial disparities in PCa, incidence and mortality rates remain significantly different among AAM and EAM; suggesting an important contribution of molecular and genetic factors<sup>5</sup>.

In addition to outcome differences between racial/ethnic groups, PCa behaves heterogeneously from patient to patient, making the optimal management strategy for this tumor a subject of ongoing debate<sup>6</sup>. This is because the natural history of the disease is still unknown, as well as what are the characteristics that make it more aggressive in certain cases. To adequately treat these patients, risk stratification models have been created to establish prognosis biomarkers and predict the response to treatments. These models have traditionally been based on clinical and analytical parameters such as stage, Gleason differentiation grade and prostate-specific antigen (PSA) value<sup>7 8 9</sup>. While these features are still useful, their performance in many cases remains suboptimal<sup>10</sup>. Advances in DNA sequencing and the study of the human genome have made it possible to determine a series of molecular factors that may influence the course of prostate cancer.

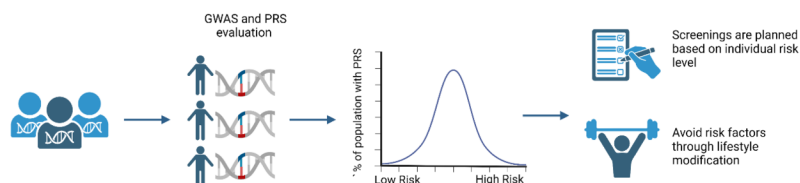
In the last decade, genome-wide association studies (GWAS)<sup>11</sup> have been utilized to translate findings of risk SNPs towards clinical utility, to identify genetic predictors of prostate cancer risk. For example, the polygenic risk score (PRS)<sup>12</sup> is calculated from the sum of the number of risk alleles carried by an individual and weighting each one by its estimated size from GWAS data. This model shows promise in identifying individuals with much higher or lower lifetime risk than the average male, and can also improve the predictive value of prostate-specific antigen (PSA) screening<sup>13</sup>. For tumor analyses, the Decipher Prostate Cancer Test is a genomic test that is based on the expression of 22 RNA markers and serves as a prognostic marker in patients who have undergone radical prostatectomy. This allows post-surgical risk stratification and prediction of the probability of metastasis and cancer-specific mortality to determine the need for adjuvant treatment<sup>14</sup>. Furthermore, an increasing number of somatic and germline tests are performed in patients with prostate cancer as they determine hereditary risk and guide treatment decisions in cancer<sup>15</sup>.

However, the studies behind these genomic applications lack racial diversity. In this literature review, we outline the currently available genomic applications to estimate the risk of individuals developing prostate cancer and to identify precision oncology treatment strategies, and how disparities have been approached using these applications.

## Polygenic Risk Score (PRS)

Analysis of well-powered GWAS and next-generation sequencing (NGS) data has resulted in the identification of numerous single nucleotide polymorphisms (SNPs) that contribute to overall prostate cancer risk. Although a single SNP itself has a modest predictive power for complex disease outcomes, accumulating various risk-associated SNPs into a Polygenic Risk Score (PRS) has shown to improve predictive significance while also providing valuable information for risk stratification<sup>16</sup>. Prostate cancer, like most cancers, is more likely to be a polygenic disease influenced by a combined effect of multiple genetic variations. To date, GWAS studies have identified 269 common germline genetic variants associated with prostate cancer susceptibility<sup>17 18 19</sup>. The combined effect of SNPs is approximated to account for a quarter of the familial risk of prostate cancer. Therefore, it is increasingly desirable to combine genetic data into a PRS to help predict PCa risk and to stratify the probability of developing the disease into the high and low-risk groups<sup>20 21</sup>.

### *Clinical utility of PRS*



Prostate cancer screening is crucial for attenuating morbidity and mortality<sup>22 23 24 25</sup>. However, the traditional method of PSA screening is infamous for false-positive rate and potential harm due to overtreatment of benign disease<sup>26 27</sup>. The US Preventive Service Task Force recommended the consideration of family history and race/ethnicity to identify men who would benefit the most from early PSA screening. While family history and race/ethnicity are indirect assessments of inherited risk, which can be prone to environmental exposures, PRS creates an opportunity to directly measure inherited PCa risk. A cohort study of 3225 men showed that PRS acts as an independent predictor for PCa; thereby, incorporating PRS into the current risk prediction model based on family history, PSA and age could create a better stratification tool with improved predictive capacity<sup>27 28</sup>. Even among unbiopsied men with low level of serum PSA of 1-3 ng/ml, PRS can be used to predict biopsy outcomes and identify men with high PCa risk<sup>29</sup>. PRS's predictive power offers an informative tool to target PSA screening efforts for men with a higher risk of early PCa onset and to guide decisions for a more active clinical approach to those with a higher risk of aggressive PCa<sup>27 30</sup> (Figure 1) Additionally, there is evidence indicating that the cumulative effect of known polygenic risk factors

can modify the risk estimate of mutations in BRCA1 and BRCA2, with penetrance of BRCA1 and BRCA2 varying as much as 26% and 61% respectively, depending on whether the individual is at the 5th or 95th percentile of prostate cancer<sup>31</sup>.

**Figure 1:** *Utilization of PRS to predict individual risk of prostate cancer (Created using BioRender.com)*

### *Disparity in genomic application*

Although PRS predictive power is high, PRS studies suffer from a significant deficit in the inclusion of African Americans, which represent only around 3% of the participants for GWASs published through 2015<sup>32 33</sup>. The insufficient inclusion of African Americans leads to a disproportion in identifying risk-associated SNPs and compromises the predictive potential of PRS over this minority group<sup>19</sup>. As a result, there might be an imbalance in how PRS can improve care for patients of European descent versus patients of African descent<sup>32</sup>. In a multi-ethnic study of 80,481 participants, prostate cancer PRS performance was superior in those with genetically defined European ancestry than in those with African ancestry, which comprised 89.3% and 7.8% of the study population respectively<sup>28</sup>. This disparity is inevitable considering the bias introduced in European-dominated GWAS<sup>28 34</sup>. Known health disparity might also contribute to the diminished predictive power of PRS in minority groups. For instance, limited healthcare access leads to missing diagnosis information and failure of early detection of PCa, paving way for systemic differences in age of diagnosis across different ethnic groups and leading to inequitable risk stratification<sup>28 34</sup>.

A recent trans-ancestry GWAS of 127,006 controls and 107,247 prostate cancer cases discovered 86 new risk variants, totaling the known risk variants to 269<sup>19</sup>. In this study, PRS is shown to have a larger contribution to overall PCa risk for AAM because variants with odds ratio >1.10, which have a greater effect on PRS, are more common in African American participants. Notwithstanding, AAM also have mean PRS that are approximately 2.18 times higher than that of EAM<sup>19</sup>. These findings are consistent with the conclusion that known risk variants substantially accounted for the estimated 75% higher prostate cancer incidence in African Americans when compared to non-Hispanic white<sup>35</sup>.

There has been considerable effort to attenuate the disparity presented in PRS studies. To compensate for the lack of diversity in GWASs, a study scaled ancestry-specific PRS distributions that, when considered separately in each ethnic group, can help identify individuals with higher PCa risk in each group<sup>36</sup>. Another study conducted a cross-validated search on a dataset that comprised only men with African genetic ancestry and identified three SNPs that significantly improved the performance of PRS in the studied population<sup>37</sup>. While more efforts are underway to improve diversity in the field of GWAS and improve PRS performance in minority groups, substantial gaps remain in our understanding.

### **Genomics of Tumor Biology**

Decipher Prostate is a genomic classifier (GC) test to screen patients for prostate cancer and provides an independent prediction of early clinical metastasis and Prostate Cancer-Specific Mortality following biopsy or radical prostatectomy (RP)<sup>38, 39, 40, 41</sup>. Decipher was created by compiling the genes of 192 metastatic patients with increasing PSA levels over 5 years and comparing them with 271 patients from a retrospective, nested case-control study, culminating in a 22 gene marker signature, known as the Decipher GC<sup>42</sup>. Decipher GC includes the expression profiles of coding and non-coding RNA (ncRNA) which is important because genes involved in metastatic disease progression are significantly affected by ncRNAs. Other PCa screeners that do not establish ncRNA may lose the sensitivity to report prognostic information present in GC<sup>14</sup>. Patient RNA can be extracted from primary prostate cancer specimens that are fixed with formalin and paraffin. After analysis, a Decipher score between 0 and 1 is generated, with low scores of 0.0-0.44, average scores of 0.45-0.59, and high scores of 0.60-1.0. Higher scores indicate an increased likelihood of adverse pathological outcomes<sup>41 43</sup>. In particular, patients with lower GC scores tend to have lower incidence of metastasis while higher GC scores give a prognosis of increased metastasis<sup>39</sup>. The clinical utility of Decipher has been verified specifically in intermediate and advanced PCa patients<sup>44</sup>. Further validation is needed to verify the disparity between PCa screening of AAM and EAM using Decipher GC.

## *Clinical Utility of Decipher*

Because Decipher can independently predict metastatic behavior in PCa patients, clinicians can make preliminary treatment decisions by differentiating between low and high-risk individuals, preferentially treating those predicted with high GC scores<sup>40</sup>. In comparison, Gleason scores, PSA levels, and other qualitative features of PCa do not adequately distinguish the risk of continued PCa progression and thereby does not offer a proper identification of low and high-risk PCa patients. By stratifying patients based on their GC score, personal treatment can be subsequently established. Patients with low GC scores do not necessitate aggressive PCa treatment options such as postoperative radiation, but those with higher GC scores can immediately be benefitted by aggressive secondary therapy when identified<sup>44 45</sup>.

### *Disparity in genomic application?*

The Decipher genomic classifier (GC) can aid in clinical decision making, due to its high expected performance. However, African American men (AAM) are underrepresented in most studies evaluating CG, so we do not have sufficient data in this population<sup>46</sup>.

Several studies have sought to investigate this aspect, recruiting a greater number of AAM patients. They demonstrate that the biological characteristics of prostate tumors are substantially different in AAM compared to EAM, and further suggest that AAM patients are associated with a higher risk of aggressive disease and have higher decipher than non-African-American men<sup>46 4748</sup>. This findings prompt for a careful monitor of AAM patients post radiotherapy prostatectomy. The studies also suggest that GC is a stronger predictor in AAM than in EAM<sup>4647</sup>. One study investigated the variation in the distribution and prognostic value of molecularly defined PCa transcriptomic subtype classifiers by race using Decipher. Five classifiers that identify prostate tumor subtypes were studied and found that the subtypes differed in frequency between AAM and EAM. The association between subtypes and a genomic risk score differed by race, suggests that some subtypes may have differential prognostic value between racial groups, independent of tumor clinicopathology.<sup>49</sup> Another prospective study was conducted to determine the genomic risk of reclassification (GrR) between conventional clinical risk classifiers and the Decipher score, using a clinically balanced cohort of African-American men and non-African-American men. This study found that the majority of AAM men had a higher Decipher score than EAM patients, thus AAM were twice as likely to experience genomic risk of reclassification<sup>50</sup>. Additionally, in a multi-institutional retrospective analysis of 1,152 patients (596 AAM and 556 EAM), Decipher score was compared with Gleason grade (GG) groups and a positive relationship was found between these two parameters such that a higher Gleason grade is associated with a higher Decipher score<sup>48</sup>. The study also found that AAM has a higher Decipher scores only in lower GG group (GG1/2). However, the average genomic-risk score (average of 19 signatures excluding Decipher) is significantly lower in AAM when compared to EAM with high GG group (GG 4/5) group. This findings imply that racial disparity existed might be more profound in the lowest and highest GG group<sup>48</sup>. These differences in the tumor biology between AAM and EAM may provide an explanation for the racial disparities in prostate cancer.

### **Germline and Somatic Testing:**

The decline in cost and the expansion in the availability of NGS has enabled the application of germline and somatic testing in routine clinical practices<sup>51 5253</sup>. While Polygenic Risk Scores and Decipher help determine the risk of recurrence and prognosis from primary prostate cancer, germline, and somatic testing determine heritable risk and guide treatment decisions in advanced disease settings<sup>54</sup>.

The assessment of germline genetics helps assess an individual's specific cancer risk, aids family cancer screening, and also informs treatment possibilities<sup>54</sup>. Somatic mutations are acquired over the course of an individual lifespan. Identification of somatic mutation requires the sequencing of DNA from tumor tissue, circulating tumor cells or circulating tumor DNA (ctDNA) in the blood. Since somatic mutations are often subjected to change over time due to genetic instability, repeated somatic testing might be appropriate as the cancer progresses through treatment<sup>54</sup>. Identification of germline and somatic mutations can help guide treatment options in the advanced disease setting. Tumor genetic testing can identify both somatic

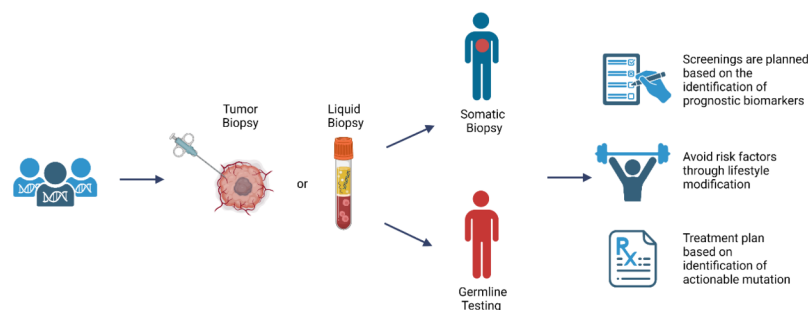
and germline mutations. However, tumor testing should not be performed as a substitution for germline testing given challenges in distinguishing between somatic and germline mutations. In the event that there is an identification of somatic mutation which has implication of cancer predisposition (BRCA1), then a confirmatory germline test is highly recommended<sup>55 54</sup>.

### *Clinical utility of Germline and Somatic Testing:*

In the era of precision medicine, genetic testing is widely considered in clinical practice as it helps to tailor the treatment for complex and heterogeneous diseases such as prostate cancer. By sequencing the tumor genome with NGS, actionable biomarkers can be identified<sup>51</sup>.

With approximately 5%-10% of mutations being germline mutations<sup>56</sup>, germline testing is essential in identifying risk biomarkers or germline mutations that are associated with increased cancer susceptibility. In the setting of PCa, the highest risk levels was reported in the presence of homologous recombination repair (HRR) gene BRCA1/2, which confers a 4-8 fold increase in risk<sup>32 57</sup>, followed by the presence of HOXB13 mutation, a gene encoding homeobox transcription factor B13, which has been associated with a 4 fold increase in susceptibility<sup>58 59</sup>. Studies have also shown that pathogenic mutations in BRCA1/2 and HOXB13 increase the risk for earlier onset of PCa<sup>57</sup>. Men with DNA mismatch repair gene mutations (*MLH1*, *MSH2*, and *MSH6*) have a 2-4 fold greater susceptibility to develop PCa<sup>60</sup>. Emerging data suggests that NBS1, FANCA and other DNA repair genes are associated with increased PCa risk and choice of treatment<sup>61</sup>.

The implications of germline and somatic mutation expand to being able to act as a molecular target for several drugs. For example, TOPARP- A Trial<sup>62</sup> have demonstrated improved response to the PARP inhibitor (PARPi), Olaparib, among men with metastatic castrate resistant prostate cancer (mCRPC) harboring DNA-repair defects (BRCA1/2 and ATM). Following this trial, the United States Food and Drug Administration granted Breakthrough Therapy designation to Olaparib. Also, the presence of BRCA1/2 and other DNA repair genes have been associated with improved response to platinum-based chemotherapy, and the presence of DNA mismatch repair genes have been associated with response to anti-PD-1 immunotherapy<sup>6364</sup>. With new advances, more clinically actionable mutations will appear and more diagnostic and therapeutic implications for somatic and germline testing would emerge (Figure 2). Continued efforts are needed to determine if these emerging targeted therapies have the same clinical utility in diverse populations.



**Figure 2:** *Clinical Utilization of Somatic and Germline testing in men with prostate cancer (Created using BioRender.com)*

### *Disparities in genomic application:*

As genomic data guide subsequent therapy, differential access to genomic testing can widen disparities in clinical trial participation. To date, AAM have been underrepresented in germline and somatic genetic studies of prostate cancer<sup>64</sup>. The lack of racial diversity in current genetic studies has a potential to exacerbate current disparities in health care.

As the result of the deficiency in racial representation in the genetic studies, the genetic variants that increase cancer risk in AAM and other minority groups are likely to be overlooked. Understanding genetic variant among different racial groups might explain the underlying biological cause for a higher prevalence and worsened prognosis in AAM with PCa. European American men were associated with increased ERG and ETS expression, and decreased SPINK1 expression. The AAM group was associated with higher expression of CRYBB2, GSTM3, with increased expression of SPINK1<sup>48</sup>. Compared to EAM, mutations in ZFH3 as well as focal deletions in ETV3 were more frequent in tumors from AAM and also MYC amplifications were more frequent in tumors from AAM men with metastatic PCa<sup>65</sup>. TMRSS2 and FOXA1 alterations continued to be more frequent in EAM in the metastatic setting<sup>66</sup>. Recent data suggest that AAM with PCa exhibit genetic alterations in highly penetrant germline genes as well as low-penetrant single nucleotide polymorphisms (SNP). Higher rates of germline variants of uncertain significance (VUS) have been reported in the AAM population than European ancestry patients with PCa, the meaning of which remains to be elucidated. More studies are needed to facilitate the possible reclassification of VUS<sup>32</sup>. In addition, it has been found that in AAM, the mutational frequency within 8q24 confers a higher incidence of PCa, an earlier age of onset, and a more clinically aggressive disease. The diagnosis of PCa has also been associated with several additional loci at 8q24<sup>32</sup>. Risk SNPs have a relatively small effect size and the underlying etiology of the non-coding changes remains under study.

However, these studies that evaluate germline and somatic alterations in African American men have shown that there is no significant difference in mutation rate of actionable genes between AAM and EAM with PCa<sup>64 65 6667</sup>.

In the metastatic setting, germline and somatic genetic testing is an important part of clinical management<sup>68</sup>. This review will focus on comparing the mutation rate of actionable genes between AAM and EAM with metastatic PCa (the stage of disease has higher mutational burden), as seen in Table 1 and 2. In order to achieve this, we conducted a bibliographic search in PubMed to search for multi-racial prostate cancer studies with result on genes with clinical actionability and report on race/ethnicity. We used the keywords: Racial disparity in germline testing of prostate cancer, tumor mutation across racial group, prevalence of germline mutation in prostate cancer, African American men, germline, prostate cancer, racial disparity in somatic testing of prostate cancer, and racial disparity in genetic alteration of prostate cancer. We found 4 studies analyzing PCa somatic mutations and 6 studies analyzing PCa germline mutations in the metastatic or lethal PCA setting. We then removed studies that did not have data for metastatic or lethal prostate cancer, which includes the Sartor et al. study, Kwon et al. study, and Nicolosi et al. study. Finally, we removed the Schumacher et al. and Mahal et al. study, because they used previous versions of GENIE compared to the Kamran et al. study. In the end, we included studies of somatic mutations total: the Koga et al<sup>67</sup> study which includes data from the MC3 (Multi-Center Mutation Calling in Multiple Cancers) call set from the Pan-Cancer Atlas Project of The Cancer Genome Atlas (TCGA), from the Foundation cohort and also from prostate cancers profiled with the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT); and the Kamran et al<sup>69</sup> studio that uses data extracted from the American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange (GENIE), version 8.1. In summary, we were left with a total of 5 studies (2 somatic and 4 germline). We identified the most frequent actionable mutations in PCa in these studies and analyzed the rates of somatic and germline mutations expressed in the different ethnic groups.

Mutation	Associated with increased Cancer Risk	Therapeutic Indication	Somatic Test for metastatic PCa	Somatic Test for metastatic PCa	Somatic Test for metastatic PCa
			Mutation Rate in European descendant (%)	Mutation Rate in African descendant (%)	Reference

Mutation	Associated with increased Cancer Risk	Therapeutic Indication	Somatic Test for metastatic PCa	Somatic Test for metastatic PCa	Somatic Test for metastatic PCa
BRCA 2	x	PARPi	4.45% 10.02%	4.23% 9.73%	Kamran et al. <sup>69</sup>
ATM	x	PARPi	7.29% 5.75%	9.86% 3.78%	Koga et al. <sup>67</sup>
PALB2	x		0.83%	2.16%	Kamran et al. <sup>69</sup>
CHECK2	x	PARPi	2.32%	1.08%	Koga et al. <sup>67</sup>
MSH2	x	Checkpoint Inhibitor	1.30%	1.62%	Koga et al. <sup>67</sup>
MSH6	x	Checkpoint Inhibitor	1.76%	1.08%	Koga et al. <sup>67</sup>
FANCA	x	PARPi	1.11%	0.00%	Koga et al. <sup>67</sup>
NBN	x	PARPi	0.65%	1.08%	Koga et al. <sup>67</sup>
CDK12 (somatic only)		Checkpoint Inhibitor	5.55% 4.73%	11.27% 7.57%	Kamran et al. <sup>69</sup>
					Koga et al. <sup>67</sup>

Table 1. *Multi-racial cohorts assessing the prevalence of mutation in genes with established and emerging clinical actionability in AAM and EAM with metastatic PCa, Somatic Test.*

Mutation	Associated with increased Cancer Risk	Therapeutic Indication	Germline Test for metastatic PCa	Germline Test for metastatic PCa	Germline Test for metastatic PCa
			Mutation Rate in European descendant (%)	Mutation Rate in African descendant (%)	Reference
BRCA 1	x	PARPi	0.5% 0.77% 0.87%	2.0% 0.0% 0.0%	Ledet et al. <sup>64</sup> Na et al. <sup>70</sup> Pritchard et al. <sup>65</sup>
BRCA 2	x	PARPi	5.0% 3.07% 4.77% 5.10%	4.0% 0.0% 0.0% 0.90%	Ledet et al. <sup>64</sup> Na et al. <sup>70</sup> Pritchard et al. <sup>65</sup> Plym et al. <sup>71</sup>
ATM	x	PARPi	1.0% 1.53% 1.01%	0.0% 3.33% 0.14%	Ledet et al. <sup>64</sup> Na et al. <sup>70</sup> Pritchard et al. <sup>65</sup>
PALB2	x		0.50% 0.43%	0.50% 0.0%	Ledet et al. <sup>64</sup> Pritchard et al. <sup>65</sup>
CHECK2	x	PARPi	2% 1.01%	0.0% 0.0%	Ledet et al. <sup>64</sup> Pritchard et al. <sup>65</sup>
MSH2	x	Checkpoint Inhibitor	0.20% 0.14% 0.70%	0.0% 0.0% 1.80%	Ledet et al. <sup>64</sup> Pritchard et al. <sup>65</sup> Plym et al. <sup>71</sup>
MSH6	x	Checkpoint Inhibitor	0.50% 0.14% 0.30%	0.50% 0.0% 0.00%	Ledet et al. <sup>64</sup> Pritchard et al. <sup>65</sup> Plym et al. <sup>71</sup>

Mutation	Associated with increased Cancer Risk	Therapeutic Indication	Germline Test for metastatic PCa	Germline Test for metastatic PCa	Germline Test for metastatic PCa
PMS2	x	Checkpoint Inhibitor	0.30% 0.70%	0.50% 0.00%	Ledet et al. <sup>64</sup> Plym et al. <sup>71</sup>
FANCA	x	PARPi	0.30%	0.00%	Plym et al. <sup>71</sup>
NBN	x	PARPi	1% 0.14% 0.00%	0.0% 0.0% 0.90%	Ledet et al. <sup>64</sup> Pritchard et al. <sup>65</sup> Plym et al. <sup>71</sup>

Table 2. *Multi-racial cohorts assessing the prevalence of mutation in genes with established and emerging clinical actionability in AAM and EAM with metastatic PCa, Germline Test.*

#### *BRCA 1 and 2:*

BRCA1 and BRCA2 mutations are associated with aggressive PCa with higher risk for nodal and distant metastasis as well as poor survival outcome<sup>72</sup>. Two studies identify a similar rate of BRCA2 somatic mutations among EAM and AAM (4.45-10.02% in EAM and 4.23-9.73% in AAM with metastatic PCa)<sup>6769</sup>.

In the case of germline variants, three separate multi-racial studies identified an incidence of BRCA 1 germline mutation in 0.5-0.87% of EAM compared to 0-2.0% in AAM (Table 1), and note a frequency of BRCA 2 germline mutation of 3.07-5.1% in EAM and 0-4% n AAM (Table 2)<sup>64 65 70 71</sup>. In a study comprised of 2098 AAM and Ugandan men, making it the largest study of germline mutation in African descendants, BRCA1 mutations were found in 0.72% and BRCA2 mutations were identified in 2.1% of the metastatic PCa patients<sup>73</sup>.

#### *ATM:*

ATM is another mutation that has been associated with aggressive PCa<sup>70 73</sup>. Two separate multi-ethnic studies found no significant difference in ATM somatic mutation in EAM and AAM with metastatic prostate cancer (5.75-7.29% and 3.78-9.86% respectively)<sup>67 69</sup> (Table 1). Three separate studies also noted similar rates of ATM germline variants in EAM with metastatic PCa (1-1.53%)<sup>6465 70</sup> compared to reported rates amongst AAM with metastatic PCa (0-3.33%) (Table 2). In a study with more than 2000 men of African ancestry, the incidence ATM germline variants was 1.8% in patient with metastatic PCa<sup>73</sup>.

#### *PALB2:*

PALP2 mutation is associated with 6.3 higher risk for aggressive PCa<sup>74</sup>. The rate of PALB2 somatic mutation is not significantly higher between EAM (0.83%) and AAM (2.16%) with metastatic PCa (Table 1)<sup>67</sup>. The rates of PALB2 germline mutation, on the other hand, is similar in both races with a range from 0.43 to 0.5% in EAM and from 0 to 0.5 % in AAM with metastatic prostate cancer (Table 2)<sup>6465</sup>.

#### *CHEK2 :*

CHEK2 is a tumor suppressor gene located on chromosome 22q and is associated with a significantly higher prevalence in men with metastatic PCa compared with localized PCa. CHEK2 encodes a cell cycle checkpoint protein kinase that plays a role in the regulation of tumor protein 53 (TP53) and DNA repair. The rates of CHEK2 somatic mutations is 2.32% in EAM and 1.08% in AAM (Table 1)<sup>67</sup>. The studies reported CHEK2 germline mutation range from 1.01-2% in EAM and 0% germline mutation rate in the AAM (Table 2)<sup>6465</sup>.

#### *Lynch syndrome:*

Lynch syndrome is an inherited cancer predisposition syndrome with an increased risk of numerous malignancies, doubling the risk of PCa. It is caused by germline mutations in the mismatch repair genes MLH1,



MSH2, MSH6 and PMS2<sup>75</sup>. The included studies show a rate of somatic mutations in the EAM population ranging from 1.30-1.76%. The AAM population presents a similar expression rate with a range that varies from 1.08-1.62% (Table 1)<sup>67</sup>. Regarding germline mutations, the EAM population presented a range from 0.14-0.70%, while the AAM population presented a range from 0.0-1.80% (Table 2)<sup>64 65 71</sup>.

*NBN* :

NBN encodes for Nibrin a protein within the Mre11-RAD50-NBS1 double-stranded DNA break repair complex. NBN is a newly emerged gene that is identified as PCa-susceptible<sup>76</sup>. For the NBN mutation, the included studies presented a somatic mutation rate of 0.65% in EAM, while the AAM population presented a rate of 1.08% (Table 1)<sup>67</sup>. The EAM population presented a germline mutation rate of 0.0-1% while the AAM population has an NBN germline mutation rate of 0.0-0.9%(Table 2)<sup>6465 71</sup>.

*CDK12*:

The prevalence of CDK12 somatic mutations in the setting of metastatic PCa is higher in AAM (7.57-11.27%) than in EAM (4.73-5.55%)<sup>67 69</sup> (Table 1), but this difference is not significant. Nevertheless, in the study Koga et al<sup>67</sup> did report statistically significant difference in CDK12 deletion, a subtype of CDK12 mutation, with a higher mutational frequency in AAM than in EAM with metastatic PCa (2.16% vs. 0.18% respectively).

Analyzing and comparing the percentage of patients in each study, we noticed that the Ledet et al<sup>64</sup> trial included a total of 867 patients, of which 188 are African American (21.6%) and 669 (77.2%) Caucasian patients. Kamran et al<sup>69</sup> evaluated a total of 20,191 patients with various types of tumors, of whom > 80% were Caucasian patients and only 8.6% were AAM. Na et al<sup>70</sup> included a total of 799 patients, of which 613 were EAM (76.7%), 119 patients were AAM (14.9%), and 67 patients (8.4%) were of other races. Lastly, the Koga et al<sup>67</sup> study included 861 patients with PCa, of whom 250 men were AAM (29.0%) and 611 men were EAM (71.0%). The studies with the most African American representation were the germline studies with Ledet et al<sup>64</sup> and Rong Na et al<sup>70</sup> with 21.6% and 14.9% respectively. Even so, this population continues to be underrepresented and its results could not be reliably extrapolated. A more racial inclusive cohort is needed to produce a more representative data.

Mutations in metastatic PCa	Mutation Rate in European descendant (%)	Mutation Rate in African descendant (%)	Reference
TP53	45.3% 38.1%	43.2% 25.4%	Koga et al <sup>67</sup> Kamran et al <sup>69</sup>
PTEN	37.5% 10.4%	24.3% 7%	Koga et al <sup>67</sup> Kamran et al <sup>69</sup>
TMPRSS2-ERG	31.6% 0.9%	14.1% 2.8%	Koga et al <sup>67</sup> Kamran et al <sup>69</sup>

Table 3. *The prevalence of TP53, PTEN and TMPRSS2-ERG mutations in AAM and EAM with metastatic PCa.*

We also examined the specific racial differences between the mutation rate of the top 5 mutations in metastatic PCa: AR, TP53, PTEN, TMPRSS2-ERG and RB1. Out of these 5 mutations, TP53, PTEN and TMPRSS2-ERG are shown of have significant differences in mutation rate between AAM and EAM with metastatic PCa according to more than one study. For this reason, we focused on these 3 mutations to analyze the differences between the two ethnicities specifically in metastatic PCa (Table 3). The most strikingly consistent dissimilarities may be the lower frequencies of rearrangements and PTEN mutations<sup>67</sup>. Mutation of TP53, PTEN, and TMPRSS2-ERG fusion are among the most prevalent genetic defects found in lethal metastatic prostate cancer. Koga et al<sup>67</sup> showed that in prostate cancer, TMPRSS2-ERG rearrangements

(31.6% vs 14.1%) and PTEN deletions (37.5% vs 24.3%) were less frequent in AAM. It also showed that AAM had a 43.2% mutation range versus 45.3% for EAM in TP53 mutation. An analysis by Kamran et al<sup>69</sup> also demonstrated similar trend: TP 53 mutation in 38.1% of EAM participants and in 25.4% of AAM; PTEN aberration in 10.4% of EAM and in 7% of AAM. However, TMPRSS2-ERG fusion is lower in EAM participant than in AAM (0.9% vs. 2.8% respectively), which is different from the trend found in the Koga et al.<sup>67</sup> study. Even though various studies analyzing these genetic aberrations in metastatic PCa have yielded agreeable findings where AAM has lower mutational frequencies in these genes compared to their EAM counterparts<sup>64-69</sup>, more studies are needed to confirm the racial differences in mutational frequencies in these genes.

These findings conflict with the more aggressive features of prostate cancer in AAM men. It is hard to imagine that less frequent deletions of these genes can contribute to more aggressive features of prostate cancer in AAM. The lower prevalence of PTEN mutation, TP53 aberration and TMPRSS2-ERG fusion among AAM tumors suggests that other molecular alterations or pathways are likely to account for racial disparities in PCa outcomes. Therefore, the emergence of precision medicine targeting these mutations might further exacerbate racial disparity in PCa.

#### *Racial Disparity in Clinical Trials Enrollment :*

Despite racial disparities in prostate cancer incidence and outcome, there is a low enrollment of AAM patients in clinical trials. In a study analyzing 72 prostate cancer trials with start date ranging between 1987 and 2016, EAM accounted for 96% of all trials' participants<sup>77</sup>. With the advancement of precision medicine, it is imperative to improve representation in trial enrollment in order to ensure a proper validated biomarkers, and subsequently, an appropriate treatment decision for the general population, especially for those from marginalized, high-risk background<sup>78</sup>. This review identifies clinical trials started after 2016 that investigated personalized therapy for prostate cancer in order to examine the representation of AAM across prostate cancer precision therapy trials. We carried out a literature search on clinical trial registries (ClinicalTrials.gov) using the keywords: PDL-1, Pembrolizumab, Nivolumab, Cemiplimab, Durvalumab, PARPi, Veliparib, Olaparib, Niraparib, Rucaparib, Talazoparib, Lutetium and 177Lu. The objective was to find clinical trials that started after 2016, have been completed or active but not enrolling, have results, and show reports of participant's race/ethnicity. We eliminated the trials that did not meet this condition and we found a total of 14 trials. Of these, we eliminated 1 trial that was irrelevant, leaving us with 13 trials<sup>79-91</sup>.

Clinical Trial Identifier	Study Name	Study Start Year	Investigated Drug	
NCT02923180 <sup>79</sup>	MGA271	2017	Enobilituzumab	L
NCT02952534 <sup>80</sup>	TRITON 2	2017	Rucaparib	m
NCT02987543 <sup>81</sup>	PROfound	2017	Olaparib	m
NCT03016312 <sup>82</sup>	IMbassadore250	2017	Atezolizumab	m
NCT03093428 <sup>83</sup>		2017	Pembrolizumab	m
NCT03148795 <sup>84</sup>	TALAPRO-1	2017	Talazoparib	m
NCT03179410 <sup>85</sup>	PICK-NEPC	2017	Avelumab	
NCT03204812 <sup>86</sup>		2017	Durvalumab and Tremelimumab	m
NCT03338790 <sup>87</sup>	CheckMate 9KD	2018	Nivolumab	m
NCT03406858 <sup>88</sup>		2018	Pembrolizumab and HER2Bi-Armed Activated T Cells	m
NCT03511664 <sup>89</sup>	VISION	2018	177Lu-PSMA-617	m
NCT03516812 <sup>90</sup>		2018	Olaparib	C
NCT04089553 <sup>91</sup>		2019	AZD4635, Oleclumab and Duravalumab	m
				T

**Table 4:** Representation of race/ethnicity in prostate cancer clinical trials using personalized therapy

In the last decade, there has been unprecedented progress in treatment options for patients with prostate cancer resulting in an ever-growing range of options. This raises the question of whether these are all the right options for individual patients to receive optimal therapy. Unfortunately, despite new advances in the field, the representation of African American men in these clinical trials to determine ethnic differences in clinical benefit remains inadequate<sup>92,93</sup>.

Examining the trials activated after 2016, we found that the inclusion of African American patients remains low (<5%) compared to that of European American patients in prostate cancer clinical trial for precision oncology, even reaching 0 recruitment of African American patients as in the trial NCT03093428 (Table 4). The future personalized treatment of PCa is based on these ongoing clinical trials, so the deficit in enrollment of African American participants might inhibit the generalization of the result to this subgroup of patients. Therefore, this existing disparity may have an impact on the potential benefit in survival, quality of life, and optimal therapies for African American patients.

Approximately 12% of men in the United States are African American<sup>92</sup>. Since AAM have twice the risk of developing PCa compared to EAM, a proposed representation could be 24% in clinical trials. However, the current average enrollment of AAM to prostate cancer clinical trials overall is only around 3%<sup>92,93</sup>. In only one of the trials that we analyzed, the number of AAM patients included did exceed that percentage, but this was not the case in the rest.

## Conclusion

A majority of prostate cancer studies present an underrepresentation of the minority populations. This comprises a fundamental problem since African-American patients have the highest risk of suffering from PCa and the highest risk of tumor aggressiveness<sup>94</sup>.

There are known differences in the biological characteristics of prostate tumors in AAM than in EAM<sup>48</sup>, so it is crucial to improve the representation of AAM in prostate cancer studies in order to better elucidate these biological differences. The current deficit in African American participants in prostate cancer studies contributes to a potential limitation of the predictive power of genomic applications such as PRS or Decipher used to assess risk in PCa. As a result, there could be gaps in recommendations that can be provided to this population. Available genomic data on prostate cancer are also affected by the underrepresentation of African-American men in germline and somatic genetic studies of prostate cancer<sup>67</sup>. The lack of sufficient inclusion may hinder the ability to translate findings to clinical care and subsequently, the ability to offer personalized treatment. These limitations might exacerbate the existing racial disparities in prostate cancer outcomes.

While the reasons behind these disparities are multifactorial, it is important to address them at all levels. Health disparities are often attributed to the lack of socioeconomic resources for minorities that usually reduce accessibility to healthcare<sup>92,95</sup>. The difficulties in completing visits for clinical trials can also be limited by the distance to cancer centers and the lack of transportation support. Improving accessibility to studies is an important factor to take into account, perhaps by increasing fund supporting the treatment, housing, and transportation for underrepresented minorities who are enrolled in a study.

Another barrier might be the lack of access to the information about the studies and trials. Therefore, there should be efforts in improving the understanding of the demographic makeup of institutional catchment areas and increasing the community outreach to promote greater diversity in study participation. It would also be necessary to establish national support and dissemination programs for the trials that are being carried out in each center and substantially increase attention to the recruitment capacity of centers. Finally, there is a longstanding mistrust between the African American population and the health care system due to the mistreatment of African Americans in research studies such as the Tuskegee Airmen Syphilis Study<sup>96</sup> and the Henrietta Lacks case<sup>97</sup>. This issue can be addressed by improving the racial representation of health care providers since patients from minority backgrounds are reported to be more likely to enroll in research study when they are approached by providers from the similar racial backgrounds<sup>98,99</sup>. In summary, more efforts should be made to improve the diversity of patients included in genomic and clinical studies to generate

more evidence that will ultimately help determine the best possible treatment for them.

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