







Article

Prevalence of Genetic Mutations in Patients with Metastatic Prostate Cancer in a Cohort of Mexican Patients

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Abstract: Background: Prostate cancer is a malignant neoplasm of the male genitourinary system with the highest incidence worldwide. Susceptibility genes related to aggressiveness and prognosis, such as BRCA1/2, ATM, PTEN, have been identified. Currently, reports related to germline mutations in patients with prostate cancer in Latin American populations are very limited or absent. In the Mexican population, reports are also limited, especially in the context of metastatic prostate cancer. Determining the prevalence of these mutations is relevant to predict the potential aggressiveness of tumors and allow the use of targeted therapies, such as PARPi inhibitors. **Objective:** Determine the prevalence of germline mutations in patients with metastatic prostate cancer and establish their clinical characteristics at diagnosis. **Material and Methods:** Sixty-nine patients with metastatic PCa underwent testing and genetic analysis using the Comprehensive Multi-Cancer Hereditary Cancer Panel. The prevalence of germline mutations was assessed, and the cohort was divided into two groups for the evaluation and analysis of clinical characteristics between the mutated and non-mutated populations. **Results:** We identified mutations in 15 out of 69 patients (21.73%), while 54 patients (78.26%) had no mutations. Pathogenic mutations were observed in 15.9% of patients, Variants of Uncertain Significance (VUS) in 34.78%, and 5.79% had both. The most frequent mutations included ATM (11.54%), BRCA1 (11.54%), BRCA2 (7.69%), FANCA (7.69%), and FANCM (7.69%). No statistically significant differences were found in PSA levels, age at diagnosis, and resistance to castration between the two groups. **Conclusions:** Our study unveiled a mutation rate of 21.73%, marked by a significant prevalence of ATM, FANCA, FANCM, and Variants of Uncertain Significance (VUS). This pattern deviates from findings in other series, underscoring the necessity for improved access to clinical genetic testing in our population.

Keywords: prostate cancer; germline mutations; BRCA



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1. Introduction

Prostate cancer (PCa) is the malignant neoplasm of the male genitourinary system with the highest incidence worldwide and represents one of the leading causes of cancer and mortality in men [1,2]; the proportion of PCa diagnosed at an advanced stage has increased from 3.9% to 8.2% in the last decade in the United States alone [1]. In the Mexican population, PCa is also one of the most commonly diagnosed cancers with one of the highest cancer-related mortality rates due to the absence of a coordinating entity for cancer prevention and control in Mexico, in addition to a fragmented healthcare system [3].

Genetics is one of the most important factors in PCa, especially in men with a family history of neoplasia; heritability is estimated at up to 30% and has been documented in

several studies. Of all the predisposing genes, breast cancer susceptibility genes BRCA1 and BRCA2 are among the most studied as they are closely related to the aggressiveness and prognosis of PCa [4,5]. Some clinical studies have shown that patients with these mutations are more likely to have lymph node involvement or distant metastases at diagnosis with shorter disease-free survival than patients without these mutations [6].

BRCA is an androgen receptor (AR) repairer, and its pathway plays an important role in the onset and development of PCa. Castration-resistant PCa patients with mutations in somatic or germline variants of DNA damage repair genes, particularly BRCA1 and 2, may be sensitive to poly-ADP-ribose polymerase inhibitors (PARPi) [7]. The phase III PROfound clinical trial showed that PCa patients with homologous recombination repair (HR) gene mutations may benefit from olaparib monotherapy. In particular, the risk of radiographic progression (66%) or death could be reduced in patients with mutations in BRCA1/2 and ATM [8], resulting in guidelines recommending screening for all patients with high-risk, locally advanced, metastatic PCa, and those with a family history of malignancy [9,10].

Nowadays, reports related to germline mutations in patients with PCa in the Latin American population are very limited or non-existent. Mexico is no exception, as there are currently few hospitals where genetic testing is performed. Regarding the prevalence of germline mutations in Mexico, there are only two studies that have partially evaluated specific mutations in the Mexican population and their association with BRCA. Moreover, only one study has explored their interaction with PCa. A study by Villarreal-Garza et al. determined the association of the BRCA gene with a high prevalence of BRCA mutations in Mexican women with ovarian (28%) and breast cancer (15%) [11,12]. In a study by Martínez-Nava et al., the genetic prevalence of BRCA1, BRCA2, and VDR in Mexican patients revealed the crucial role of BRCA1 in the risk of aggressiveness of PCa [13]. Therefore, the present study aims to describe the prevalence of germline mutations in a population of patients with metastatic PCa in a Mexican cohort.

2. Material and Methods

To determine the status of germline mutations in the Mexican prostate cancer population, 69 patients with metastatic PCa underwent evaluation, and genetic testing was performed. A prospective cross-sectional study of these 69 patients with PCa was conducted from January 2021 to July 2023.

3. Study Design

This study was prospective and included patients with hormone-naïve, castration-sensitive, and castration-resistant metastatic PCa. It took place at a single Hospital Center in Mexico, which is a tertiary referral hospital in the country. The institutional review committee approved this study, adhering to the current guidelines of the International Conference on Harmonization for Good Clinical Practice and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

4. Patients and Interventions

Eligible patients were required to have documented prostate adenocarcinoma confirmed by a histopathological report and distant metastatic disease, as evidenced by at least one lesion on a bone scan and/or non-regional lymph node or visceral involvement on thoracoabdominal tomography. Prior treatment was not an exclusion criterion; thus, patients with a history of docetaxel, androgen deprivation therapy (ADT), or radiotherapy were eligible. Newly diagnosed metastatic patients without prior therapy were also included in this study.

Concerning the disease stage, we encompassed metastatic patients who were hormone refractory, castration sensitive, and castration resistant (defined as PCa that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone < 50 ng/dL). This study comprised all metastatic patients seen at the urology department during the defined period possessing a complete clinical record and consenting to genetic testing.

Exclusion criteria involved patients lacking a histopathological report in their records, those with localized or locally advanced disease, and individuals who declined the genetic test. Only one patient declined participation, as he refused to provide a blood sample when offered. All potential participants received comprehensive explanations about the testing procedure, expected waiting times for results, therapeutic options in case of germline mutations, and, if mutations unrelated to PCa were detected, the patient and their family were offered the option of genetic counseling at our center.

5. DNA Sequencing

The tests were conducted using a blood sample of circulating DNA extracted from peripheral blood collected from each patient meeting the inclusion criteria, which required a histopathologic diagnosis of metastatic PCa confirmed by radiographic imaging studies (CT and bone scan). Following the signing of the informed consent form, each patient underwent the Comprehensive Hereditary Cancer Panel for multiple cancers. This test, developed and with analytical performance characteristics determined by the Quest Diagnostics Nichols Institute in San Juan Capistrano, has been validated according to CLIA regulations and is utilized for clinical purposes with GTR Test IDHelp number GTR000592394.2. The panel analyzes 66 genes, including, but not limited to, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMP1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN1B, CDKN2A (p16, p14), CHEK2, DICER1, EGFR, EPCAM, FANCA, FANCC, FANCM, FH, FLCN, GALNT12, GREM1, HOXB13, MAX, MEN1, MET, MTF, MLH1, MRE11 (MRE11A), MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, POT1, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RECQL, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMARCA4, SMAD4, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, and XRCC2. The panel also includes variant alterations of uncertain significance (VUS), which were determined by consulting an online database (ClinVar—<http://www.ncbi.nlm.nih.gov/clinvar/>, accessed on 1 July 2023), and these are inclusive until study closure in 1 July 2023.

6. Statistical Analysis

We conducted a comprehensive analysis to assess the incidence of all genetic variables and determined the association between the occurrence of germline mutations and the PSA value at diagnosis. Additionally, we analyzed epidemiological and clinical characteristics among different cohorts, including age at diagnosis and Gleason score.

For the analysis of the difference in age at diagnosis between the two cohorts, Bartlett's test was initially employed. It revealed non-homogeneous variances; consequently, the Mann–Whitney U test was applied to compare the two populations. To analyze the dichotomous variable of castration resistance, a chi-square hypothesis test was performed to compare proportions. For the analysis of the PSA level at diagnosis, Bartlett's test was first conducted. Upon determining non-homogeneous variances, the Wilcoxon test was used for analysis between the cohort with and without mutations. These statistical methods were chosen to ensure robust and appropriate comparisons between different cohorts, providing a comprehensive understanding of the associations and characteristics within the studied population.

7. Results

7.1. Analysis of Patient Characteristics

Study Population

A total of 69 patients, all Mexican individuals with radiographically positive metastatic prostate cancer, were included in this study. Statistical analysis indicated no statistically significant differences in the median age at diagnosis between those with mutations (70.3 ± 7.5 years) and those without mutations (72 ± 9.5 years) ($p = 0.1785$). In both cohorts, more than 50% of patients had a Gleason group grade with ISUP greater than four, constituting 74% in patients without mutations and 73.3% in patients with mutations (Table 1).

Table 1. Demographic variables.

Variable	Patients without Genetic Mutations (n = 54)	Patients with Genetic Mutations (n = 15)	p-Value
Age at diagnosis	72 ± 9.5 years	70.3 ± 7.5 years	0.2083
PSA level at diagnosis	663.15 ± 1468.56 ng/mL	2260.11 ± 5623.25 ng/mL	0.1453
Family history	13 (24.07%)	4 (26.66%)	
Gleason Group Grade			
1	3 (5.5%)	2 (13.3%)	
2	5 (9.2%)	1 (6.6%)	
3	6 (11.1%)	1 (6.6%)	
4	16 (29.6%)	6 (40%)	
5	24 (44.4%)	5 (33.3%)	
CASTRATION RESISTANCE	28 (51.8%)	9 (60%)	0.7708

7.2. Pathogenic, Likely Pathogenic, and Variants of Unknown Significance (VUS)

We identified 15 patients with pathogenic/likely pathogenic mutations, constituting 21.73% of the study population, while 54 patients did not exhibit these mutations (78.26%). Within our cohort, twenty-four patients presented variants of unknown significance (VUS), accounting for 34.78%, and four patients showed VUS associated with a pathogenic/likely pathogenic mutation (5.79%) (Figure 1).

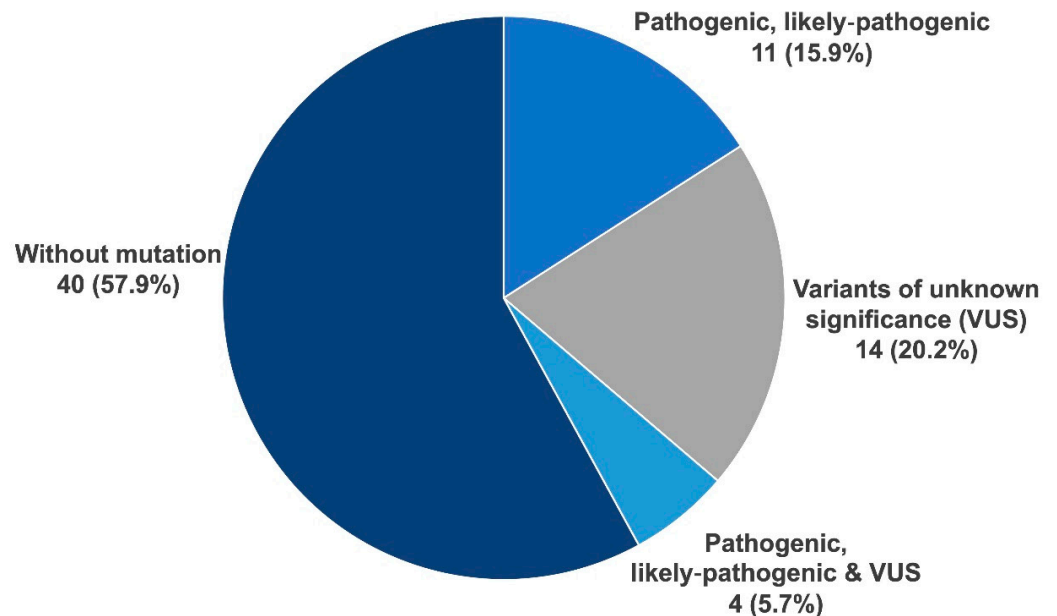


Figure 1. Distribution chart of patients with metastatic prostate cancer.

Among the pathogenic/likely pathogenic mutations, the most frequently observed were ATM (11.54%), BRCA1 (11.54%), BRCA2 (7.69%), FANCA (7.69%), and FANCM (7.69%). Additionally, we detected 13 different mutations within the pathogenic/likely pathogenic group (Figure 2). The most frequent VUS mutations were FANCA 10%, FANCM 7.5%, ATM 5%, BRCA2 5%, CHEK2 5%, the distribution of the frequencies of VUS is presented in Figure 3.

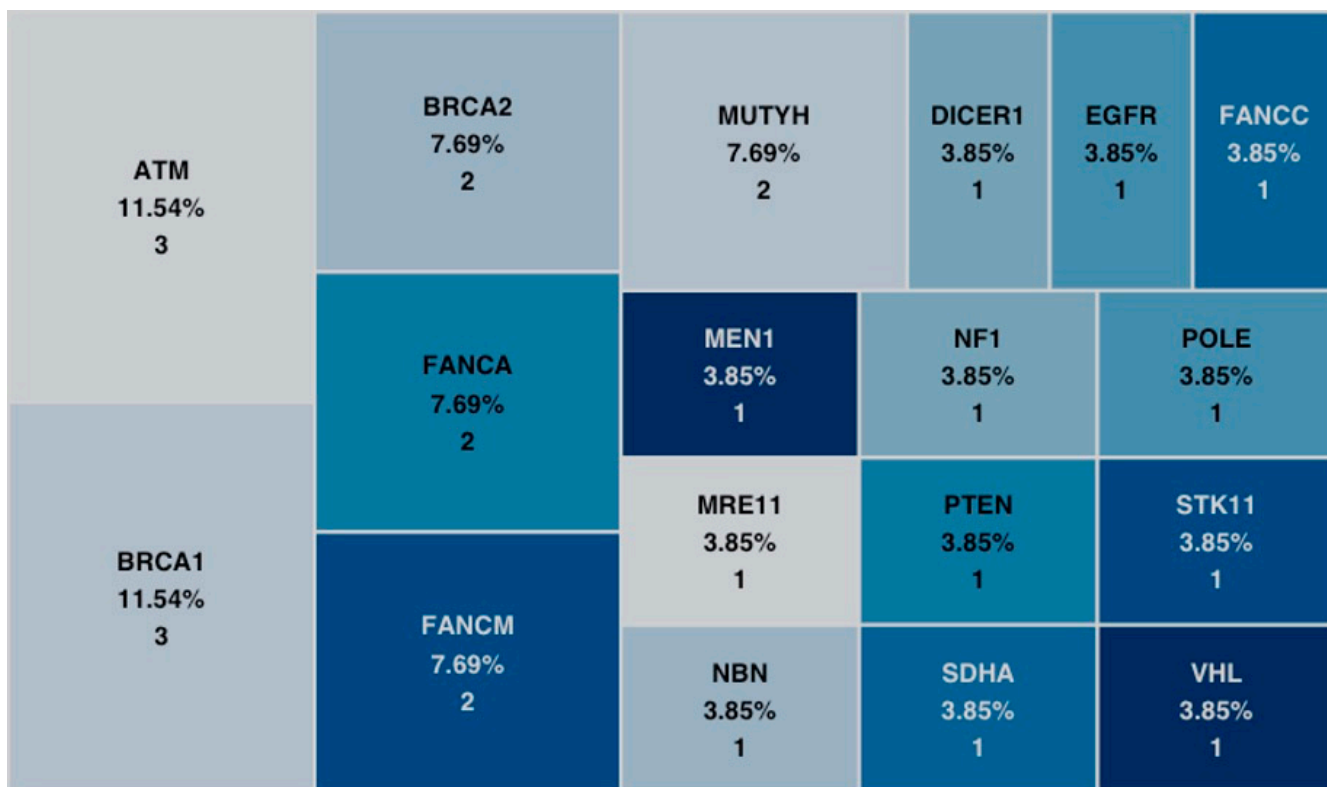


Figure 2. Treemap of the Pathogenic and likely-pathogenic mutations analyzed.

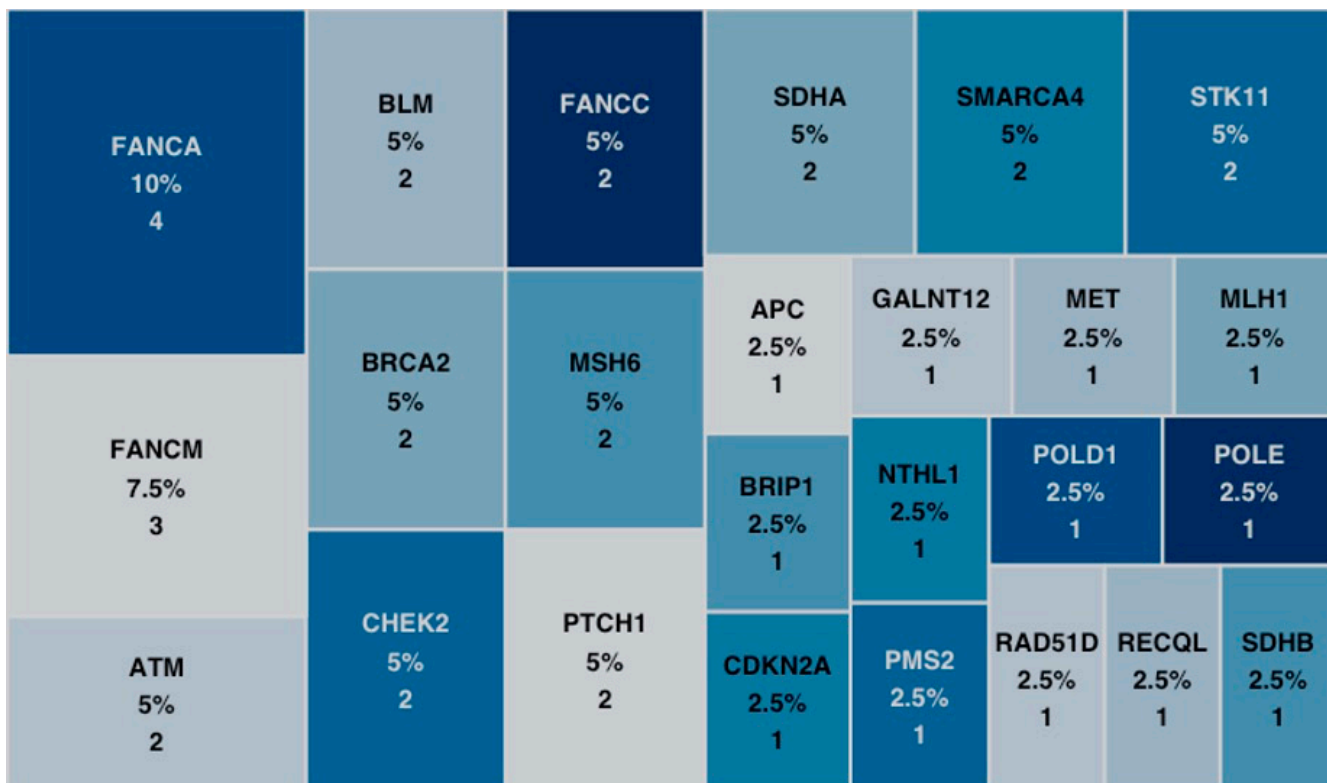


Figure 3. Treemap of the Variants of unknown significance (VUS) analyzed.

7.3. Castration Resistance

The resistance to castration was comparable in both cohorts, with no statistically significant difference observed: 51.8% in the group without mutations versus 60% in the group with mutations ($p = 0.7708$) (Table 1).

7.4. PSA Level at Diagnosis

No statistically significant differences were found in PSA level at diagnosis. Patients with mutations exhibited a PSA level of 2260.11 ± 5623.25 ng/mL, while patients without mutations had a PSA level of 663.15 ± 1468.56 ng/mL ($p = 0.1668$).

8. Discussion

Currently, there is a well-established understanding that PCa has a robust genetic association. The identification of populations with an elevated prevalence of unique high-penetrance risk factors, such as BRCA2 in metastatic disease, coupled with the increased availability and reduced cost of sequencing, has prompted the extension of germline genetic testing recommendations. This extension now includes patients with prostate cancer who are at high risk, locally advanced, and have metastatic disease [14].

BRCA1/2 mutational investigations have garnered increased attention in recent years, attributed in part to the success of PARPi in clinical trials [6–8]. While much of this research has centered on European and North American populations, there has been a scarcity of studies on Latin American populations. This investigation into germline mutations in the Mexican PCa population contributes to understanding the prevalence of these mutations in our specific demographic.

While our cohort may be smaller compared to studies conducted in specific populations [15,16], the results of our study do not indicate that Mexican patients with metastatic PCa carrying mutations had an earlier age of presentation (70.3 ± 7.5 vs. 72 ± 9.5 years, $p = 0.1785$). Statistical significance was not achieved in this variable. However, we observed a similar number of mutations compared to other series, evaluating them in the context of metastatic disease. Our study obtained a prevalence of 21.73%, resembling the 23% of mutations in DNA repair genes reported by Robinson et al., with 8% of these mutations in germline DNA repair [17]. In 2016, Pritchard et al. studied 692 patients with metastatic and castration-resistant PCa who underwent germline genetic testing. They reported germline mutation rates ranging from 4.6% in localized disease to 11.8% in metastatic disease. The most common genetic alterations included BRCA2 (5.3%), CHEK2 (1.9%), ATM (1.6%), and BRCA1 (0.9%)—findings that offer a valuable reference for the genetic landscape in metastatic PCa [18].

The PROREPAIR-B study, evaluating treatment outcomes in metastatic PCa patients, identified germline DNA repair mutations in 16% of the 419 participants, with the most common mutations being 14 in BRCA2, eight in ATM, and four in BRCA1 [19]. In contrast, our study presents distinctive findings, showing a higher frequency of ATM mutations at 11.54%, along with BRCA1 at 11.54%, BRCA2 at 7.69%, FANCA at 7.69%, and FANCM at 7.69%. This discrepancy is noteworthy, particularly in light of the recent FDA approval of olaparib and rucaparib for patients with BRCA1/2 mutations. When compared to specific populations, like Ashkenazi Jews, our study reveals notable differences, especially in the frequency of BRCA1 mutations, which was found to be between 1.15% and 1.2% [20,21]. An intriguing finding in our population was the percentage of mutations found in ATM genes at 11.54%. This is relevant considering current evidence suggesting that PARP inhibitors may be less effective in ATM-associated PCa. Abiraterone, enzalutamide, and docetaxel, however, do not show decreased efficacy in carriers of this mutation. This implies that these agents may remain viable treatment options for this subgroup. Nevertheless, it underscores the importance of continued study and inclusion of this significant patient subgroup in clinical trials, particularly those exploring new agents and combination strategies with PARP inhibitors [22].

There are several hypotheses that could explain the observed differences in mutation prevalence among studies. One factor to consider is the variance in the number of mutation analyses performed. For instance, in a study by Pritchard et al., only 20 genes were included [18].

This discrepancy in the scope of mutations analyzed may introduce bias when comparing prevalences directly. Another hypothesis, as reported by Villarreal-Garza et al., suggests that the Mexican population might have a higher incidence of BRCA1/2 mutations [12]. This notion underscores the importance of conducting a multicenter population study involving a larger cohort of Mexicans with PCa.

A subsequent study in 867 patients with metastatic PCa evaluated the rates of pathogenic variants, probably pathogenic variants, and variants of unknown significance (VUS) in cancer genes in patients who identified themselves as Caucasian and African American and showed that pathogenic and probably pathogenic variants of known cancer genes did not vary by race, age, or sex, but variants of unknown significance (VUS) were predominant in African American patients, which is consistent with our population in which we found 40.57% [23]. This effect was also observed in studies using databases from a commercial germline testing provider, Color Genomics™, where they analyzed 1351 men with PCa at any stage who underwent germline testing; 78% of these men identified as Caucasian, 11% as Ashkenazi Jewish, 3% as African American/Canadian, 2% as Hispanic, 2% as Asian/Pacific Islander, and 4% as other, demonstrating higher rates of VUS in the African American/Canadian, Hispanic, and Asian/Pacific Islander populations; it is important to emphasize the low participation of Latino populations in this type of study [24]. It has become increasingly evident that variants of uncertain significance (VUS) present a challenge for clinicians and families alike. These variants may signify normal human variation or indicate an elevated risk of cancer. The potential misanalysis of VUS remains a concern, exposing patients and their families to harm, including unnecessary and invasive surveillance or incorrect surgical interventions [25].

Our results align with the current literature, emphasizing the crucial role of performing genetic tests and expanding access. We observed a significant prevalence of germline mutations at 21.73% in Mexican patients with metastatic PCa [5,26,27], which is consistent with findings in other cohorts ranging from 11.8% to 23% [17–19]. These data underscore the importance of enhancing access to genetic testing for men with metastatic PCa, as they identify candidates for PARP inhibitor treatment lines, ultimately contributing to improved overall survival [28,29].

This study has some limitations, primarily stemming from the relatively small number of patients analyzed, which could potentially introduce selection bias. Statistical significance in the comparison of the rate of resistance to castration was not achieved between both cohorts. The cross-sectional design of this study raises the possibility that the observed result may be associated with the duration of treatment, and the inclusion of patients with varying treatment histories, including exposure to docetaxel or abiraterone, may influence the rate of circulating DNA mutations. It is important to note that genetic mutations may vary between different stages of PCa, even within the same patient and timeline [30–32]. Given the cost and limited application of genetic testing in Mexico, this study provides valuable insights into the prevalence of certain mutations in our population. While this study represents one of the first comprehensive evaluations of germline genes in a Mexican population with metastatic PCa, it is recognized that further updates of the database and additional extraction of mutation information through multicenter studies will be necessary for a more comprehensive understanding of our population.

9. Conclusions

While our study stands as one of the pioneering investigations in the Mexican population with metastatic PCa, it is essential to acknowledge its significant limitations. The identification of a high number of germline mutations in Mexican patients with metastatic PCa (21.73%), particularly the noteworthy prevalence of ATM (11.54%), FANCA (7.69%),

and FANCM (7.69%) mutations, underscores the importance of further exploration in this population.

However, it is crucial to recognize the need for a larger sample size to optimally evaluate the germline landscape in this ethnically unique population. The observed high rate of variants of unknown significance (VUS) in this cohort (40.57%) highlights the imperative for increased genetic testing.

The results underscore the necessity for enhanced access to clinical genetic testing and expanded research opportunities to address disparities and underrepresentation among Latin American PCa patients. Further studies are critical to comprehensively understand the germline genetic components contributing to disparities in PCa risk and outcomes in this population.

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Institutional Review Board Statement: This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of our medical institution; approval number of Institutional Review Board: EMGS-SP-402.

Informed Consent Statement: All patients/participants gave written informed consent to participate in this study.

Data Availability Statement: The patient information sheet, patient consent form, and patient investigation booklets used in this clinical trial are available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AR	Androgen receptor
ADT	Androgen deprivation therapy
PARPi	Poly-ADP-ribose polymerase inhibitors
PCa	Prostate cancer
PSA	Prostate-specific antigen
VUS	Variants of unknown significance

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