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Review Article

Implementing Pharmacogenomic and Genetic Testing into Prostate Cancer Clinics: A Literature Review of Current Trends and Applications

Joshua M. Germany[1,2*] and Julie Martin[1,2]

[1]*Prisma Health Cancer Institute, Greenville, SC, USA;* [2]*School of Medicine Greenville, University of South Carolina, Greenville, SC, USA*

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Abstract

Prostate cancer (PC) is the second leading cause of death among American men, with most patients receiving androgen deprivation therapy and eventually developing resistance to treatment. The 5-year survival rate from 2015–2020 for men with distant disease was 33%, demonstrating the need for more optimal treatment regimens for patients with distant or metastatic PC. Pharmacogenomic (PGx) testing, a component of precision medicine, focuses on the way a patient's genome affects drug metabolism. Combining PGx testing with current genetic testing provides an innovative and personalized approach to treating PC while both reducing adverse events and optimizing treatment dosages to fit the patient's genetic make-up. This review paper describes how clinicians can use PGx testing in combination with genetic testing for PC patients.

Introduction

According to the American Cancer Society, prostate cancer (PC) is the second leading cause of death among American men, and about 1 in 8 men will be diagnosed with PC in their lifetime (https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html). PC can be divided into four categories. Localized PC is confined to the prostate. It includes a broad spectrum of disease severities, covering indolent diseases not requiring treatment to aggressive diseases requiring intense treatment, typically including the use of androgen deprivation therapy (ADT).[1] ADT targets the hypothalamic-pituitary-gonadal axis in efforts to reduce the level of serum testosterone equivalent to chemical castration (serum testosterone levels of <50 ng/mL).[2,3] Most patients on ADT eventually develop resistance to treatment and are classified as castration-resistant PC. The second and third categories differ based on the presence or absence of metastases. These patients are classified as having either nonmetastatic castration-resistant PC or metastatic castration-resistant PC (mCRPC). Patients may present with metastatic disease, or they may develop metastatic disease without being treated with ADT. These patients fall into the last category, metastatic castration-sensitive PC, and may still be effectively treated with ADT.[1]

The National Cancer Institute Surveillance, Epidemiology, and End Results Program lists the 5-year survival rate of PC patients diagnosed with localized disease as >99%; however, when diagnosed with distant disease, the 5-year survival rate declined to 34.1% (https://seer.cancer.gov/statfacts/html/prost.html). This drastic difference shows the need to further optimize treatments for patients with metastatic PC. Precision medicine considers information regarding a patient's genome, home environment, and general lifestyle choices in addition to clinical knowledge regarding patient disease when creating a personalized treatment plan for patients.[4] Since the completion of the Human Genome Project in 2003, there have been rapid advancements in applying genetic information to the care of oncology patients.[5] The ability to genetically characterize PC has opened the door to use precision medicine to optimize treatment decisions for men with PC based on their genetic profile.[6]

The current literature poorly differentiates between genetics, genomics, pharmacogenetics, and pharmacogenomics. The National Cancer Institute defines genetics as the study of genes with a focus on hereditary traits passed down from parents to offspring (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/genetics) and genomics as the study of how all DNA in a person interacts with itself and the environment (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/genomics). The National Cancer Institute considers the terms pharmacogenetics and pharmacogenomics to be interchangeable, defining them as the

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[*]**Correspondence to:** Joshua Germany, Prisma Health Cancer Institute, 900 W. Faris Rd, 3rd Floor, Greenville, SC 29605, USA. ORCID: https://orcid.org/0009-0009-6287-0945. Tel: +864-455-3600, Fax: +864-455-3618, E-mail: Joshua.germany@prismahealth.org

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Table 1. The United States National Cancer Institute Indications for Prostate Cancer Germline Genetic Testing

Patients who present with prostate cancer and any of the following:
1. A positive family history of prostate cancer
2. ≥1 first degree relative with prostate cancer at age ≤60 years (exclude relatives with clinically localized Grade Group 1 disease)
3. Ashkenazi Jewish ancestry
4. Men with metastatic prostate cancer
5. Patients with a personal history of prostate cancer and intermediate-risk prostate cancer and intraductal/cribriform histology
6. Patients with a personal history of prostate cancer and a personal history of exocrine pancreatic cancer, breast cancer, colorectal, gastric, melanoma, pancreatic cancer, upper tract urothelial cancer, glioblastoma, biliary tract cancer, and small intestinal cancer.

Recommendations are from the National Cancer Institute, Genetics of Prostate Cancer (PDQ®)–Health Professional Version Table 2. Indications for Prostate Cancer Genetic Testing (https://www.cancer.gov/types/prostate/hp/prostate-genetics-pdq#_1842).

study of how a person's genes affect their response to drugs (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pharmacogenetics). Germany and Kueber define pharmacogenomics as a broader term used to describe acquired and inherited variants across the entire genome.[4] UpToDate defines pharmacogenetics as a subcategory of pharmacogenomics with pharmacogenetics focusing primarily on specific DNA polymorphisms or coding variants and their effect on drugs (https://www.uptodate.com/contents/overview-of-pharmacogenomics). This paper will primarily focus on genetics, pharmacogenetics, and pharmacogenomics, using pharmacogenetics and pharmacogenomics interchangeably under the abbreviation (PGx), as reflected throughout the literature.

PGx testing can be performed on healthy body cells (germline testing) to gather information on how a patient will metabolize a drug.[4] Benefits of combining genetic and PGx testing for treating PC patients include the possibility to personalize cancer therapies, optimize prescribed medication and dose administered, and avoid potential adverse events.[4,6] The amount of genetic testing in clinics greatly outweighs PGx testing, with >75% of oncology clinicians ordering somatic next-generation sequencing for their patients and PGx testing lagging far behind. While the reasons for this gap vary from clinic to clinic, some may be due to a general lack of knowledge regarding PGx testing, how and when to order tests, and how to interpret test results.[7] Knowing the advantages and differences between genetic and PGx testing can facilitate the implementation of PGx testing with genetic testing in PC clinics, closing the gap between the two.

In 2019, Weitzel *et al*. published a four-step approach to implementing PGx testing into a primary care setting.[8] The four steps are as follows: patient identification, PGx test ordering, application of PGx test results, and patient education.[8] This paper applies this four-step approach to PC clinics, shows how PGx testing intersects with genetic testing and describes the effects of known variants on current treatments for PC.

Methods

Step 1: patient identification

There is little data in the literature specifically addressing what percentage or population of PC patients should receive PGx testing. Alternatively, there are several guidelines for general genetic testing. UpToDate recommends genetic testing for males with newly diagnosed very low-, low-, or intermediate-risk PC if they have a family history of the disease or intraductal histology, which is enriched for *BRCA1 and BRCA2 gene* mutations (https://www.uptodate.com/contents/molecular-prognostic-tests-for-prostate-cancer). Tuffaha *et al*. published a scoping review in 2023 on the current guidelines for genetic testing in PC.[9] Out of the 23 guidelines and consensus statements reviewed, the most recommended genetic testing for men with metastatic PC. The recommendations, however, varied regarding who to test, testing methods and implementation.[9] The current National Comprehensive Cancer Network guidelines on genetic testing for the risk of developing PC are shown in Table 1 (https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf) Clinicians need to be properly informed of the benefits, risks, and barriers to testing. Genetic testing can provide information for both the patient's risk of developing PC in the future, the severity of PC the patient may develop, and if the patient has any germline mutations that could be present in other blood relatives. UpToDate says that males with germline mutations in *BRCA2* are at increased risk of PC and have more aggressive disease features (https://www.uptodate.com/contents/genetic-risk-factors-for-prostate-cancer). Genetic testing can also provide information on homologous repair defects, which might predict sensitivity to poly(ADP-ribose) polymerase inhibitors, immune checkpoint inhibitors, and other biomarkers recently shown to be integral in PC treatment decisions.[10]

PGx testing can provide information on the way a patient metabolizes certain drugs, leading to improved dosing and a reduction in adverse events.[4,6] Therapies used to treat metastatic PC, such as Taxotere (docetaxel), have been found to cause adverse events, including neutropenia and anemia.[1] PGx test results could show that a patient is a slow metabolizer of docetaxel and that the patient has a reduced clearance time of the drug. Without knowing this information, a patient may be unintentionally overdosed, causing an adverse event. Alternatively, a patient may be a rapid metabolizer of a drug and need a higher dose to have the same effect.

When choosing which patients to test, clinicians also need to be aware of testing barriers, including cost of testing, turnaround time for results, race and ethnicity differences, and ethical considerations. New technological advancements with next-generation sequencing have lowered testing costs, lowered turnaround time, and increased test availability.[4,11] In 2022, Morris *et al*. published a systematic review, finding 77/108 (71%) studies about PGx guided treatment to be either cost-saving or cost-effective.[12] However, the cost of PGx testing and insurance coverage should still be considered per individual case.

The test turnaround time, the time it takes for results once samples are sent, varies from days to weeks.[8] Timing is especially important for clinicians choosing treatment plans for PC patients due to the need for some patients to begin treatment soon after their

initial diagnosis. Clinicians need to choose genetic and PGx tests with shorter turnaround times for patients requiring immediate intervention. For patients not requiring immediate treatment, early testing should still be considered. Testing early after initial diagnosis, regardless of staging, allows access to the data for future use as needed. This reduces the effect turnaround time could have if patients undergo testing only to inform advanced treatment options.[11]

Race and ethnicity are important elements to consider when choosing a patient for PGx testing. Some PC studies in the United States have shown a lack of data in African-American men compared to patients of European and Asian descent.[13] While most data on PC-associated loci show similarities between men of European and men of African descent, some loci in men of European descent have fewer effects, no effects, or even the opposite effect compared to the loci in men of African descent. One study reported that Asian men with mCRPC on docetaxel had higher incidences of hematological complications compared to Western populations. Asian populations have been found to be more prone than other populations to myelosuppression with docetaxel and other taxanes.[14]

There are ethical considerations that need to be addressed with patients before testing. Patients need to be fully informed on the possible implications of PGx testing, including unfavorable test results and violations of privacy. Some patients may not desire to know if they or their children have a variant placing them at a higher risk for developing disease in the future. Other patients may worry about life insurance issues arising from test results.[11] These barriers can slow the implementation of genetic and PGx testing in PC clinics, and clinicians should heavily consider each barrier before testing a patient. Before testing, clinicians must fully address these barriers with patients.

Step 2: understanding the tests

Understanding the process involved with genetic and PGx testing can facilitate patient education. Testing requires collecting DNA samples from patients. DNA information can be collected via various methods, including collecting blood samples, saliva samples, and buccal swabs.[6] Blood samples serve as an excellent source of genetic material and have been successful in detecting both prostate-specific antigens and circulating tumor cells, providing a more detailed view of tumor heterogeneity than conventional biopsy and characterizing differentially expressed miRNAs or miRNA panels involved in tumor progression.[15] Buccal swabs are also able to collect genetic data for germline testing. However, despite being a rapid collection technique, buccal swabs may be unreliable and fail to gather enough material for genetic testing if the patient has eaten or drunk something prior to sample collection.[16] When choosing a PGx test, it is important to ensure that the test will provide information on the actionable genes of interest. Some PC-specific actionable genes as discussed below include *HSD3B1, SLCO2B1, SULT1E1, CYP3A5, CYP17A1, and CYP1B1*.

Nomenclature

Clinicians must understand foundational genetic terminology and information to properly interpret genetic and PGx test results. In the literature, the term "mutation" is now more commonly referred to as a genetic "variant", and "single nucleotide polymorphism (SNP)" is also called a "single nucleotide variant (SNV)". Genetic variants and SNV nomenclature can be difficult to interpret in literature, and the nomenclature can be broken down into various components.[17] The first component describes the location of the gene on the chromosome. The chromosome containing the gene of interest is numbered 1–22 or named "X" or "Y" if it is a sex chromosome. Each chromosome has two arms, the short arm and the long arm, referred to as "p" and "q", respectively. The targeted gene is given a number based on how many positions away from the centromere it is located. Variants in the *BRCA1* gene have been associated with PC.[12] The full name used to describe the location of *BRCA1* is 17q12.1, meaning that *BRCA1* can be found on chromosome 17 on the long (q) arm at position 12.1.[17]

The next component describes variants in genes. While there is currently no standard for naming genetic variants found across the literature, the Human Genome Variation Society provides guidelines and recommendations that help understand the names found in the literature. It is recommended to use a letter prefix to indicate the type of sequence used. Common letter prefixes are "c" for a coding DNA reference, "g" for a linear genomic reference, and "p" for a protein reference sequence. Amino acid changes are typically described using three-letter abbreviations, and nucleotide changes are typically described using a single-letter abbreviation. Specific abbreviations describe the variant type, such as ">" to describe a substitution and "del" to describe a deletion. For example, the variant description "g.123. A>G" indicates a substitution of the nucleotide Adenosine to Guanine at position "123" in the reference sequence "g".[18] Another example is *EGFR* L858R c.2573T>G (p.Leu858Arg). Nucleotide 2573 in the *EGFR* gene has undergone a substitution from thymine to glutamine, which changes the amino acid sequence from leucine to arginine at codon 858.[17]

Another common way to label a SNP is using the "rs" number (also called the "rsID and RefSNP") found in the Single Nucleotide Polymorphism Database (dbSNP). Each SNP has a nonredundant designated rs number given by the dbSNP in efforts to further standardize nomenclature when discussing variants and SNPs.[19]

Step 3: application of the pharmacogenomic test results

PGx genes and variants in prostate cancer

PGx-related genes encode proteins involved in drug metabolism and can be used to predict how a patient with PC will respond to systemic therapy. Table 2 summarizes some of these genes and their corresponding germline variants.[20–25]

HSD3B1

The *HSD3B1* gene (OMIM 109715) encodes 3β-hydroxysteroid dehydrogenase-1 (3βHSD1), an enzyme responsible for catalyzing adrenal androgen precursors into dihydrotestosterone (DHT). 3βHSD1 can become resistant to ubiquitination and degradation if there is an amino acid change (p.367T>N) in addition to a single nucleotide variant (SNV) (rs1047303, NM 000862.3: c.1100 C>A) in exon 4 of the *HSD3B1* gene. This resistance to degradation results in an increased concentration of the enzyme and an increase in DHT production, which has been linked to the development of CRPC.[20] The variant 3βHSD1 enzyme with a *HSD3B1* (1245C) allele and 367T variant has been associated with higher levels of protein accumulation, which results in increased levels of DHT.[21]

A 2016 study by Hearn *et al*. compared the association between inheriting the *HSD3B1* (1245C) allele and progression-free survival (PFS), distant metastasis-free survival, and overall survival (OS) of patients with PC.[26] PFS was significantly associated with *HSD3B1* and decreased as the number of inherited *HSD3B1* alleles increased, with a median of 6.6 years in homozygous wild-type men (95% confidence interval (CI), 3.8 to not reached), 4.1 years in heterozygotes (95% CI, 3.0 to 5.5), and 2.5 years in homozygous variant men (95% CI, 0.7 to not reached); $p = 0.011$. Distant

Table 2. Genes and their corresponding variants with their associated PGx related effects on therapy

PGx gene	Germline variant	Effect on therapy	Reference
HSD3B1	rs1047303 and (1245C) 367T	Increased DHT production	20,21
SLCO2B1	rs12422149	Resistance to ADT	20
SULT1E1	rs3775777, rs4149534, rs10019305, rs3775770, rs4149527, and rs3775768	Increased time to treatment failure and increased sensitivity to abiraterone	22
CYP17A1	rs2486758	Lowered PFS and resistance to abiraterone acetate	20,23
CYP3A4	rs2740574	Enhanced Docetaxel clearance	24
CYP3A5	rs776746	Enhanced Docetaxel clearance	24
VAC14	rs875858	Predictor of docetaxel-induced neuropathy	25

ADT, androgen deprivation therapy; DHT, dihydrotestosterone; PFS, progression free survival; PGx, pharmacogenomic.

metastasis-free survival was also found to decrease as the number of variant alleles inherited increased, with a median of 9.1 years in homozygous wild-type men (95% CI, 7.4 to not reached), 6.8 years in heterozygotes (95% CI, 4.3 to 7.4), and 3.6 years in homozygous variant men (95% CI, 1.0 to 7.3) ($p = 0.014$). Additionally, OS decreased according to the number of variant *HSD3B1* alleles inherited, with a median of 9.7 years (95% CI 6.7 to 12.1) in homozygous wild-type men, 6.8 years (95% CI 5.2 to 8.0) in heterozygotes, and 4.6 years (95% CI 1.6 to 7.5) in homozygous variant men ($p = 0.0042$).

SLCO2B1

The solute carrier organic anion transporter family member 2B1 (*SLCO2B1*) transports testosterone, dehydroepiandrosterone sulfate, and drugs like abiraterone. Several studies have found correlations with SNVs in the *SLCO2B1* gene and resistance to ADT targeting the androgen axis. For example, the rs12422149 variant has been associated with increased sensitivity to abiraterone.[20]

Terakawa *et al*. studied the association between the expression level of *SLCO2B1* and PC recurrence after radical prostatectomy.[27] There was a significantly higher level of *SLCO2B1* expression in multiple tested categories, including the Gleason score (GS $\leq$ 6 vs GS = 7; $p = 0.047$, GS = 7 vs GS $\geq$ 8; $p = 0.002$), pathological primary tumor (pT2 vs pT3/4; $p < 0.001$), and surgical margin status (positive vs negative; $p = 0.013$). It was concluded that PC patients with a high level of *SLCO2B1* expression demonstrated worse disease-free survival than PC patients with lower levels of *SLCO2B1* expression.

SULT1E1

Estrogen is important for the pathogenesis and progression of PC. One member of the cytosolic sulfotransferase superfamily, estrogen sulfotransferase (*SULT1E1*), catalyzes reactions involving the sulfonation of estrogenic compounds. Agarwal *et al*. evaluated 832 single-nucleotide polymorphisms from 61 genes involved in the androgen metabolic pathway.[22] The purpose of this study was to search for any trends between the SNPs and time to treatment failure in men with mCRPC receiving abiraterone acetate therapy. *SULT1E1* was found to have six single nucleotide polymorphisms (rs3775777, rs4149534, rs10019305, rs3775770, rs4149527, and rs3775768) associated with time to treatment failure and therefore could serve as potential biomarkers for patients receiving abiraterone acetate therapy.

Cytochrome P450

Cytochrome P450 (CYP) is a superfamily of membrane proteins that catalyze phase 1 oxidation or demethylation reactions in drug metabolism and other substances. *CYP3A5* promotes luminal cell growth and metabolizes intraprostatic androgens. *CYP3A5* is expressed primarily in normal prostate cells but is expressed at lower levels in prostate tumor cells. This suggests that polymorphisms in *CYP3A5* can increase the risk of PC.[28] CYP 17α-hydroxylase/17,20-lyase (*CYP17A1*) is expressed in roughly half of prostate cancers, and plays a significant role in the synthesis of androgens in cancer cells.[29] Abiraterone in combination with prednisone is used to treat both mCRPC and metastatic castration-sensitive PC.[30] Abiraterone is a *CYP17A1* inhibitor; however, variants found in the CYP17A1 gene have been associated with resistance to abiraterone.[20]

Crucitta *et al*. investigated the relationship between the SNV *CYP17A1* rs2486758 (c.-362T>C) and the use of abiraterone to treat patients with mCRPC.[31] Sixty patients with mCRPC treated with abiraterone underwent PGx testing using DNA extracted from blood samples. Patients with the SNV *CYP17A1* rs2486758 (c.-362T>C) demonstrated a shorter median PFS and prostate-specific antigen-PFS (PSA-PFS) compared to patients carrying the TT genotype. This finding suggested an association between the SNV *CYP17A1* rs2486758 (c.-362T>C) and poorer clinical outcomes in patients with mCRPC receiving abiraterone therapy.[23]

Step 4: patient education

After analyzing test results and using results to inform future treatment, clinicians must be able to communicate the results and decisions to patients.[8] Patient knowledge and understanding of test results allow them to make more informed decisions on their health.[4] As with other lab and test results, clinicians must communicate the significance of the test results to the patients, as this understanding can increase patient confidence in their treatment plan.[8] For example, if PGx testing results in a dose modification of an ongoing treatment, the patient might feel more comfortable with the change if they understand the dosing rationale.

Patient health literacy needs to be considered when discussing results. PGx testing can yield large volumes of information, with an average of 14 pages outlining multigene panel results. These lengthy reports can be confusing to both clinicians and patients. When discussing with patients, it is important for clinicians to focus on the clinically actionable results, so patients do not feel overwhelmed or lost. Printed or electronic documentation summarizing the testing and results could potentially facilitate communicating results with patients. These summaries should be concise, simple, and easy to interpret.[8] Additionally, clinicians need to note genetic and PGx information in patient charts for other medical providers to use.[4]

Table 3. United States of America Food and Drug Administration (US FDA) approved drugs used to treat prostate cancer, the use in literature, and the corresponding actionable biomarkers/genes of interest

Drug name	Uses and indications in literature	Biomarker/gene	Country	Reference
Atezolizumab*	Treat mCRPC patients in a clinical trial (2021)	*BRAF, ALK, EGFR, CD274 (PD-L1)*	United States of America	32
Avelumab*	Treat mCRPC patients in a clinical trial (2021)	*CD274 (PD-L1)*	United States of America	33
Docetaxel with prednisone	mCRPC (2023)	*ESR, PGR* (Hormone Receptor)	United States of America	US FDA and National Cancer Institute (https://www.cancer.gov/about-cancer/treatment/drugs/prostate)
Durvalumab* with Olaparib	Treat mCRPC patients in a clinical trial (2018)	*ALK, EGFR, CD274 (PD-L1)*	United States of America	32
Flutamide and Goserelin Acetate	Locally confined and advanced PC (2023)	*G6PD* (Flutamide) and *ESR, PGR* (Goserelin Acetate)	United States of America	US FDA and National Cancer Institute
Ipilimumab*	mCRPC that has progressed post docetaxel chemotherapy (2014)	*HLA-A, ALK, EGFR, CD274 (PD-L1)*	United States of America	22,32
Lutetium Lu 177 Vipivotide Tetraxetan	prostate-specific membrane antigen (PSMA)-positive mCRPC (2022)	*FOLH1 (PSMA)*	United States of America	US FDA and National Cancer Institute
Nivolumab* plus Ipilimumab	Treat mCRPC patients in a clinical trial (2019)	*BRAF, CD274 (PD-L1), ALK, EGFR, ERBB2 (HER2)*	United States of America	32,33
Olaparib	Deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone (2023)	*BRCA, ERBB2 (HER2), ESR, PGR* (Hormone Receptor), *PPP2R2A*	United States of America	US FDA and National Cancer Institute
Pembrolizumab*	Treat mCRPC patients in a clinical trial (2020)	*BRAF, CD274 (PD-L1), ALK, EGFR, ERBB2 (HER2)*	United States of America	32,33
Talazoparib Tosylate	*HRR* Gene-mutated mCRPC (2023)	*BRCA, ERBB2 (HER2)*	United States of America	US FDA and National Cancer Institute

*Immunotherapy drugs. mCRPC, metastatic castration-resistant prostate cancer; PC, prostate cancer. Drug names were found on the US FDA Table of Pharmacogenomic Biomarkers in Drug Labeling (https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling).

Clinicians should also be able to supply the patient with external resources to learn more about the test results. Several online websites and databases can educate both clinicians and patients on genetic and PGx testing. The National Cancer Institute has pages designated for the genetics of cancer as well as a dictionary of genetic terms (https://www.cancer.gov/publications/dictionaries/cancer-terms). The U.S. Food and Drug Administration (FDA) also provides an updated list of biomarkers and genes related to PC therapies. The FDA-approved medications for PC are listed in Table 3.[22,32,33] Another resource for clinicians to utilize is genetic counselors. Genetic counselors are trained to educate patients on personal and family concerns regarding a hereditary trait found in PGx testing, cancer surveillance and prevention, additional testing for the patient and their high-risk family members, and more.[34] A genetic counselor may be more equipped to discuss PGx test results and future applications. Clinicians may consider referral to a genetic counselor when patient test results have clinical actionability.

Applications in clinic/current treatment

Docetaxel

Since its FDA approval in 2004, docetaxel (Taxotere) has been used as a chemotherapy treatment for mCRPC. Docetaxel is metabolized by *CYP3A4* and *CYP3A5* and is transported by the influx transporter *SLCO1B3*. The SNVs *CYP3A4* (rs2740574) or *CYP3A5* (rs776746) have been correlated with enhanced docetaxel clearance, and the docetaxel dose for these patients should be adjusted accordingly. Variants in *SLCO1B3* (rs11045585) have been associated with increased leukopenia/neutropenia in patients receiving docetaxel treatment.[24] Therefore, knowing a patient has the *SLCO1B3* (rs11045585) variant before starting docetaxel treatment could allow for dose modification to prevent or reduce leukopenia/neutropenia.

Variants in *CYP1B1* have also been associated with changes in treatment response of docetaxel-based combination therapies. Patients with one copy of the *CYP1B1*1* ancestral allele had a

better prognosis than patients with two copies of the *CYP1B1*3* (rs1056836) variant when treated with docetaxel combined with estramustin, thalidomide, or prednisone. The *CYP1B1* 4326GG polymorphism has been linked to docetaxel clinical response, possibly acting as a new biomarker for mCRPC treatment.[24]

Hertz *et al*. studied SNVs associated with docetaxel-induced neuropathy, finding that a *VAC14* (rs875858) SNV could serve as a predictor of docetaxel-induced neuropathy.[25] Patil *et al*. studied the pharmacokinetic variability of docetaxel based on genetic variations.[35] The present study analyzed the polymorphic loci on the absorption, distribution, metabolism, and elimination genes from blood samples of 50 patients undergoing docetaxel treatment for head and neck cancer or PC. The target variants included *CYP3A4* (A392G), *CYP3A5* (A6986G), *SLCO1B1* (G1187A) and *ABCB1* (C1236T, G2677T, C3435T). The authors concluded that none of the genetic variants explained the interindividual variability in metabolizing docetaxel, and there was no basis for individual dosing based on variants in these genes.

Immunotherapy

Immunotherapy is another type of PC treatment. Some PC immunotherapies are ipilimumab, nivolumab, tremelimumab, pembrolizumab, and durvalumab.[32,35] The genes associated with a greater likelihood of response to these drugs can be found in Table 3. A low percentage of mCRPC patients are responsive to immunotherapy; for example, only around 5–17% of mCRPC patients are estimated to respond to pembrolizumab monotherapy. Low responsiveness is likely due to low infiltration of T cells, low tumor mutation burden, low PD-L1 expression, and an immunosuppressive tumor microenvironment.[33]

Genetic testing could help avoid and overcome immunotherapy resistance by targeting specific PC genetic aberrations. Aberrant gene-due resistance to therapy includes overexpression of human epidermal growth receptor type 2 of tyrosine kinase (*HER2*), phosphatidyl inositol 3-kinase-Akt/mammalian target of rapamycin pathway, suppression of apoptosis machinery by overexpression of antiapoptotic *Bcl-2* gene, and suppression of proteolytic cleavage of poly(ADP-ribose) polymerase-1 (PARP-1) preventing apoptosis-proper DNA fragmentation.[33] Further research directly linking PGx testing with immunotherapy for PC should be conducted to allow clinicians to make better decisions when applying PGx testing with immunotherapy to patient care.

Radiotheranostics

Radiotheranostic therapies use radiation-emitting molecules to damage target cell DNA and trigger cell death. Radiotheranostic molecules are typically composed of a radionuclide, a chelator, and a ligand/probe that binds to target cells.[31] In PC, two molecular targets for radiotheranostic therapies are prostate-specific membrane antigen (PSMA) and gastrin releasing peptide receptor. PSMA-11, PSMA-I&T, PSMA-617, and ^{68}Ga-RM2 are examples of radiotheranostic therapies in which PSMA-11, PSMA-I&T, and PSMA-617 inhibit PSMA and ^{68}Ga-RM2 targets gastrin releasing peptide receptor.

Applying PGx testing to radiotheranostic therapy has the potential to further personalize treatment options by increasing the efficiency of therapy and reducing toxicity. Germline mutations in the *CHEK2* gene have been associated with the response to lutetium-177-PSMA-617. Somatic mutations in *TP53*, *CHEK2*, and *ATM* were found to be associated with a lack of response to treatment with Actinium-225-PSMA therapy.[36]

Privé *et al*. investigated variations in DNA damage repair genes and the corresponding tumor response to PSMA-RLT.[37] The study found no association between the DNA damage repair genes and responsiveness to PSMA-RLT. Van der Doelen *et al*. studied the quality of life of 13 patients with mCRPC receiving actinium-225-PSMA radiotheranostic therapy, searching for possible biomarkers present in tissue biopsies.[38] The group concluded that patients with DNA damage repair alterations tended to have longer overall survival.

Future directions

PGx testing in cancer patients is an emerging field of research. While the total amount of literature on PGx testing in PC patients is relatively low, the results of these studies show the significant advantages of PGx testing. More research is needed, and additional data needs to be collected to better standardize the recommendations for implementing genetic and PGx testing in PC clinics. These projects should focus on identifying which PC patient populations should receive PGx testing, emphasizing the stage of disease and the setting for combining PGx testing with genetic testing. There is a lack of testing among African Americans with PC in the United States, providing a knowledge gap for future research. Future studies should also address ways to minimize the barriers to genetic and PGx testing. This review paper is limited in international generalizability as it primarily focuses on studies and recommendations in the United States of America. As additional research on this topic is published, a systematic review should be conducted to enhance clinicians' understanding of genetic and PGx testing in PC clinics and to inform future recommendations.

Conclusions

In conclusion, genetic and PGx testing is a growing field of research, particularly in patients with PC. The first step of testing begins with selecting a patient. While some guidelines exist for genetic testing, there are few data regarding which patient populations with PC benefit the most from PGx testing. The treating clinician should make a well-informed decision for their patient considering the possible application of test results and the barriers to testing. To interpret test results correctly, clinicians must stay up to date with current trends. Numerous PGx-related genes, such as *HSD3B1, SLCO2B1, SULT1E1, CYP3A5, CYP17A1*, and *CYP1B1*, have been associated with PC, and variants in these genes can affect patient treatment. Genetic and PGx testing can be used to determine the expression of these genes and their potential effect on treatment, allowing clinicians to personalize the treatment based on the patient's testing profile. Clinicians should consider patient health literacy when communicating test results and consider referral to a genetic counselor as appropriate.

PGx testing can be applied to various treatment options for PC, including chemotherapy, immunotherapy, and radiotheranostics. Genetic and PGx testing are key aspects of precision medicine. It is an up-and-coming field of study and is already being used in some PC clinics. As more research is released, clinicians will be able to better combine genetic and PGx testing in their clinics and further improve overall patient care.

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Conflict of interest

The authors have no conflict of interests to declare.

Author contributions

JG designed the paper and wrote the manuscript. JM critically reviewed and completed the manuscript. All authors made significant contributions to this study and approved the final manuscript.

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