Implementing pharmacogenomic and genetic testing into prostate cancer clinics

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Prostate cancer (PC) is a significant health concern, being the second leading cause of death among American men. The standard treatment for advanced PC often involves androgen deprivation therapy (ADT), yet many patients eventually develop resistance, resulting in castration-resistant prostate cancer (CRPC).

The prognosis for metastatic PC remains poor, with a 5-year survival rate of only 33% from 2015-2020. This highlights the critical need for improved treatment strategies. Pharmacogenomic (PGx) testing, which examines how a patient's genetic makeup influences drug metabolism, represents a promising approach to tailor treatments more effectively and minimize adverse effects.

Precision medicine in oncology has advanced significantly since the completion of the Human Genome Project in 2003. Genetic testing has become a standard practice, with over 75% of oncologists utilizing next-generation sequencing to guide treatment.

However, PGx testing, which can optimize drug dosages and reduce adverse events by understanding individual genetic variations, is less frequently employed. This review focuses on the integration of PGx testing into the current genetic testing framework in prostate cancer care.

Pharmacogenomic testing, an integral component of precision medicine, is revolutionizing the approach to treating prostate cancer. By focusing on how a patient's genetic makeup influences drug metabolism, PGx testing allows for the personalization of treatment plans.

This personalized approach aims to minimize adverse events and

optimize drug dosages, ensuring treatments are tailored to the individual's genetic profile. Combining PGx testing with existing genetic testing techniques offers an innovative pathway for managing prostate cancer more effectively.

Clinicians can utilize PGx testing alongside genetic testing to enhance treatment strategies for prostate cancer patients. This approach involves understanding various PGx-related genes that encode proteins pivotal in drug metabolism. For instance, the HSD3B1 gene encodes 3β-hydroxysteroid dehydrogenase-1 (3βHSD1), an enzyme crucial in adrenal androgen conversion. Variants in HSD3B1, such as rs1047303, have been linked to increased dihydrotestosterone (DHT) production and subsequent resistance to ADT .

Similarly, genes like SLCO2B1, SULT1E1, CYP17A1, CYP3A4, and CYP3A5 have significant implications in therapy resistance and drug metabolism. For example, variants in CYP3A4 (rs2740574) and CYP3A5 (rs776746) are associated with enhanced clearance of docetaxel, a chemotherapy drug used in treating metastatic castration-resistant prostate cancer (mCRPC). Adjusting docetaxel dosages based on these genetic variants can potentially improve treatment outcomes and reduce toxicity .

Applying PGx test results in clinical practice involves a multi-step process. First, clinicians need to analyze the test results and integrate them into the treatment planning. This includes modifying dosages or selecting alternative therapies based on the patient's genetic profile. For example, patients with the HSD3B1 variant may require alternative strategies due to their predisposition to higher DHT levels and quicker progression to CRPC.

The incorporation of PGx testing alongside traditional genetic testing offers several benefits:

- Personalized treatment: Tailoring therapies to the patient's genetic profile can enhance treatment efficacy and reduce the likelihood of adverse reactions. For instance, PGx testing can identify patients who are slow or rapid metabolizers of specific drugs, allowing for dosage adjustments.
- Optimized drug dosing: Understanding genetic variations that affect drug metabolism can help determine the most effective dose for each patient, potentially improving outcomes and reducing toxicity.
- Reduction of adverse events: By predicting how a patient will respond to a particular drug, PGx testing can help avoid harmful side effects, which is especially crucial for drugs like docetaxel used in metastatic PC.

Despite the potential benefits, several challenges hinder the widespread adoption of PGx testing:

- Lack of awareness and education: Many clinicians are not fully informed about the benefits and procedures of PGx testing, which limits its use.
- Cost and insurance coverage: Although next-generation sequencing has become more affordable, PGx testing can still be expensive, and insurance coverage is not always guaranteed.
- Turnaround time: The time required to obtain test results can vary, which may delay treatment decisions for patients needing immediate care.
- Ethical and privacy concerns: Patients may have concerns about the implications of genetic testing, including potential discrimination and the psychological impact of knowing their genetic risks.

To address these challenges, researchers proposed a four-step approach for integrating PGx testing into clinical practice:

- Patient identification: Identify patients who would benefit most from PGx testing, such as those with a family history of PC or those with advanced stages of the disease.
- Test ordering: Educate clinicians on when and how to order PGx tests.
- Application of results: Use test results to tailor treatment plans, including drug selection and dosing.
- Patient education: Inform patients about the benefits, risks, and implications of PGx testing to facilitate informed decision-making.

Integrating PGx testing into prostate cancer clinics represents a significant advancement in precision medicine. By combining PGx testing with existing genetic tests, clinicians can offer more personalized and effective treatments, improving outcomes for patients with advanced prostate cancer.

Addressing the barriers to implementation through education, cost management, and ethical considerations is crucial for the successful adoption of this innovative approach in clinical practice.

The research is published in the journal *Exploratory Research and Hypothesis in Medicine*.

More information: Joshua M. Germany et al, Implementing Pharmacogenomic and Genetic Testing into Prostate Cancer Clinics: A Literature Review of Current Trends and Applications, *Exploratory Research and Hypothesis in Medicine* (2024). DOI: 10.14218/ERHM.2023.00087