Uncovering Pharmacogenomic Variability in Prostate cancer Using Big Data

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Background: Pharmacogenomics (PGx) improves clinical outcomes by enabling personalized medication, particularly for cancer patients. However, the prevalence of PGx variants and their impact on medical prescriptions have not been thoroughly investigated.

Methodology: All analyses were conducted using the *All of Us* research platform. Prostate cancer cases were identified from EHR data using SNOMED and ICD codes. A cohort of 3,633 patients with clinical-grade whole-genome sequencing (WGS) was selected, including 1,437 samples with structural variant data. PGx genotyping was performed on 15 genes, with CYP2D6 analyzed separately using a custom pipeline. Star allele types were assigned using Hail matrix data, and copy number variation was incorporated from structural variant VCFs. Pharmacogenomic insights were assessed by comparing metabolizer status with prescribed medications.

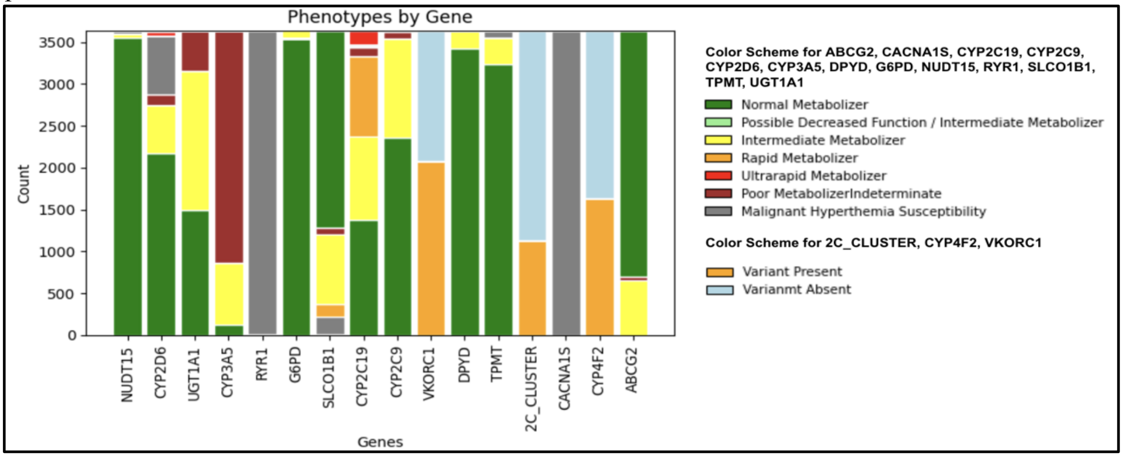

Figure 1. Identified PGx gene phenotype frequency

Results: A total of 3,633 prostate cancer patients with WGS and EHR data were analyzed, including 1,437 with structural variant data.

Pharmacogenomic (PGx) genotyping identified 98.16% of phenotypes (Figure 1), with CYP2D6 having the highest rate of indeterminate results (80.35% identified). All patients carried at least one actionable phenotype, and 98.9% had actionable phenotypes for at least two genes, with a mean of 4.7 per patient. The most common actionable phenotypes were in CYP3A5 (96.6%), CYP2C19 (61.4%), and UGT1A1 (58.9%), with significant ancestry differences observed.

A total of 1,688,922 medication exposures were recorded, including 223,875 CPIC A-level drug exposures. Most patients (88%) were prescribed at least one CPIC A-level drug, with a 2.24-fold increase in prescriptions post-diagnosis (P = 7e-152). The most common actionable CPIC A-level drugs were omeprazole, pantoprazole, and atorvastatin (Figure 2). Notably, 61.1% of patients had an actionable phenotype for a CPIC A-level drug they were prescribed. The proportion of actionable drug prescriptions increased significantly after diagnosis (P = 2e-111).

Conclusions:

We found a prevalence of actionable PGx variants among prostate cancer patients. Frequent exposure to corresponding medications underscores the potential benefits of incorporating pharmacogenomic guidelines into clinical care.

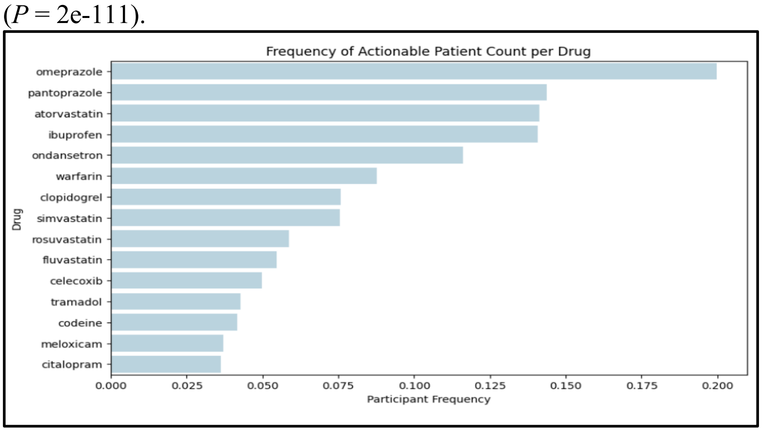

Figure 2. Frequency of actionable medication exposure in the patient cohort