Pharmacogenomic Actionability in 15,000 Patients with Next-Generation-Sequencing-Enabled Copy Number Variation and Novel Haplotype Detection

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INTRODUCTION

Less than 40% of patients with major depressive disorder (MDD) achieve clinical remission after first-line antidepressant treatment.

Pharmacogenomic (PGx) testing may improve drug selection and/or dosing in patients with genetic variation(s) altering pharmacokinetics through CYP2D6 and CYP2C19.

Primary objective: To evaluate the prevalence of PGx and novel actionability in a large, real-world cohort of patients receiving psychiatric care who were referred for clinical PGx testing via the Tempus nP assay.

METHODS

A subset of patients who underwent Tempus nP PGx testing between April 2020 and November 2022 as part of their psychiatric care were selected. Tempus nP combines whole-exome sequencing (WES) and MassArray in a College of American Pathologists / Clinical Laboratory Improvement Amendments-accredited laboratory.

CYP2D6 and CYP2C19 phenotypes were defined as "actionable" based on CPIC guidelines and the FDA Table of Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations (Section 1). Two levels of actionability were defined: "Potentially actionable" if patients had actionable genetic results (see Table 2) and "Clinically actionable" when associated medications were reported.

Continental ancestry proportions were predicted from WES data using a supervised version of the ADMIXTURE algorithm. The FDA Table of Substrates, Inhibitors, and Inducers was used to estimate CYP2D6 phenoconversion in patients with medication data. We imputed a novel PGx haplotype called CYP2C using the bioinformatics software GLIMPSE.

Lastly, we prioritized and combined actionability from all sources for patients with medication and WES data, allowing computation of differences in patients with actionable findings depending on assay features.

RESULTS

Table 1. Cohort characteristics (N=15,000)

Age, median (range)	30 (0.5-98)
Gender, n (%)	
Male	5,296 (35%)
Female	9,493 (63%)
n/a	211 (2%)
Diagnosis, n (%)	
MDD	6,713 (56%)
GAD	5,747 (48%)
ADD	2,901 (24%)
BPD	1,237 (10%)
PTSD	1,110 (9%)
SCZ	80 (1%)

In 15,000 patients undergoing clinical PGx testing, 63% were female, the median age was 29, and the most common diagnoses were depression, anxiety, and attention deficit hyperactivity disorder.

Table 2. CYP2C19/CYP2D6 Phenotypes and potential actionability

Phenotype	CYP2C19, n (%)	CYP2D6, n (%)
Poor	422 (3%)	876 (6%)
Intermediate	4,028 (27%)	5,887 (39%)
Normal	6,051 (40%)	7,826 (52%)
Rapid	3,601 (24%)	N/A
Ultrarapid	997 (7%)	510 (3%)
Actionability		
Potentially*	4,988 (33%)	7,230 (48%)

*Potentially actionable CYP2C19 phenotypes include poor, rapid, and ultrarapid. Potentially actionable CYP2D6 phenotypes include poor, intermediate, and ultrarapid.

Sixty-five percent of patients had actionable phenotypes for CYP2D6 and/or CYP2C19.

Figure 1. Potential actionability by race/ethnicity and gene

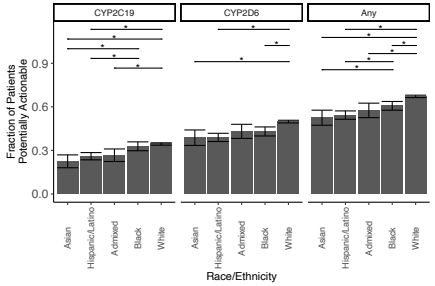

Figure 1. Proportion tests between pairs of ancestries are displayed as horizontal lines. *indicates statistical significance.

Figure 2. Clinical actionability for medications attempted and considered

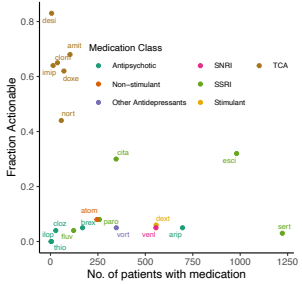

Figure 2. Each point represents a psychiatric medication with PGx prescribing guidance. The x-axis represents how many patients had the medication, and the y-axis shows how frequently those patients had clinically actionable PGx results.

Table 3. Combined actionability attributable to established PGx guidelines, the emerging CYP2C haplotype, and phenoconversion

Initial Actionability	No. of Patients	% of Patients	% of Actionability Considered NGS Dependent
PGx	2732	66	2
CYP2C	402	10	100
Phenoconversion	464	11	1
None	516	13	1
Any	3598	87	11

Incorporating emerging evidence from the novel CYP2C-TG haplotype resulted in an actionable phenotype for an additional 10% of patients. Finally, a clinician's assessment of the medication list for CYP2D6 inhibitors identified an additional 11% of patients with an actionable phenotype.

CONCLUSIONS

Evaluation of a large, real-world patient population receiving PGx testing identified a high proportion of patients with potential actionability for medication prescribing decisions. While this analysis focused on two genes (*CYP2D6* and *CYP2C19*), other emerging genes may also play a role and further increase potential actionability of PGx testing.

This study underscores the potential value of CNV allele assignment in *CYP2D6* genotype/phenotype calling and detection of novel haplotypes in *CYP2C*. When accounting for these variations, as well as phenoconversion, the majority of patients displayed some level of actionability.

This information is critical for clinicians, laboratories, and researchers to consider when applying PGx in psychiatry care.

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