

Potential Clinical Impact of Testing for Higher Threshold of *CYP2D6* Copy Number Variation

Lauren Marcath, PharmD¹, Elizabeth Fieg, MS, CGC¹, Robert Rigobello, MS, CGC¹, Jason Chibuk, MS, CGC¹, Yue Zhou, PhD¹, Yue Wang, PhD, FACMG^{1,2}

1. Baylor Genetics, Houston, TX, USA

2. Department of Molecular & Human Genetics, Baylor College of Medicine, Houston, TX, USA

Introduction

- CYP2D6* is one of the most clinically important pharmacogenes, but also one of the most polymorphic.
 - CYP2D6* can have copy number variation (CNV), which can be impactful to function and predicted phenotype.¹
- Association for Molecular Pathology joint consensus recommendation includes guidance for testing *CYP2D6* CNVs but does not specify the number of copies to test for.²
- Purpose of this analysis was to determine how often distinguishing three versus four *CYP2D6* copies would be clinically impactful.

Methods

- Retrospective review of consecutive clinical PGx tests for *CYP2D6* results.
- Genomic DNA was analyzed using next-generation sequencing (NGS) with the following alleles tested: *1, *2, *3, *4, *4.013, *5, *6, *7, *8, *9, *10, *12, *13, *14, *15, *17, *21, *29, *31, *34, *36, *39, *40, *41, *42, *49, *53, *56, *59, *68, *69, *83, *109, *114, *119.
- CYP2D6* CNV at 5'UTR, intron 2, exon 9 were assessed through quantitative PCR where up to 4 copies could be detected.
- If four copies were detected at any tested CNV loci, the case was reviewed to determine if the fourth copy was clinically impactful (defined as having a change in *CYP2D6* predicted CPIC-defined phenotype categorization³).
 - CPIC guidance was reviewed to determine which medications would have differing recommendations with a change in predicted phenotype categorization.⁴
- Descriptive statistics were calculated.

Results

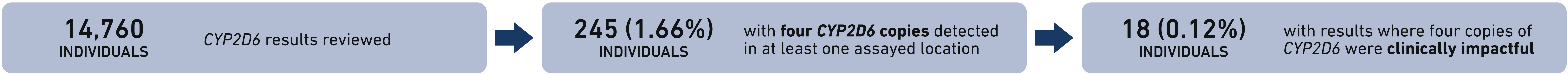


Table 1. *CYP2D6* Diplotype and Activity Score (AS) Results

Observed result with 4 copies vs. potential result if capped at 3 copies.

Results With 4 Copies		If Limited to 3 Copies
Normal Metabolizer		Intermediate Metabolizer
*17/*41x3 (AS: 1.25)	➡	*17/*41x2 (AS: 1)
*1x2/*4.013+*4 (AS: 2)	➡	*1/*4.013+*4 (AS: 1)
*2x2/*4.013+*4 (AS: 2)	➡	*2/*4.013+*4 (AS: 1)
*2x2/*4x2 (AS: 2)	➡	*2/*4x2 (AS: 1)
*1x2/*68+*4 (AS: 2)	➡	*1/*68+*4 (AS: 1)

Ultra-Rapid Metabolizer		Normal Metabolizer
*1x3/*4 (AS: 3)	➡	*1x2/*4 (AS: 2)
*1x3/*6 (AS: 3)	➡	*1x2/*6 (AS: 2)
*2x3/*4 (AS: 3)	➡	*2x2/*4 (AS: 2)
*1x3/*41 (AS: 3)	➡	*1x2/*41 (AS: 2.25)
*2x3/*41 (AS: 3)	➡	*2x2/*41 (AS: 2.25)

Table 2. Medications with Differing CPIC Recommendations Based Upon Phenotype Change⁴

Observed result with 4 copies vs. potential result if capped at 3 copies.

Normal Metabolizer Results with 4 Copies	➡	Intermediate Metabolizer If Limited to 3 Copies	 ONCOLOGY	<u>Tamoxifen</u> (standard dosing → consider alternative)
			 PAIN	<u>Codeine</u> (standard dosing → if no response, use non-tramadol opioid), <u>hydrocodone</u> (standard dosing → if no response, use non-codeine and non-tramadol opioid), <u>tramadol</u> (standard dosing → if no response, use non-codeine opioid)
			 PSYCHIATRY	<u>Tricyclic antidepressants</u> (standard dosing → 25% dosage reduction), <u>paroxetine</u> (standard dosing → lower starting dose and slower titration)

Ultra-Rapid Metabolizer Results with 4 Copies	➡	Normal Metabolizer If Limited to 3 Copies	 GI	<u>Ondansetron</u> (select alternative → standard dosing), <u>tropisetron</u> (select alternative → standard dosing)
			 PAIN	<u>Codeine</u> (avoid use → standard dosing), <u>tramadol</u> (avoid use → standard dosing)
			 PSYCHIATRY	<u>Paroxetine</u> (select alternative → standard dosing), <u>tricyclic antidepressants</u> (avoid use → standard dosing), <u>vortioxetine</u> (selective alternative → standard dosing)

Conclusions

- In a large cohort of individuals with *CYP2D6* results, 1.66% had four *CYP2D6* copies detected in at least one assayed location and a subset of those individuals had results where testing four copies was clinically impactful.
 - Predicted phenotype reclassification from ultra-rapid (results with 4 copies) to normal metabolizer (if reporting limited to 3 copies) could result in medication use that would be recommended to avoid.
 - Similarly, reclassification of normal (results with 4 copies) to intermediate metabolizer (if reporting limited to 3 copies) could result in medication use that would otherwise be recommended to avoid or initiated at a lower dosage.
- Laboratories should assess for four *CYP2D6* copies as this may affect predicted phenotypes and be clinically impactful for a small number of cases.

References:

- Nofziger C, Turner AJ, Sangkuhl K, et al. PharmVar GeneFocus: *CYP2D6*. Clin Pharmacol Ther. 2020;107(1):154-170. doi:10.1002/cpt.1643
- Pratt VM, Cavallari LH, Del Tredici AL, et al. Recommendations for Clinical *CYP2D6* Genotyping Allele Selection: A Joint Consensus Recommendation of the Association for Molecular Pathology, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and the European Society for Pharmacogenomics and Personalized Therapy. J Mol Diagn. 2021;23(9):1047-1064. doi:10.1016/j.jmoldx.2021.05.013

3. CPIC Guideline for *CYP2D6* and Ondansetron and Tropisetron: ClinPGx <https://www.clinpgx.org/guideline/PA166251457>. Accessed 11 August 2026.

4. GSI: Genotype Selection Interface: ClinPGx <https://www.clinpgx.org/genotype>. Accessed 5 August 2026.