Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* Genotype and Use of 5-HT_3 Receptor Antagonists: 2026 Update

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5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are used to treat nausea and vomiting and in the prevention of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting. Most of the 5-HT_3 receptor antagonists (i.e., ondansetron, tropisetron, dolasetron, palonosetron, and ramosetron) are metabolized by CYP2D6, but the extent of CYP2D6 involvement varies. *CYP2D6* genetic variation can influence the metabolism of these medications, particularly ondansetron and tropisetron, thereby affecting drug efficacy. This guideline is an update to the 2016 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and use of ondansetron and tropisetron and includes updated information on *CYP2D6* genetic testing and evidence tables. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for 5-HT_3 receptor antagonists based on *CYP2D6* genotype, particularly where genetic variation is associated with reduced drug efficacy (updates at https://www.clinpgx.org/guideline/PA166251457).

This document is an update to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and use of ondansetron and tropisetron, which was last updated in December 2016.[1] The guideline text and evidence tables have been updated to reflect new evidence, including all medications in the 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist class. The guideline update was prompted by a recent systematic review and meta-analysis of the literature.[2] A concise summary of key changes is provided in the **Supplemental Material**. Detailed guidelines for use of 5-HT_3 receptor antagonists as well as analyses of cost effectiveness, are beyond the scope of this review. CPIC guidelines are periodically updated, and updates for this guideline are available on the ClinPGx website: https://www.clinpgx.org/guideline/PA166251457.[3]

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2D6* genotype and ondansetron, granisetron, tropisetron, palonosetron, dolasetron, and ramosetron was conducted as detailed in the **Supplemental Material**. The evidence is summarized in **Table S1**.

GENE: *CYP2D6*

The Pharmacogene Variation (PharmVar) Consortium is a publicly available resource that provides haplotype-based (star allele) nomenclature to facilitate standardized description and reporting of pharmacogene variation. PharmVar currently lists over 170 distinct star (*) alleles for the highly polymorphic *CYP2D6* gene locus which are summarized in the ***CYP2D6* Allele Definition Table**.[3–5] The frequencies of these star alleles

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Received January 13, 2026; accepted March 12, 2026. doi:10.1002/cpt.70291

differ significantly across ancestrally diverse populations (see ***CYP2D6* Allele Frequency Table**).[3] Alleles are categorized into predicted function groups with activity values ranging from 0 to 1, listed in Table 1, as follows: normal function (activity value 1; e.g., *CYP2D6*1*), decreased function (activity value 0.5; e.g., *CYP2D6*17* or 0.25; e.g., *CYP2D6*10*), and no function (activity value 0; e.g., *CYP2D6*5*). Additional information is provided in the **Supplemental Material**.

Genetic test interpretation

Clinical laboratories typically interrogate *CYP2D6* genetic variants of known functional consequences in the general population. Genotypes are assigned using star (*) allele nomenclature, which can be found at the PharmVar website (https://www.pharmvar.org/gene/CYP2D6). Each star allele (or haplotype) represents a specific combination of variants identified by the test. Tables on the ClinPGx website contain lists of the PharmVar-defined *CYP2D6* star alleles, the combinations of variants that define each allele, their associated function, and allele frequencies across major ancestral populations.[3] The combination of inherited alleles (maternal and paternal) determines a person's diplotype, also referred to as genotype (e.g., *CYP2D6*1/*4*). The *CYP2D6* activity score is calculated by adding the activity values assigned to each allele in a reported diplotype. For example, a *CYP2D6 *1/*5* diplotype has an activity value of 1 for **1* and 0 for **5* with the sum of these activity values totaling 1 for this diplotype's activity score. Additional details about calculating *CYP2D6* activity score can be found in the **Supplemental Material**.

Since *CYP2D6* is prone to structural variations, including gene deletions, duplications, multiplications, and rearrangements with the *CYP2D7* pseudogene, clinical laboratories often report on *CYP2D6* copy number variation. Accurate determination of *CYP2D6* copy number variants is essential as they impact a diplotype's activity score, and ultimately, the phenotype assignment and associated therapeutic recommendation. As an example, *CYP2D6*5* represents a gene deletion, whereas gene duplications are reported as *CYP2D6*1x2* and **2x2* with the "x" indicating the number of identical gene copies. If an allele harbors two or more different gene copies, these are listed separately; *CYP2D6*68 + *4* and **36 + *10* are examples where an allele has an extra copy of a hybrid gene in addition to a **4* or a **10*.[6] Additional information regarding *CYP2D6* copy number variation can be found in the **Supplemental Material**. Clinical allele function, as described in the ***CYP2D6* Allele Functionality Table**, was determined based on reported *in vivo* and/or *in vitro* data when available.[3] Table 1 defines each predicted phenotype based on CYP2D6 activity score and provides a few example diplotypes. See the ***CYP2D6* Diplotype-Phenotype Table** online for a complete list of possible diplotypes and their corresponding predicted metabolizer phenotype assignments.[3] Of note, since the last publication of this guideline, *CYP2D6* genotype to phenotype translations have been standardized and activity values updated for some alleles impacting their translation to phenotype.[7] A brief explanation explaining the rationale of this change can be found in the **Supplemental Material**.

The limitations of genetic testing as described here include[1]: rare variants are often not detected[2]; known star (*) alleles not tested for will not be reported, and, instead, the patient will be reported as **1* or another allele by default; and[3] tests are not designed to detect unknown or *de novo* variants. For more details on interpreting *CYP2D6* test results, including activity score calculations and phenotype assignment, please see the **Supplemental Material** Genetic Test Interpretation Section.

Table 1 Assignment of predicted CYP2D6 phenotypes based on genotype

Phenotypes[a]	Activity score range	Activity score or genotype[b]	Examples of *CYP2D6* diplotypes (see complete list online)[b]
CYP2D6 ultrarapid metabolizer	> 2.25	> 2.25	**1/*1xN, *1/*2xN, *2/*2xN*[c]
CYP2D6 normal metabolizer	1.25 ≤ x ≤ 2.25	2.25	**2x2/*10*
		2.0	**1/*1, *1/*2*
		1.75	**1/*10x3*
		1.5	**1/*17, *2/*29*
		1.25	**1/*9, *1/*10, *1/*41*
CYP2D6 intermediate metabolizer	0 < x < 1.25	1	**1/*5*
		0.75	**10/*17, *29/*41*
		0.5	**10/*10, *10/*41, *41/*41*
		0.25	**4/*10, *4/*41*
CYP2D6 poor metabolizer	0	0	**3/*4, *4/*4, *5/*5, *5/*6*
CYP2D6 indeterminate	n/a	An individual carrying one or two uncertain function alleles	**1/*22, *1/*25, *22/*25*

Abbreviation: n/a, not applicable. [a]See the ***CYP2D6* Allele Frequency Table** for ancestry-specific allele and phenotype frequencies.[3] [b]Many more actionable *CYP2D6* alleles and diplotypes exist. For a complete list of alleles with function assignments and allele activity values, including citations for allele function, see the ***CYP2D6* Allele Functionality Table**.[3] For a complete list of *CYP2D6* diplotypes and predicted phenotypes, see the ***CYP2D6* Diplotype to Phenotype Table**.[3] [c]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see the **Supplemental Material** for additional information on how to translate diplotypes into phenotypes.

Available genetic test options

See **Supplemental Material** online and the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/) for more information on commercially available clinical testing options including information for the key attributes of alleles recommended for clinical testing and a minimum set of variants that should be included in clinical genotyping assays for *CYP2D6* and other pharmacogenes recommended by the Association for Molecular Pathology (AMP).[8]

Incidental findings

Currently, there are no diseases or conditions which have been consistently linked to variation in the *CYP2D6* gene independently of drug metabolism and response.

DRUGS: 5-HT$_3$ RECEPTOR ANTAGONISTS

Background

5-HT$_3$ receptor antagonists, which include ondansetron, tropisetron, granisetron, dolasetron, palonosetron, and ramosetron, are used for nausea and vomiting, with specific indications varying by agent, such as prevention of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting.[9,10] The 5-HT$_3$ receptor antagonists suppress nausea and vomiting by selectively binding to 5-HT$_3$ receptors both centrally and peripherally, thereby preventing serotonin-mediated emetogenic signaling and exhibiting a steep dose–response curve.[11–13] The 5-HT$_3$ receptor antagonist class is the cornerstone of prophylactic therapy for moderately to highly emetogenic chemotherapy and radiotherapy.[14] All medications in this class are effective in the prevention of nausea and vomiting; the main differences between these drugs are due to variation in pharmacokinetic (e.g., metabolic pathways and half-life) and pharmacodynamic (e.g., binding affinity and receptor internalization) considerations.[15] The 5-HT$_3$ receptor antagonists are generally well tolerated, although headaches, constipation, and transient elevations in liver enzymes are common side effects. Ondansetron has also been associated with cardiac adverse events such as QTc prolongation (see "*Other Considerations*" section).[14]

Ondansetron is metabolized into four inactive metabolites by multiple cytochrome P450 enzymes, including CYP1A1, CYP1A2, CYP3A4, and CYP2D6, followed by glucuronide conjugation to metabolites without clinically relevant pharmacologic activity.[16,17] Tropisetron is extensively metabolized by CYP2D6 with a minor contribution by CYP3A4 to inactive metabolites and further conjugated to glucuronides and sulfates.[17,18] Dolasetron, palonosetron, and ramosetron are also metabolized by multiple cytochrome P450 enzymes, including CYP2D6, while granisetron is the only known 5-HT$_3$ receptor antagonist that is not metabolized by CYP2D6, which has important clinical implications.[19–21] CYP3A4 is responsible for the demethylation of granisetron to 9′-desmethyl granisetron; however, there are no data to support *CYP3A4* genetic variation impacting granisetron metabolism.[22,23]

Linking genetic variability to variability in drug-related phenotypes

Application of an evidence-grading framework indicates a moderate level of evidence supporting an association between *CYP2D6* variation and variability in ondansetron and tropisetron efficacy (see **Table S1**). However, available data are insufficient to support recommendations based on toxicity outcomes. Data are also insufficient linking *CYP2D6* genotype with phenotypic variability for toxicity and efficacy for dolasetron, palonosetron, and ramosetron. This body of evidence, rather than randomized clinical trials involving pharmacogenetic testing, provides the basis for the ondansetron and tropisetron dosing recommendations in **Table 2**. Although the evidence underlying this recommendation is limited, it is supported by the quality of these studies, the data showing increased metabolism of ondansetron and tropisetron (and other CYP2D6 substrates) in CYP2D6 ultrarapid metabolizers (UMs), and the availability of a suitable alternative to ondansetron and tropisetron not affected by CYP2D6 metabolism (i.e., granisetron).[9,24,25] Ondansetron is metabolized by several CYP enzymes, while tropisetron is primarily metabolized by CYP2D6, but both have substantial data available supporting the clinically relevant role of CYP2D6 in this process.[16–19]

To date, five studies have found an association of decreased antiemetic effect to ondansetron and tropisetron (e.g., vomiting) in CYP2D6 UMs, one of which was conducted in pediatric patients.[26–30] The strongest evidence for this association comes from studies with ondansetron in the postoperative nausea and vomiting setting, with more limited evidence in other clinical contexts (e.g., chemotherapy-induced nausea and vomiting). Three additional pediatric studies did not find an association between *CYP2D6* genotype and postoperative nausea and vomiting or chemotherapy induced nausea and vomiting; however, the strength of evidence is limited by the small numbers of UMs included in these studies.[31–33] Although CYP2D6 poor metabolizers (PMs) had higher tropisetron serum concentrations compared to all other phenotypes measured 6 hours after administration, the clinical impact on nausea and vomiting are unknown. Three studies evaluating electrocardiograms found no significant association between *CYP2D6* genotype and electrocardiogram changes induced by dolasetron or ondansetron; however, these studies were underpowered.[34–36]

Therapeutic recommendations

Table 2 summarizes the therapeutic recommendations for ondansetron and tropisetron based on CYP2D6 phenotype, which remains unchanged since the 2016 guideline. UMs having duplications of functional alleles (e.g., *CYP2D6*1x2* or **2x2*) were shown to have increased clearance of ondansetron and tropisetron, resulting in a lower area under the plasma concentration–time curve and an increased risk of vomiting.[24,26,27,29,37] Thus, in CYP2D6 UMs an alternative 5-HT$_3$ receptor antagonist antiemetic not metabolized by CYP2D6 (i.e., granisetron) should be considered (Moderate recommendation). The strength of these recommendations is described in the Supplement and based on the evidence provided in **Table S1** and the availability of suitable antiemetics not metabolized by CYP2D6. Currently, there are limited published data to support a recommendation in CYP2D6 intermediate metabolizers (IMs) and PMs. Although dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6 (**Table S2**), insufficient evidence are available regarding the

Table 2 Dosing recommendations for ondansetron and tropisetron based on *CYP2D6* phenotype

CYP2D6 Phenotype[a]	Activity score	Implications for phenotypic measures	Therapeutic recommendations	Classification of recommendations[b]
CYP2D6 ultrarapid metabolizer	>2.25	Increased metabolism to less active compounds when compared to normal metabolizers (NMs) and is associated with decreased response to ondansetron and tropisetron (e.g., vomiting).	Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron)[c,d]	Moderate
CYP2D6 normal metabolizer	1.25≤x≤2.25	Normal metabolism of ondansetron and tropisetron	Initiate therapy with recommended starting dose[c]	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation based on insufficient evidence	No recommendation
CYP2D6 poor metabolizer	0	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation based on insufficient evidence	No recommendation
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

Abbreviation: n/a, not applicable. [a]The online ***CYP2D6* Diplotype-Phenotype Table** provides a complete list of possible diplotypes and phenotype assignments (3). [b]Rating scheme described in **Supplemental Material**. [c]Drug–drug interactions, the involvement of other metabolizing enzymes, and patient characteristics (e.g., age, renal and hepatic function) should be considered when selecting alternative therapy, as emerging evidence may further clarify the role of enzymes beyond CYP2D6 in the metabolism of these agents. [d]Dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6. Limited evidence is available regarding the utilization of *CYP2D6* genetic variation to guide the use of these drugs. See **Tables S3 and S4**.

effect on nausea and vomiting (**Tables S3 and S4**) (CPIC level C-no recommendation).

Pediatrics

The 5-HT_3 receptor antagonists are widely used and recommended to prevent and treat chemotherapy-induced nausea and vomiting, as well as postoperative and radiation-induced nausea in children.[10] At the time the original guideline was developed, no pediatric studies were available. In this update, four studies are included that investigated pediatric patients receiving ondansetron for postoperative nausea or chemotherapy-induced nausea and vomiting.[27,31,32,35] Only one study concluded that CYP2D6 UMs experienced more chemotherapy-induced nausea and vomiting, whereas the other studies found no association between outcomes and metabolizer status, with all studies having low numbers of UMs.[27,31,35] Therefore, the recommendations in **Table 2** apply to both adult and pediatric populations. However, as the CYP2D6 catalytic activity is still developing in neonates especially during their first month after birth, the impact in this population might be different compared to adults or older children and warrants further investigation.[38]

Biogeographical groups

These recommendations are derived from studies that primarily included individuals of European ancestry as defined elsewhere.[39] Although additional studies including individuals from other ancestry groups are needed, the effects of functional *CYP2D6* genetic variants on 5-HT_3 receptor antagonist exposure or treatment outcomes are expected to be consistent across biogeographic groups. However, selecting *CYP2D6* genetic tests appropriate for the patient population (those including clinically relevant genetic variants observed in that population) is critical to ensure accurate phenotype prediction (see the "Caveats" section below).

Recommendations for incidental findings

No recommendations for incidental findings have been provided, given the lack of consistent evidence supporting associations between any of the assessed variants and inherited diseases or conditions independent of drug metabolism and response. For recommendations pertaining to other drugs potentially affected by *CYP2D6* variation, visit https://www.clinpgx.org/cpic/guidelines to review the applicable CPIC guidelines.

Other considerations

The syndrome of congenital prolongation of the QT interval of the electrocardiogram is associated with a risk of potentially fatal polymorphic ventricular tachycardia, which is commonly referred to as torsades de pointes.[40] In September 2011, the FDA issued a safety communication reporting a change to the medication label by adding a warning to avoid ondansetron use in patients with congenital long QT syndrome (http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm). The alert also recommended electrocardiogram monitoring for patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmia, or patients taking concomitant medications that prolong the QT interval. In June 2012, the FDA issued another safety communication reporting changes to the ondansetron label regarding intravenous dosing (http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm). This alert recommended that no single intravenous dose should exceed 16 mg. The alert noted new evidence suggesting that QT prolongation is dose dependent. Therefore, in patients for whom genetic testing predicts intermediate or poor CYP2D6 metabolism, potentially elevated blood levels of ondansetron suggest that these

patients might have a greater risk for torsades de pointes even with the 16 mg maximum dose.[41,42] Although theoretical concerns exist, there is currently a lack of high-quality clinical data to support or refute an association between CYP2D6 PM status and increased QTc prolongation.[34,35] Of note, a recent systematic review of 170 trials involving more than 23,000 adults found no association between ondansetron and an increased risk of QT-prolongation-related major adverse cardiac events.[43] However, most patients received a single dose of ondansetron, the incidence of a serious adverse cardiovascular event was rare and only 11.7% of trials included electrocardiogram follow-up.[43] While the risk of major adverse cardiac events related to QT prolongation may be lower than historically perceived, they do not exclude the risk of QT prolongation. Continued caution and appropriate monitoring in high-risk populations remain warranted.

CYP2D6 genetic variants do not account for all variability that is observed for ondansetron or tropisetron response. In addition to patient-specific factors (such as smokers vs. nonsmokers, male vs. female), other genes have been implicated in the response to ondansetron including the *ABCB1* gene and the serotonin 5-HT3A and 5-HT3B receptors genes.[25,44–46] Genetic variation in *CYP3A5* has been found to influence concentrations of R-ondansetron; however, to date, there is no data describing how this impacts antiemetic efficacy in individuals taking ondansetron or tropisetron.[24] One study found variation in *CYP3A5* and *CYP1A1* impacts systemic clearance and exposure of granisetron in pregnant women.[23] Currently, pharmacogenomic data are limited to genetic variation in *CYP2D6* and the aforementioned study involving granisetron, with no additional reported associations involving other metabolic enzymes or 5-HT_3 receptor antagonists. Further studies are needed to clarify the impact of genetic variation in these pathways on antiemetic response.

Implementation of this guideline. The guideline provides resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see "*Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support*" in the **Supplemental Material**).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of using *CYP2D6* genotype to guide ondansetron and tropisetron use is that patients with genotypes that are associated with a decreased response (i.e., CYP2D6 UMs) may be identified and alternative antiemetics administered. At this time, the evidence does not justify increasing the dose in CYP2D6 UMs because dose adjustments based on this phenotype have not been studied and a detailed recommendation of dosing for the different CYP2D6 phenotypes is missing. Additionally, there is a single intravenous maximum dose of 16 mg in the FDA labeling, which might prevent increases in dosing in certain situations. *CYP2D6* genotyping is reliable when performed in qualified laboratories (e.g., Clinical Laboratory Improvement Amendments (CLIA) or European Molecular Genetics Quality Network (EMQN)-certified) and a minimum of alleles are tested per AMP guidelines.[8] However, as with any laboratory test, a possible risk to patients is an error in genotyping or phenotype prediction, along with the presence of a rare genomic variant not tested for, which could have long-term adverse health implications for patients.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Rare *CYP2D6* variants may not be included in the genotype test used, and patients with rare variants may be assigned a *CYP2D6*1* "reference" genotype by default, indicating that both alleles match the *CYP2D6* NG_008376.4 reference sequence. Thus, a reported "wild-type" or "reference" allele could potentially harbor a no function or decreased function variant. In certain instances, defaulting may also occur to other alleles (e.g., if the *CYP2D6*40*-defining variant is not tested, the default assignment is **17*). Furthermore, it is important to include gene copy number testing to identify CYP2D6 UMs as well as individuals with other structural *CYP2D6* variations.[6] Clinicians must understand molecular diagnostics of *CYP2D6* may produce differing genotyping results between diagnostic laboratories depending on assay design. Like all diagnostic tests, *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider when making their therapeutic choice for each patient. Furthermore, there are several other factors that cause potential uncertainty in the genotyping results and phenotype predictions. These are discussed in detail in the **Supplemental Material**.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines or for any errors or omissions.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

We acknowledge the critical input of Dr Mary V. Relling and members of the Clinical Pharmacogenetics Implementation Consortium (CPIC), funded by the National Institutes of Health.

FUNDING

This work was funded by the (i) National Institutes of Health (NIH) for CPIC (U24HG013077) and PharmGKB (U24HG010615), (ii) American Lebanese Syrian Associated Charities (ALSAC), and (iii) Medical

Research Future Fund Genomics Health Future Mission (MRF/2024900). RC is supported by a VESKI FAIR Fellowship. CM is supported by a University of Melbourne RTP Scholarship. MS is in parts supported by the Robert Bosch Stiftung Stuttgart, Germany. SEL is on an advisory board for McKesson Corporation.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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