Supplement to:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* Genotype and Use of 5-HT$_3$ Receptor Antagonists: 2026 Update

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DATA AVAILABILITY

All tables and materials referenced in this supplement are available at https://www.clinpgx.org/guideline/PA166251457 (1).

GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* Genotype and Use of 5-HT_3 Receptor Antagonists is published in full on the ClinPGx website (https://www.clinpgx.org/guideline/PA166251457) (1). Relevant information will be reviewed periodically and updated guidelines published online.

UPDATES IN SUPPLEMENT

- **Updated Evidence**: Incorporates new evidence from September 2015 to January 8, 2026, highlighting recently available pediatric data not previously included.
- **Expanded Drug Scope:** Includes all 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists (ondansetron, tropisetron, dolasetron, palonosetron, ramosetron, granisetron).
- **Standardized Phenotype Translation:** Updated activity score cutoffs and consensus-based CYP2D6 phenotype assignments.
- **Enhanced Genetic Testing Guidance**: Emphasizes copy number variation (CNV) detection, the Association for Molecular Pathology (AMP) minimum allele set, and PharmVar resources.
- **Implementation Resources:** Added resources to facilitate incorporation of *CYP2D6* genotype results into electronic health records with clinical decision support and updated allele frequency information.
- **Clinical Recommendations:** No change to therapeutic recommendations for ondansetron and tropisetron compared with the 2016 guideline.

LITERATURE REVIEW

We searched the PubMed® database (1966 to January 8, 2026) for the following keywords: (cytochrome P450 2D6 or CYP2D6) AND (ondansetron, granisetron, tropisetron, palonosetron, ramosetron, dolasetron, 5-HT_3 receptor antagonists). The search was limited to studies conducted in humans or relevant experimental models and written in the English language. Review articles and studies only published as abstracts were excluded. Using these search terms, 97 publications

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were identified. Inclusion criteria included publications that incorporated analysis for the associations between *CYP2D6* genotype and 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist pharmacokinetic parameters or 5-HT_3 receptor antagonist-related clinical outcomes in patients. 62 publications were screened based on the inclusion criteria, (**Figure S1)** and 22 were included in our review (**Table S1)**.

GENE: *CYP2D6*

Genetic Test Interpretation

CYP2D6 genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide variants (SNVs) and/or structural variants (SVs, often also referred to as copy number variants or CNVs), including gene duplications, multiplications, deletions and hybrid genes containing *CYP2D7*-derived sequences that are interrogated during genotyping analysis. *CYP2D6* haplotypes are often reported using star allele (*) nomenclature to allow for the standardization of genetic variant annotation (2-4). A complete list of *CYP2D6* star alleles along with the genetic variants that define each star allele is available on the **CYP2D6 Allele Definition Table** which provides a summary of the core allele definitions listed by PharmVar (1). Allele information can also be directly obtained through the PharmVar API. Knowing which SNVs or other genetic variants a particular test interrogates is important as the inclusion or exclusion of certain genetic variants in a pharmacogenetic test could affect star-allele calling and the reported diplotype result. We also refer to Ji *et al.* for additional information on pharmacogenomic testing and strategies and technical considerations for clinical laboratories (5).

Clinical laboratories usually report a diplotype (often referred to as a genotype), which is the summary of inherited maternal and paternal star alleles (e.g. *CYP2D6*1/*10*, where an individual inherited a **1* allele and a **10* allele). Commonly reported *CYP2D6* star alleles are categorized into function groups (e.g., increased function, normal function, decreased function, or no function) based on an allele's assigned activity (***CYP2D6* Allele Functionality Table**) (1). The predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype.

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Calculating CYP2D6 Activity Score. A scoring system developed by Gaedigk *et al*. provides a uniform approach to a predicted CYP2D6 phenotype from genotype (6, 7). The scoring system was updated by Caudle *et al.* in 2019 to improve standardization of *CYP2D6* genotype to phenotype translation as there were inconsistencies of metabolizer classification between guidelines and clinical genetic testing laboratories using a consensus-based approach with CYP2D6 international experts (7). The updated activity scoring system was used for this guideline update to translate *CYP2D6* genotype into phenotype (7). The activity values (AVs) assigned to each allele are added together to calculate the CYP2D6 activity score (AS) for the reported diplotype. For example, to calculate the activity score of a *CYP2D6*1/*10* diplotype, the activity value of **1* (AV = 1) and the activity value of **10* (AV = 0.25) are totaled to provide an activity score of 1.25 for this *CYP2D6* diplotype. A value of 0.25 is a categorical value indicating decreased activity and not that the allele has 25% of activity compared to the normal function *CYP2D6*1* reference allele which has an AV of 1. CYP2D6 activity scores translate genotype into phenotype as follows: AS of 0 = poor metabolizer (PM), AS of $0 < x < 1.25$ = intermediate metabolizer (IM), AS of $1.25 \leq x \leq 2.25$ = normal metabolizer (NM), and AS greater than 2.25 = ultrarapid metabolizer (UM). Therefore, a pharmacogenetic test result of *CYP2D6*1/*10* would result in a CYP2D6 activity score of 1.25 and a predicted phenotype of NM.

CYP2D6 Structural and Gene Copy Number Variants. Given that *CYP2D6* is subject to CNV (gene duplications, multiplications, deletions and hybrid genes containing *CYP2D7*-derived portions), clinical laboratories may report gene copy number if tested. Most patients will have a normal copy number of 2, with one gene copy inherited maternally and one gene copy inherited paternally. When two *CYP2D6* gene copies are present, the diplotype is most often reported as *CYP2D6*1/*1* but as *CYP2D6 (*1/*1)2N* by some laboratories, where "*2N*" represents the patient's total gene copy number. A copy number of "1" indicates the presence of a *CYP2D6* gene deletion (the patient possesses only one gene copy), and a copy number of "0" indicates both *CYP2D6* genes are deleted. Of note, *CYP2D6*5* is the star allele designation describing alleles harboring a whole gene deletion. A gene deletion present on one chromosome is typically reported as e.g., *CYP2D6*2/*5,* but some laboratories may report the genotype as *CYP2D6 (*2/*2)1N*, where "*1N*" represents gene copy number and the *CYP2D6*5* allele is inferred, and homozygous gene deletions are reported as *CYP2D6*5/*5* or *CYP2D6 (*5/*5)0N*. PharmVar has

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published recommendations to facilitate standardized reporting of structural variation and gene copy number variants (4).

A copy number greater than two indicates the presence of a *CYP2D6* gene duplication or multiplication. When a *CYP2D6* gene duplication is present, the diplotype may be reported as *CYP2D6 (*1/*2)3N*, where "*3N*" represents the total gene copy number. A clinical laboratory may not have quantitatively measured copy number or which allele has the duplication but rather indicate an additional gene copy or copies are present (e.g., *CYP2D6*1/*2* duplication or *CYP2D6 (*1/*2)xN*). In instances where a duplication/multiplication is present and the exact copy number is not reported, most patients likely have a total gene copy number of 3, i.e., have a gene duplication such as **2x2* on one allele. However, individuals carrying as many as 13 *CYP2D6* gene copies have been reported (8). Clinical laboratories may not determine which allele is duplicated; therefore, when calculating CYP2D6 activity score, the duplication must be considered for each allele reported in the diplotype (9). For example, a genotype result of *CYP2D6 (*1/*4)3N* indicates a patient has three gene copies, with either two copies of the *CYP2D6*1* allele and one copy of the *CYP2D6*4* allele (*CYP2D6*1x2/*4*) predicting normal metabolism (AS = 2), or one copy of the *CYP2D6*1* allele and two copies of the *CYP2D6*4* allele (*CYP2D6*1/*4x2*) predicting intermediate metabolism (AS = 1). Other examples illustrating the importance of knowing copy number and which allele has the duplication or multiplication, include *CYP2D6 (*1/*10)xN* which is either a normal metabolizer (*CYP2D6*1/*10x2*, AS = 1.5 or *CYP2D6*1x2/*10*, AS = 2.25) or an ultrarapid metabolizer (*CYP2D6*1x2/*10x2*, AS = 2.5 or *CYP2D6*1x3/*10*, AS = 3.25). As these examples illustrate, phenotype prediction will be more accurate if quantitative CNV testing is performed, and the test also determines which allele has the duplication or multiplication. Consequences of *CYP2D6* CNV on pharmacotherapy have been reviewed by Jarvis *et al*., Turner *et al*, and Taylor *et al* (4, 10, 11).

A duplication may not be detected by copy number assays when paired with the *CYP2D6*5* allele (gene deletion). A *CYP2D6*2x2/*5* diplotype, for example, has a gene duplication on one allele and a gene deletion on the other for a total number of two gene copies. This diplotype may be reported as *CYP2D6*2/*2*. Note that CPIC *CYP2D6* tables do not support *CYP2D6*

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diplotypes where the allele with the duplication/multiplication is unknown (e.g. *CYP2D6 (*1/*2)3N).*

Other structural variants include gene copies that consist of *CYP2D6* and *CYP2D7*-derived sequences (3, 4, 12, 13). An overview of these variants can also be found in the "Structural Variation" document provided on the *CYP2D6* PharmVar gene (https://www.pharmvar.org/gene/CYP2D6). The no function *CYP2D7::CYP2D6* hybrid genes, collectively listed as *CYP2D6*13*, may not be detected by a particular genotype test or gene copy number testing (4, 14). In such cases, the test may detect only the allele present on the second chromosome and report the diplotype as homozygous for that allele. For example, a *CYP2D6*1/*13* diplotype (AS = 1) may be reported as *CYP2D6*1/*1* (AS = 2). Depending on the *CYP2D6*13* structure and what a test is interrogating, a *CYP2D6*13* may also be reported as a *CYP2D6*5* gene deletion; in this case, the predicted phenotype is the same. Hybrid genes can also occur in more complex structures (i.e., nonidentical duplications/multiplications) and cause positive gene duplication test results that may lead to an overestimation of activity and false-positive prediction of ultrarapid metabolism (4, 13, 15). For example, a *CYP2D6*1/*13+*2* diplotype (AS = 2, predicting normal metabolism) may be assigned as *CYP2D6*1/*2xN* or **1xN/*2* (AS ≥3 predicting ultrarapid metabolism) if only exon 9 is interrogated for copy number testing. Additional information can be found in the PharmVar Tutorial on *CYP2D6* Structural Variation Testing and Recommendations on Reporting (4).

Limitations of the Star (*) Nomenclature and Allele Assignments. PharmVar star (*) allele nomenclature provides suballele definitions (e.g., *CYP2D6*2.001, CYP2D6*4.002*), but these are typically not distinguished by current testing. This is of no consequence for *CYP2D6*4*, because all **4* suballeles share the 1847G>A variant that causes aberrant splicing and absence of functional protein. However, for *CYP2D6*2* it is uncertain whether any of the synonymous variants or variants in noncoding regions defining the suballeles convey a functional consequence (for all or some substrates). Also, there is no, or little, information regarding suballele frequencies because test laboratories do not discriminate between the suballeles. In addition, there are likely numerous known variants and suballeles not designated by PharmVar at this time (investigators and clinical laboratories are encouraged to submit novel information to PharmVar).

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The accuracy of a pharmacogenomic test depends on the number of sequence variants or star alleles tested. If no variants are found, a *CYP2D6*1* will be the 'default' assignment. Depending on which sequence variants are interrogated, the allele assignment may vary. For example, if 2851C>T (p.R296C) is present, but 1022C>T (p.T107T) is not, the assignment is *CYP2D6*2*. In contrast, if 1022C>T is also present, the allele would be assigned as *CYP2D6*17*. Similarly, if an 18-base pair long insertion at position 1864 (p.174_175insFRPx2) is not tested, a *CYP2D6*40* will be reported as a *CYP2D6*17*, **2,* or **1* depending on which other variants were interrogated. Additional examples are provided in the PharmVar *CYP2D6* GeneFocus paper (3).

The variant positions provided above and below are according to the *CYP2D6* genomics reference sequence (RefSeq) NG_008376.4 which corresponds to the sequence present in the GRCh38 genome build. The M33388 "legacy" RefSeq contains errors causing certain SNV positions to shift by 1-base when mapped to the NG_008376.4. PharmVar uses NG_008376.4 for allele definitions and strongly encourages the use and reporting of positions in respect to NG_008376.4.

A variant (rs5758550) in a distal enhancer region has been reported to impact allele activity on the transcriptional level (16, 17). Specifically, *CYP2D6*2* alleles lacking the "enhancer" SNV were reported to have decreased function. However, a subsequent study found the enhancer SNV did not lead to improved prediction of endoxifen concentrations in breast cancer patients using tamoxifen (18). Another study was inconclusive as to whether the small observed effects were indeed caused by the enhancer SNV or were due to its incomplete linkage with other variants within the gene (19). Furthermore, it was also reported this SNV can occur on many other star alleles besides *CYP2D6*2*, and the portion of an allele with and without rs5758550 may considerably vary among biogeographical groups (20). It remains uncertain whether the effect of this SNV on CYP2D6 activity *in vivo* is of clinical significance. rs5758550 is currently not included in common *CYP2D6* genotyping panels, nor is it included in star allele definitions. Furthermore, a recent report described new haplotypes involving distant variants that may impact CYP2D6 expression of *CYP2D6*2* and **35 (21)*. These findings require independent replication to assess their clinical impact and utility.

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Available Genetic Test Options

Commercially available genetic testing options change over time. The Genetic Testing Registry provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr. Desirable characteristics of pharmacogenomic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members as well as the American College of Medical Genetics and Genomics (ACMG) (22, 23). CPIC recommends clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables adhere to these allele nomenclature standards. Moreover, these tables (**Allele Definition Tables, Allele Functionality Tables, and Allele Frequency Tables)** may be used to assemble lists of known functional and actionable genetic variants and their population frequencies, which may inform decisions as to whether pharmacogenomic tests are adequately comprehensive with the interrogated alleles (1). Furthermore, the Association for Molecular Pathology (AMP) has published a recommendation 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 (1, 24). AMP's minimum sets of alleles can also be found on the ClinPGx website (https://www.clinpgx.org/ampAllelesToTest).

Other Considerations

The effects of *CYP2D6*17* on drug metabolism appear to be substrate-specific and may vary by medication or by the ethnic population studied (25, 26). A recent study demonstrated increased activity of **17* towards risperidone, specifically in African-American patients (27). There is a paucity of data though for **17* and 5-HT_3 receptor antagonists to suggest that its activity differs from its current classification of decreased function for these drugs.

The use of CYP2D6 enzyme inhibitors can impact a patient's predicted phenotype to a reduced enzymatic activity which is known as phenoconversion (28). For example, when a strong CYP2D6 inhibitor like fluoxetine is used, a person can convert from normal metabolism to poor metabolism while exposed to such drugs (28). This is important as pharmacogenetic testing alone does not predict a patient's response or toxicity to a medication and consideration of concomitant medications should be evaluated when interpreting *CYP2D6* genotype results and applying therapeutic recommendations to patient care (28).

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LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Table S1** is graded on a scale of high, moderate, and weak based upon the level of evidence (29):

- **High:** Evidence includes consistent results from well-designed, well-conducted studies. High confidence that the available evidence reflects the true magnitude and direction of the net effect and further research is very unlikely to change the magnitude or direction of this net effect.
- **Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.
- **Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information. Further research may change the magnitude and/or direction of the net effect.

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors taken into account in evaluating the evidence supporting therapeutic recommendations include: data from *in vivo* pharmacokinetic and pharmacodynamic studies (including pre-clinical data), activity determined with *in vitro* systems expressing the reference (*CYP2D6*1*) and variant-containing *CYP2D6* sequences, *in vitro* CYP2D6 enzyme activity measured in liver tissue extracts isolated from individuals of known *CYP2D6* genotypes.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for recommendations adopted from the rating scale for evidence-based guidelines on the use of antiretroviral agents (30):

- **Strong** recommendation for the statement**:** The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

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- **Moderate** recommendation for the statement: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.
- **Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- **No recommendation**: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (31-35). See https://www.clinpgx.org/guideline/PA166251457 for resources to support the adoption of CPIC guideline for *CYP2D6* Genotype and Use of 5-HT_3 Receptor Antagonists within an EHR (1, 36, 37). Based on the capabilities of various EHRs and local preferences, we recognize approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating *CYP2D6* genotype results in an EHR to guide ondansetron and tropisetron use.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should include key attributes. Pharmacogenetic test results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (38). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted drug metabolism phenotype (**Table 1, main manuscript; *CYP2D6* Diplotype to Phenotype Table**) (1). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **Ondansetron/Tropisetron Pre- and Post-Test Alerts and Flow Chart**) (1).

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Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how *CYP2D6* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see https://www.clinpgx.org/guideline/PA166251457) (1).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables to provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (see https://www.clinpgx.org/guideline/PA166251457) (1).

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SUPPLEMENTAL TABLE S1. EVIDENCE LINKING *CYP2D6* TO 5-HT$_3$ RECEPTOR ANTAGONIST PHENOTYPE

Type of experimental model (*in vitro, in vivo*, preclinical or clinical)	Major findings	References	Level of evidence[a]
Ondansetron			
Clinical	CYP2D6 ultrarapid metabolizer status (as determined by genotyping) is associated with decreased **ondansetron** AUC for S-ondansetron enantiomer only (no influence on racemic mixture).	Stamer, *et al*. (2011)(39)	Moderate
Clinical	*CYP2D6* genotype or phenotype has no effect on **ondansetron** concentrations (racemic mixture).	Rauers, *et al*. (2010)(40) Ashforth, *et al*. (1994)(41)	Weak
Clinical	CYP2D6 ultrarapid metabolizer status (as determined by genotyping) is associated with decreased response to **ondansetron** (e.g., vomiting) when used for prevention of postoperative nausea and vomiting.	Candiotti, *et al*. (2005)(42) Niewiński, *et al*. (2018)(43) McFadgen, *et al.* (2019)(44)	Moderate
Clinical	CYP2D6 ultrarapid metabolizer status (as determined by genotyping) is associated with decreased response to **ondansetron** (e.g., vomiting) when used for prevention or treatment of chemotherapy-induced nausea and vomiting.	Kaiser, *et al*. (2002)(45) Edwards, *et al*. (2022)(46) Black, *et al*. (2023)(47)	Weak

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Type of experimental model (*in vitro, in vivo*, preclinical or clinical)	Major findings	References	Level of evidence[a]
Ondansetron			
Clinical	CYP2D6 intermediate metabolizer status (as determined by genotyping) is not associated with response to **ondansetron** as compared to normal metabolizers.	Perwitasari, *et al*. (2011)(48) Monte, *et al*. (2014)(49) Black, *et al*. (2023)(47) Jacobs, *et al*. (2022)(50) Niewiński, *et al*. (2018)(43)	Weak
Clinical	CYP2D6 normal metabolizer status (as determined by genotyping) is associated with decreased response to **ondansetron** (e.g., vomiting) when compared to poor metabolizers when used for prevention of postoperative nausea and vomiting.	Niewiński, *et al.* (2018)(43)	Weak
Clinical	Patients with the AA genotype (rs16947 A>G) had a significantly higher prevalence of mild nausea when **ondansetron** was used for postoperative nausea and vomiting than patients with the GG and AG genotypes.	Ribeiro, *et al.* (2024)(51)	Weak

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Type of experimental model (*in vitro, in vivo*, preclinical or clinical)	Major findings	References	Level of evidence[a]
Ondansetron			
Clinical	CYP2D6 poor metabolizer status (as determined by genotyping) is not associated with response to **ondansetron** as compared to normal metabolizers.	Niewiński, *et al.* (2018)(43)	Weak
Clinical	In pediatrics, no significant differences were detected for CYP2D6 metabolizer status (as determined by genotyping) and postoperative nausea and vomiting with **ondansetron.**	Black, *et al*. (2023)(47)	Weak
Clinical	In pediatrics, no significant association was found between CYP2D6 metabolizer status (as determined by genotyping) and **ondansetron**-induced QT prolongation.	Drögemöller, *et al*. (2022)(52)	Weak
Clinical	In pediatrics, CYP2D6 ultrarapid metabolizer status (as determined by genotyping) is associated with decreased response to **ondansetron** (e.g., vomiting) when used for prevention or treatment of chemotherapy-induced nausea and vomiting.	Edwards, *et al*. (2022)(46) Jacobs, *et al*. (2022)(50)	Weak
Clinical	In pregnant women, no significant association was found between CYP2D6 metabolizer status (as determined by genotyping) and **ondansetron**-induced QT prolongation.	Drögemöller, *et al.* (2022)(52)	Weak

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Type of experimental model (*in vitro, in vivo*, preclinical or clinical)	Major findings	References	Level of evidence[a]
Ondansetron			
Clinical	Dystonia was observed in a patient with a *CYP2D6*1/*41* genotype who received **ondansetron**.	Wong, *et al*. (2021)(53)	Weak
Tropisetron			
Clinical	CYP2D6 ultrarapid metabolizer status (as determined by genotyping) is associated with decreased **tropisetron** AUC as compared to CYP2D6 normal metabolizers.	Kim, *et al*. (2003)(54)	Weak
Clinical	CYP2D6 intermediate metabolizer status (as determined by genotyping) is associated with increased **tropisetron** AUC as compared to the normal metabolizer genotype.	Kim, *et al*. (2003)(54)	Weak
Clinical	CYP2D6 poor metabolizer status (as determined by genotyping) had higher serum concentrations of **tropisetron** than all other patients.	Kaiser, *et al.* (2002)(45)	Moderate
Clinical	CYP2D6 ultrarapid metabolizer status (as determined by genotyping) is associated with decreased response to **tropisetron** (e.g., vomiting) when used for prevention or treatment of chemotherapy-induced nausea and vomiting.	Kaiser, *et al.* (2002)(45)	Moderate

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Type of experimental model (*in vitro, in vivo*, preclinical or clinical)	Major findings	References	Level of evidence[a]
Dolasetron			
Clinical	CYP2D6 ultrarapid metabolizer status (as determined by genotyping) is associated with decreased response to **dolasetron** (e.g., vomiting) when used for prevention of postoperative nausea and vomiting.	Janicki, *et al.* (2006)(55)	Weak
Clinical	CYP2D6 poor metabolizer status (as determined by genotyping) is associated with increased **dolasetron** AUC, half-life and Cmax as compared to CYP2D6 normal metabolizers.	Adams, *et al*. (2009)(56) Li, *et al*. (2006)(57)	Moderate
Ramosetron			
Clinical	No significant differences were detected for chemotherapy induced nausea and vomiting with **ramosetron** based on CYP2D6 metabolizer status.	Kang, *et al.* (2017)(58)	Weak

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Type of experimental model (*in vitro, in vivo*, preclinical or clinical)	Major findings	References	Level of evidence[a]
Ramosetron			
Clinical	No significant association was found between CYP2D6 metabolizer status and pharmacokinetic parameters (AUC and Cmax) with **ramosetron**.	Kadokura, *et al.* (2008)(59)	Moderate
Palonosetron			
Clinical	Patients with the GG genotype (rs16947 A>G) had a significantly higher prevalence of severe nausea when **palonosetron** was used for postoperative nausea and vomiting than patients with the AG and AA genotypes.	Ribeiro, *et al.* (2024)(51)	Weak
Granisetron			
Clinical	No significant differences were detected for postoperative nausea and vomiting with **granisetron** based on CYP2D6 metabolizer status.	Janicki, *et al*. (2006)(55)	Weak

[a] Rating scheme described in the **Supplemental Material.**

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SUPPLEMENTAL TABLE S2. CYTOCHROME P450 ENZYMES INVOLVED IN THE METABOLISM OF 5-HT$_3$ RECEPTOR ANTAGONISTS

	CYP1A1	CYP1A2	CYP2D6	CYP3A4/5	Reference
Dolasetron	-	-	+	+	Sanwald, *et al*. (1996)(60)
Granisetron	-	-	-	+	Bloomer, *et al*. (1994)(61)
Ondansetron	+	+	+	+	Sanwald, *et al*. (1996)(60) Dixon, *et al*. (1995)(62) Fischer, *et al*. (1994)(63)
Palonosetron	-	+	+	+	MGI Pharma(64)
Ramosetron	+	+	+	-	Kadokura, et al.(59)
Tropisetron	-	-	+	+	Sanwald, *et al*. (1996)(60) Fischer, *et al*. (1994)(63) Firkusny, *et al*. (1995)(65)

(-): Not reported; (+): Reported

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SUPPLEMENTAL TABLE S3. DOSING RECOMMENDATIONS FOR DOLASETRON BASED ON *CYP2D6* PHENOTYPE

Phenotype	Activity score	Implications	Recommendations	Classifications of recommendations[a]
CYP2D6 ultrarapid metabolizer	>2.25	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation based on insufficient evidence	No recommendation
CYP2D6 normal metabolizer	1.25≤x≤2.25	Normal metabolism	Initiate therapy with recommended starting dose[b]	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	Increased (hydro)dolasetron AUC, half-life and/or Cmax compared to normal metabolizers; however, there is insufficient evidence that demonstrates clinical impact.	No recommendation based on insufficient evidence	No recommendation
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.

[a]Rating scheme described in **Supplemental Materials**.

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[b]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.

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SUPPLEMENTAL TABLE S4. DOSING RECOMMENDATIONS FOR PALONOSETRON AND RAMOSETRON BASED ON *CYP2D6* PHENOTYPE

Phenotype	Activity score	Implications	Recommendations	Classifications of recommendations[a]
CYP2D6 ultrarapid metabolizer	>2.25	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype.	No recommendation based on insufficient evidence	No recommendation
CYP2D6 normal metabolizer	$1.25 \leq x \leq 2.25$	Normal metabolism	Initiate therapy with recommended starting dose[b]	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

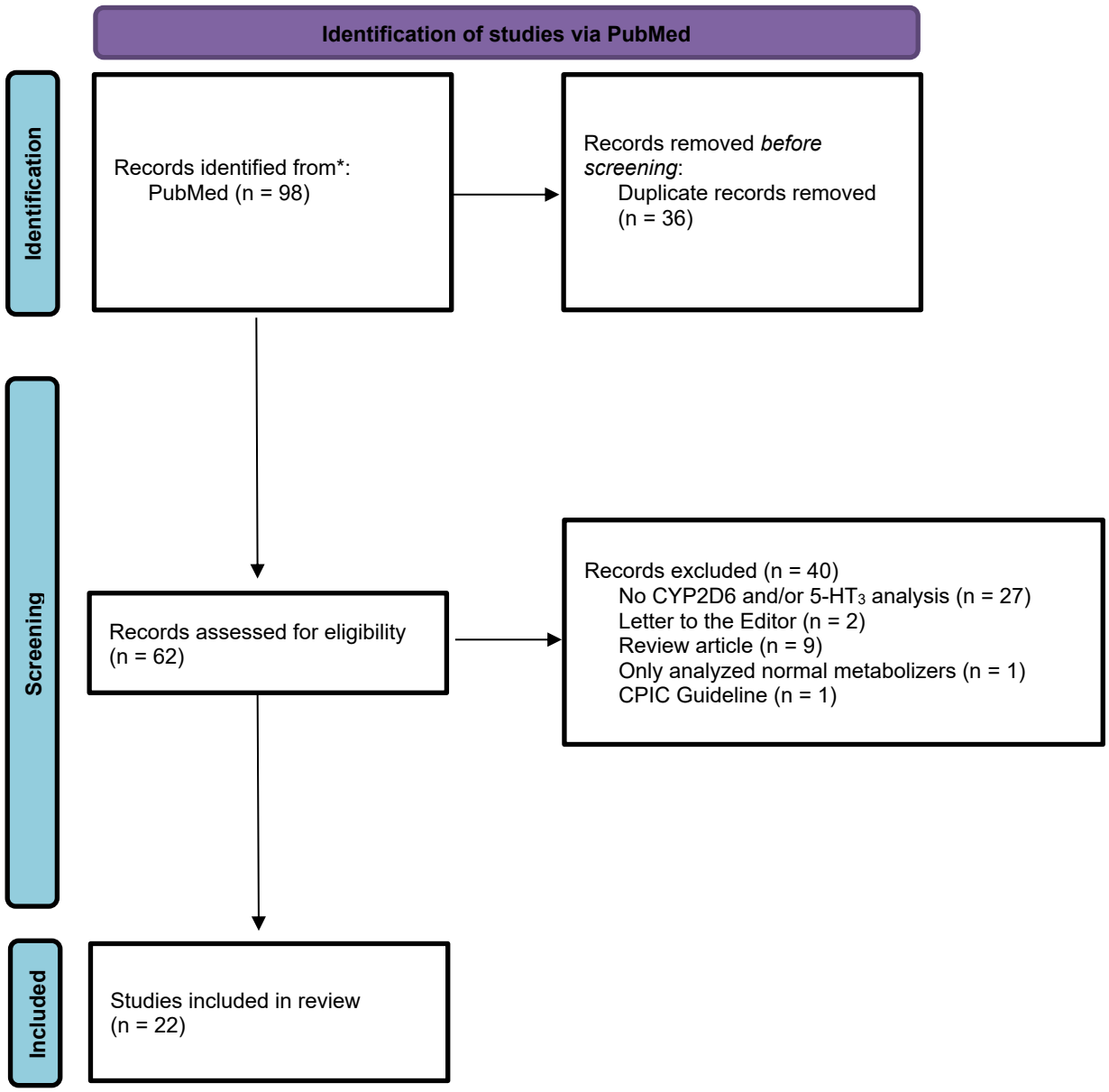
n/a, not applicable.

[a]Rating scheme described in **Supplemental Materials**.

[b]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.

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SUPPLEMENTAL FIGURE S1: PRISMA DIAGRAM



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