

Supplement to:
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of SSRIs

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GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and the dosing of SSRIs is published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be reviewed periodically and updated guidelines published online.

LITERATURE REVIEW

We searched the PubMed® database (1966 to December 2014) for the following keywords: (cytochrome P450 2D6 or CYP2D6) OR (cytochrome P450 2C19 or CYP2C19) AND (SSRI OR selective serotonin reuptake inhibitors OR fluoxetine OR paroxetine OR citalopram OR escitalopram OR sertraline OR fluvoxamine OR paroxetine) for the association between *CYP2D6* and/or *CYP2C19* genotypes and metabolism of SSRIs or SSRI-related adverse drug events or clinical outcomes. Key publications of clinical pharmacogenetic studies on SSRI pharmacokinetics and clinical outcomes are reported in **Supplemental Tables S7-S11**.

The *CYP2D6* and *CYP2C19* allele frequency tables are updates of those previously published in CPIC guidelines (1-4). Updates to the *CYP2D6* and *CYP2C19* allele frequency tables were made by searching the PubMed® database (1995 to 2014). The following criteria were used for *CYP2D6*: (CYP2D6 or 2D6 or cytochrome P4502D6) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve “full-text” and “English” literature. The following criteria were used for *CYP2C19*: (CYP2C19 or 2C19 or cytochrome P4502C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve “full-text” and “English” literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2D6* or *CYP2C19* frequency table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses).

GENES: *CYP2D6* AND *CYP2C19*

Genetic Test Interpretation

CYP2D6 and *CYP2C19* genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis. *CYP2D6* and *CYP2C19* haplotypes are assigned a star-allele (*) nomenclature to allow for the standardization of genetic polymorphism annotation (5). A complete list of *CYP2D6* and *CYP2C19* star-allele nomenclature along with the genetic variants that define each star-allele is available at <http://www.cypalleles.ki.se/cyp2d6.htm> and <http://www.cypalleles.ki.se/cyp2c19.htm>, respectively. Information regarding *CYP2D6* or *CYP2C19* haplotypes (star-alleles) is also available at PharmGKB (www.pharmgkb.org). Knowing which SNPs 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 the reported star-allele result.

Reference laboratories usually report a diplotype, which is the summary of inherited maternal and paternal star-alleles (e.g. *CYP2C19**1/*2, where an individual inherited a *1 allele and a *2 allele). Commonly reported *CYP2D6* and *CYP2C19* star-alleles are categorized into functional groups (e.g., normal function, decreased function, or no function) based on the predicted activity of the encoded enzyme (**Supplementary Tables S2 and S5**). The predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype. *CYP2D6* and *CYP2C19* phenotype-predicting tools, such as pharmacogenetic translation tables, are being developed by CPIC and can be accessed at www.pharmgkb.org. Hicks *et al.* describes the development of the *CYP2D6* translation table (6).

Calculating CYP2D6 Activity Score. Gaedigk *et al.* developed a scoring system to provide a uniform approach to assigning a predicted *CYP2D6* phenotype (7). *CYP2D6* alleles are assigned an activity value as detailed in **Supplementary Table S2**. The activity value of each allele reported in the diplotype is added together to calculate the *CYP2D6* activity score. For example, to calculate the activity score of a *CYP2D6**1/*17 diplotype, the activity value of *1 (activity value = 1) and the activity value of *17 (activity value = 0.5) are totaled to provide the *CYP2D6* activity score of 1.5. Note that a value of 0.5 indicates decreased activity and not that the activity conveyed by an allele is half of that encoded by a normal function allele. For this guideline, the

CYP2D6 activity score is used to assign a predicted phenotype as follows: activity score of 0 = poor metabolizer, activity score of 0.5 = intermediate metabolizer, activity scores ranging from 1.0-2.0 = extensive metabolizer, and activity score greater than 2.0 = ultrarapid metabolizer. Therefore, a pharmacogenetic test result of *CYP2D6**1/*17 would result in a CYP2D6 activity score of 1.5 and a predicted phenotype of extensive metabolizer.

There is a lack of consensus in regards to whether patients with a CYP2D6 activity score of 1.0 should be assigned an extensive or intermediate phenotype (4). Pharmacokinetic data suggest that patients with an activity score of 1.0 have a higher CYP2D6 metabolic capacity compared to patients with an activity score of 0.5, but less CYP2D6 enzyme activity compared to patients with an activity score of 2.0 (7, 8). Herein, we classified patients with a CYP2D6 activity score of 1.0 as extensive metabolizers, which is consistent with the CPIC guidelines for codeine and the tricyclic antidepressants (7, 9).

CYP2D6 Copy Number Variants. Because *CYP2D6* is subject to copy number variation (gene duplications, multiplications, or deletions), clinical laboratories may report gene copy number if directly tested. Most patients will have a normal copy number of 2, with one allele inherited maternally and one allele inherited paternally. When two *CYP2D6* gene copies are present, the diplotype may be reported as follows: *CYP2D6**1/*1 or *CYP2D6* (*1/*1)2N, where “2” represents copy number. A copy number of “1” indicates the presence of a *CYP2D6* gene deletion (the presence of a single gene), and a copy number of “0” indicates both *CYP2D6* genes are deleted. *CYP2D6* gene deletions are indicated by the *CYP2D6**5 allele. A gene deletion that is present on one chromosome may be reported as follows: *CYP2D6**2/*5 or *CYP2D6* (*2/*2)1N, where “1” represents copy number and the *CYP2D6**5 allele is inferred. Typically, clinical laboratories will report a homozygous gene deletion as *CYP2D6**5/*5 or *CYP2D6* (*5/*5)0N.

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 “3” represents copy number. A clinical laboratory may not report an exact copy number, but rather indicate that additional copies of the *CYP2D6* gene are present (e.g., *CYP2D6**1/*2 duplication or *CYP2D6* (*1/*2)*x*N). In instances where a duplication/multiplication is present and the exact copy number is not reported, most patients will likely have a *CYP2D6* copy number of 3. However, individuals carrying as many as 13

CYP2D6 copies have been reported (10). Clinical laboratories typically do not determine which allele is duplicated, therefore when calculating *CYP2D6* activity score the duplication must be considered for each allele reported in the diplotype (11). For example, a genotype result of *CYP2D6* (*1/*4)_{3N} indicates a patient has three copies of the *CYP2D6* gene, with either two copies of the *CYP2D6**1 allele and one copy of the *CYP2D6**4 allele, or one copy of the *CYP2D6**1 allele and two copies of the *CYP2D6**4 allele. If the *CYP2D6**1 allele carries the duplication the *CYP2D6* activity score of this diplotype will be 2, whereas if the *CYP2D6**4 allele carries the duplication, the activity score will be 1. Likewise, if the number of gene copies is not determined and it remains unknown which allele carries the duplication/multiplication, a *CYP2D6* (*4/*9)_{xN} genotype can be consistent with an IM (intermediate metabolizer) phenotype (*CYP2D6**4_{xN}/*9; activity score of 0.5) or an EM (extensive metabolizer) phenotype (*CYP2D6**4/*9_{xN} assuming that *xN* does not exceed four copies in which case the activity score is 1 for *xN*=2, 1.5 for *xN*=3 and 2 for *xN*=4). As these examples illustrate, phenotype prediction will be considerably more accurate if testing determines which allele carries the duplication/multiplication and determines the number of gene copies present. Studies have been published describing the translation of *CYP2D6* genotypes into predicted phenotypes when gene duplications or multiplications are present (2, 7, 11, 12).

Note that 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 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.

Limitations of the Star (*) Nomenclature and Allele Assignments. The star (*) nomenclature has defined multiple subvariants for an allele (e.g. *CYP2D6**2 and *4), but generally, these are not distinguished by current testing. This is of no consequence for *CYP2D6**4, because all *4 subvariants share 1846G>A causing aberrant splicing and absence of functional protein. For *CYP2D6**2, however, it is uncertain whether any of the sequence variations defining the suballeles convey a functional consequence. Also, there is no, or little, information regarding their frequencies because test laboratories do not discriminate the suballeles. In addition, there are numerous known variants and subvariants of uncertain function that have not been designated by the nomenclature committee.

It also needs to be realized that the accuracy of a genotype test depends on the number of sequence variations/allelic variants tested. If no variation is found, a *CYP2D6*1* will be the ‘default’ assignment. Depending on which sequence variations are found, the default assignment will be *CYP2D6*2* (or other). For example, if 2850C>T is present, but 1023C>T is not, the default assignment is *CYP2D6*2*. Also see ‘CYP2D6 Other Considerations’ below.

Recent findings indicate that a SNP in a distal enhancer region impacts allele activity on the transcriptional level (13, 14). It is not fully understood on which allelic variants this enhancer SNP is located. Emerging knowledge, however, suggests that a portion of *CYP2D6*2* alleles carrying the enhancer SNP convey normal activity while others lacking the enhancer SNP have reduced activity; the effect of the enhancer SNP in other haplotypes remains unknown. Presence or absence of the enhancer SNP likely also impacts the activity encoded by *CYP2D6*2xN* (duplications and multiplications). This SNP is, however, not included in current test panels. The activity score will be updated, if warranted, as new information becomes available.

CYP2C19 predicted phenotype. The predicted phenotype for a patient carrying the *CYP2C19*17* increased function allele in combination with a no function allele (e.g., *CYP2C19*2*) is less clear. Limited data suggest that *CYP2C19*17* may not compensate for the *CYP2C19*2* allele (15, 16). Herein, we classified carriers of the *CYP2C19*17* allele in combination with a no function allele as intermediate metabolizers, which is consistent with the CPIC guidelines for *CYP2C19* and clopidogrel (3).

Limited data are available to assess the predicted phenotypes for rare *CYP2C19* diplotype combinations that include *CYP2C19* alleles with decreased function and that have low frequencies in the general population (e.g., **9*, **10*). Therefore, for the purpose of this guideline the following assignments have been proposed: patients with two decreased function alleles OR patients with one normal/increased function allele AND one decreased function allele are categorized as “likely intermediate metabolizers” (e.g., *CYP2C19*1/*9*, **9/*9*, **9/*17*) and patients with one decreased function allele and one no function allele are categorized as “likely poor metabolizers” (e.g., *CYP2C19*2/*9*). For many rare alleles, no information regarding enzyme activity is currently available, and those with functional data have only been determined by in vitro studies. Consequently, the proposed “likely intermediate” and “likely poor” metabolizer assignments were developed for diplotypes that contain one allele with an established effect on enzyme activity and a second allele with limited or no available activity

data. The diplotypes in these new categories may be revised as new data become available, which will be updated on PharmGKB (www.pharmgkb.org) as needed.

Available Genetic Test Options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at <http://www.pharmgkb.org> or the Genetic Testing Registry (<http://www.ncbi.nlm.nih.gov/gtr/>) (17). The American College of Medical Genetics and Genomics (ACMG) established guidelines for laboratory testing of *CYP2D6* in relation to tamoxifen therapy (18).

Clinical laboratories may analyze for different SNPs or other genetic variants, which are dependent on the genotyping platforms used and may affect the reported diplotype leading to discrepant results between methodologies. Additionally, laboratories may differ in how *CYP2D6* copy number variants are reported, which can potentially affect phenotype prediction. Therefore, it is important to not only know the alleles interrogated by each laboratory, but also which sequence variants (e.g., SNPs, insertions, or deletions) are tested and how copy number variants are reported. Clinical laboratories commonly give an interpretation of the genotype result and provide a predicted phenotype. Phenotype assignment for this guideline is defined in the main manuscript and supplementary data, but may differ from some clinical laboratory interpretations. Any *CYP2D6* or *CYP2C19* genotyping results used to guide patient pharmacotherapy and/or deposited into patient medical records should be derived from validated genotyping platforms in clinical laboratories that implement the appropriate regulatory standards and best practices (e.g., CAP, CLIA).

Incidental Findings

A concern about genetic testing in clinical settings is that an individual's genotype may be predictive of an unrelated disease risk; however, variants in pharmacogenes have not been strongly associated with disease risk. A large candidate gene association study has identified a correlation between *CYP2C19* no function alleles (e.g., *CYP2C19**2) and lower depressive symptoms in European twins (19). A subsequent study of transgenic mice suggested that *CYP2C19* overexpression in the brain was associated with reduced hippocampal volume and behavioral markers of anxiety (20). *CYP2D6* has been investigated in candidate gene studies of depression as well as personality traits (21-33). Although some nominal associations were

identified, *CYP2D6* genetic variants are not currently considered to be predictive of depression or personality traits. Notably, a recent mega-analysis of genome wide association studies for major depressive disorder did not identify any significant association between depression risk and *CYP2C19* or *CYP2D6* (34). Small isolated studies on cancer susceptibility have been reported for *CYP2C19* and *CYP2D6*, yet neither gene is currently considered to be significantly predictive of cancer risk (35, 36).

Other Considerations

Vortioxetine and vilazodone are newer drugs that inhibit serotonin reuptake, although both drugs also have other pharmacological properties. Vortioxetine is extensively metabolized by *CYP2D6*. The FDA recommends that the vortioxetine dose should be reduced by 50% in *CYP2D6* poor metabolizers with a maximum recommended dose of 10 mg daily. Vilazodone is only minimally metabolized by *CYP2D6* or *CYP2C19*.

CYP2D6 Other Considerations

There are several factors that cause potential uncertainty in *CYP2D6* genotyping results and phenotype predictions as follows: **1)** Because it is currently impractical to test for every variation in the *CYP2D6* gene, genotyping assays may not detect rare or *de novo* variants resulting in patients being assigned a default genotype. Depending on the sequence variants (or alleles present) in a given patient, the default genotype may be *CYP2D6**1/*1 (or wild-type) or another diplotype. If the rare or *de novo* variant adversely affects *CYP2D6* enzyme function, then the patient's actual phenotype may differ from the predicted phenotype. **2)** Sub-alleles of *CYP2D6**4 and other star-alleles have been identified that harbor additional SNPs with limited or no added functional consequence (e.g., *CYP2D6**4A, *4B, *4C, and *4D). Therefore, only analyzing for the defining *CYP2D6**4 SNPs (100C>T and 1846G>A) is usually sufficient to determine a *CYP2D6* phenotype. **3)** There are multiple gene units involved in duplication and other major rearrangements. Additionally, rearranged gene structures involving *CYP2D7*-derived sequences may be misinterpreted as functional duplications (37). If the specific gene units involved in the duplication or other rearrangements are not specifically tested for, the phenotype prediction may be inaccurate and *CYP2D6* activity over-estimated. **4)** Alleles are typically assigned based on the most likely scenario of SNP linkage. For example, the vast majority of *CYP2D6**4 alleles carry two 'key' SNPs, 100C>T and 1846G>A (as noted above). If a patient is heterozygous for these

two SNPs, a *CYP2D6**1/*4 is typically assigned. However, the rare *CYP2D6**4*M* subvariant does not carry 100C>T, which in isolation defines the *10 reduced function allele. Therefore, a *CYP2D6**4*M*/*10 assignment constitutes a valid, albeit unlikely, diplotype assignment. Taking the presence or absence of additional SNPs into consideration can distinguish the two possibilities. As such, to unequivocally assign *CYP2D6* alleles/haplotypes, testing for multiple SNPs or full gene sequencing may be required. **5)** The majority of laboratories assign the most likely diplotype and do not provide information regarding alternate diplotypes; if laboratories report alternate diplotypes, it may not be accompanied by information regarding the probability of the patient having the alternate diplotype. **6)** Allele frequencies vary considerably among individuals of different ethnic backgrounds. For instance, *CYP2D6**10 is common in Asian populations while *CYP2D6**17 is common in people of Sub-Saharan African ancestry. These alleles, however, have a considerably lower prevalence in other ethnic groups such as Caucasians of European ancestry. Moreover, *CYP2D6**14*A* is present in Asian populations and the SNP defining this allele (1758G>A) is typically incorporated into Asian genotyping panels (38). Thus, the alleles that should be tested for a given population may vary considerably. **7)** Certain alleles carry genes in tandem arrangements. One such example is *CYP2D6**36+*10 (one copy of the non-functional *CYP2D6**36 and one copy of the reduced function *CYP2D6**10). This tandem can be found in Asians and is typically reported as a default assignment of *CYP2D6**10 due to the limitations of common genotyping assays. The complexities of *CYP2D6* gene analysis, interpretation, and phenotype assignment are summarized by Hicks *et al.* and Gaedigk (9, 39).

CYP2C19 Other Consideration

There are several factors to consider when genotyping *CYP2C19*. Some of these factors may cause potential uncertainty in *CYP2C19* genotyping results and phenotype predictions and are listed as follows: **1)** *CYP2C19**2 is the most common no function allele. Subvariants of *CYP2C19**2 have been identified that harbor additional SNPs with limited or no added functional consequence (e.g., *CYP2C19**2*A*, *2*B*, *2*C*, and *2*D*). Therefore, only analyzing for the defining *CYP2C19**2 SNP (c.681G>A) is considered sufficient to determine a *CYP2C19* phenotype. **2)** Because it is currently impractical to test for every variant in the *CYP2C19* gene, genotyping assays do not typically interrogate rare or novel variants. Depending on the sequence variants (or alleles present) in a given patient, the default genotype may be *CYP2C19**1/*1 (or wild-type) or another diplotype. If the rare or novel variant adversely affects *CYP2C19* enzyme

function, then the patient's actual phenotype may differ from the predicted phenotype. **3)** *CYP2C19* allele frequencies vary considerably among individuals of different ethnic backgrounds. For example, *CYP2C19**3 has a low prevalence among most ethnic groups, but has an allele frequency of approximately 15% in some Asian populations (**Supplemental Table S6**) (1). Thus, the alleles that should be tested for a given population may vary. For Asian populations, *CYP2C19**3 should be included in *CYP2C19* genotyping panels. **4)** The SNP defining the no function *CYP2C19**4 allele (c.1A>G; rs28399504) has been found in linkage with the SNP defining the *CYP2C19**17 allele (c.-806C>T; rs12248560). This haplotype is designated *CYP2C19**4B and may occur more frequently in certain ethnic groups, in particular the Ashkenazi Jewish population (1, 40, 41). *CYP2C19**17 is an increased function allele, while *CYP2C19**4B is a no function allele. Testing for *CYP2C19**4 in addition to *CYP2C19**17 may improve CYP2C19 phenotype prediction accuracy. It is noted that discrimination between *CYP2C19**4A/*17 and *1/*4B requires additional testing to determine the phase of the variants (i.e., in *cis* or *trans*) in addition to genotyping for both c.-806C>T and 1A>G (42). **5)** A recent study identified a novel allelic variant that carries the *CYP2C19**17-defining increased activity - 806C>T SNP, but also a nonsynonymous SNP, c.463G>T, that introduces a premature stop codon (p.E155X) (41). While this SNP appears to be rare, it may lead to considerable overestimation of activity in *CYP2C19**17 carriers if not interrogated. **6)** Certain genotyping platforms (e.g., Affymetrix DMET) analyze over 15 *CYP2C19* star-alleles, some of which are rare and not well characterized. Therefore, uncertainty exists when translating a genotype result into a predicted CYP2C19 phenotype in instances where a patient is found to carry a poorly characterized allele. Polyphen-2 and Sorting Tolerant From Intolerant (SIFT) algorithms computationally predict the effect of these rare and poorly characterized alleles on CYP2C19 enzymatic function (3, 43). These data may assist in diplotype interpretation in instances where a poorly characterized allele is reported, but these methods are not a substitute for *in vitro* and *in vivo* analyses.

This guideline as well as those previously published for clopidogrel and tricyclic antidepressants (3, 44) define CYP2C19 ultrarapid metabolizers as those who carry one *CYP2C19**17 allele in combination with a normal function *CYP2C19**1 allele or those who are homozygous for *CYP2C19**17. The decision to define ultrarapid metabolizers in this manner is largely based on pharmacokinetic data that show separation between *CYP2C19**17 carriers from *CYP2C19**1/*1 homozygotes (45, 46). Whether this definition of ultrarapid metabolizer is

appropriate for all CYP2C19 substrates requires further study and may depend on the impact of other metabolic pathways important for each drug. Though statistical separation in mean pharmacokinetic parameters between *CYP2C19*17* carriers and *CYP2C19*1* homozygotes has been observed, the range of pharmacokinetic data between these two genotypes often overlaps (47). Additionally, the magnitude of effect of the *CYP2C19*17* allele has been argued to be less than that observed in the opposite direction by *CYP2C19*2* or **3* alleles (47).

DRUGS: SSRIs

Background

Fluoxetine biotransformation is complex as this drug is metabolized extensively by CYP2D6 and CYP2C9 (**Supplemental Figure S1**) (48). Fluoxetine is a racemic drug that is composed of both R and S enantiomers. CYP2D6 is thought to be the major pathway for converting S-fluoxetine to S-norfluoxetine, while CYP2D6 and CYP2C9 extensively convert R-fluoxetine to R-norfluoxetine. R/S-fluoxetine and S-norfluoxetine have equal serotonin reuptake inhibition activity, but R-norfluoxetine is approximately 20 times less potent (49, 50). Although *CYP2D6* genetic variants may influence fluoxetine and S-norfluoxetine concentrations (**Supplemental Table S10**), total plasma concentrations of R/S-fluoxetine plus R/S-norfluoxetine may not vary significantly (49, 51-53). R/S-norfluoxetine has a long half-life and may take several weeks or months to reach steady-state. Limited studies have taken into consideration the long half-life of norfluoxetine. Therefore, it is unclear if an imbalance between R-fluoxetine, S-fluoxetine, R-norfluoxetine, and S-norfluoxetine concentrations caused by *CYP2D6* genetic variants would influence therapy outcomes.

Pediatric Studies

The effect of *CYP2D6* and *CYP2C9* genotypes on steady state concentrations of fluoxetine was investigated in 83 children between 10 and 17 years of age (54). Genotype analysis was limited to *CYP2D6*3*, **4*, **5* and **6* alleles along with the *xN* multiplication event. Three phenotype groups (poor/intermediate, extensive and ultrarapid metabolizers) were defined based on the number of *CYP2D6* functional alleles. Dose-normalized plasma concentrations of R/S-fluoxetine, S-norfluoxetine or total active moieties (R/S-fluoxetine + S-norfluoxetine) were reported to vary 30 to 160-fold. The R/S-fluoxetine to S-norfluoxetine ratio decreased with increasing numbers of functional *CYP2D6* alleles ($p < 0.001$), but no statistically significant

difference in total active moieties was observed across the three phenotype groups after 8 or 12 weeks of treatment. It is important to note that the study included only one poor metabolizer, which was grouped with intermediate metabolizers. The interquartile plasma concentrations for R/S-fluoxetine or S-norfluoxetine in the extensive metabolizer group overlapped the interquartile plasma concentration ranges of the poor/intermediate metabolizer group. There was no effect of *CYP2C9* genotype on steady state R/S-fluoxetine concentrations. Thus, it is reasonable to conclude from this study that steady state fluoxetine concentrations are highly variable for children 10 years of age and older, and median concentrations are comparable in patients with at least one functional *CYP2D6* allele.

For paroxetine, *CYP2D6* genotyping (> 20 allelic variants plus duplication events) was conducted as part of a dose escalation study in 27 children ranging in age from 8-11 years and 35 adolescents ranging in age from 12-17 years. Following administration of paroxetine 10 mg daily for two weeks, weight-normalized apparent oral clearance at steady state was lowest in poor metabolizer subjects (n=3 adolescents), and increased as the number of functional *CYP2D6* alleles increased. However, differences in oral clearance between the genotype groups became less apparent as the paroxetine dose increased to 20 mg per day, and no difference between genotype groups at 30 mg per day. With chronic dosing there was a progressive loss of *CYP2D6* activity such that genotype-dependent dose-exposure relationships observed at low doses were lost, and apparent oral clearance values in poor metabolizers and extensive metabolizers were similar (55).

CYP2C19 genotyping was conducted in a study investigating citalopram and metabolite concentrations at steady state in 19 adolescents, two-thirds of which were >18 years of age. Dose-corrected steady state concentrations of S- and R-citalopram and S/R ratios for patients with *CYP2C19**1/*2 genotypes (n=3) were similar to those with *CYP2C19**1/*1 genotypes (56).

Other Considerations

The inhibition of *CYP2D6* does not have an impact on those predicted to be poor metabolizers because activity cannot be further reduced (57). The clinical impact of paroxetine auto-inhibition in those who are predicted to be *CYP2D6* ultrarapid, extensive or intermediate metabolizers is not fully understood. Low or undetectable paroxetine concentrations have been observed in *CYP2D6* ultrarapid metabolizers (**Supplemental Table S8**) signifying that those individuals may not undergo phenoconversion (from ultrarapid to poor metabolizers) to a great

extent (57-59). Paroxetine drug exposure at steady state has also been observed to vary significantly between CYP2D6 phenotype groups (**Supplemental Table S8**). In contrast, some studies found that chronically administered paroxetine caused progressive loss of CYP2D6 activity resulting in oral clearance values that were similar among the phenotype groups (**Supplemental Table S8**). Higher doses of paroxetine (e.g., paroxetine 30 mg) were associated with greater CYP2D6 inhibition. Therefore, paroxetine-induced phenoconversion (from extensive to lower metabolism due to auto-inhibition) may be dose-dependent.

Other pharmacogenetic clinical guidelines and reviews exist for SSRIs. In 2007, the Duke Evidence-based Practice Center published a review of the literature and concluded that prospective studies of CYP450 genotyping in the treatment with SSRIs need to be performed to examine the utility of genotyping in clinical practice (60). In 2011, the Dutch Pharmacogenetics Working Group published pharmacogenetics-based therapeutic recommendations including recommendations for paroxetine, citalopram/escitalopram, and sertraline (61). The enclosed CPIC recommendations also reflect new literature since 2011 (through December 2014).

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Supplemental Tables S7-S11** is graded (62) on a scale of high, moderate, and weak, based upon the level of evidence:

High: Evidence includes consistent results from well-designed, well-conducted studies.

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.

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.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations (**Main manuscript Table 2**).

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighting 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 that are taken into account in evaluating the evidence supporting therapeutic recommendations include: in vivo pharmacokinetic and pharmacodynamic data, in vitro enzyme activity of tissues expressing wild-type or variant-containing CYP2D6 or CYP2C19, in vitro CYP2D6 or CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2D6* or *CYP2C19* genotypes, and in vivo pre-clinical and clinical pharmacokinetic and pharmacodynamic studies. The gene-based dosing recommendations in this guideline takes into consideration the affects *CYP2D6* or *CYP2C19* genetic variants may have on both clinical outcomes and SSRIs. Because the pharmacokinetic properties of SSRIs do not differ between healthy volunteers and patients, we evaluated pharmacokinetic data acquired from studies performed on healthy subjects and patients to assist us in determining if *CYP2D6* or *CYP2C19* genetic variants affect SSRIs.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (63): 'strong', where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; 'moderate', in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and 'optional', in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

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 (64-68). Supplementary material (**Supplemental Tables S12-S16** and **Figures S2** and **S3**) provides resources to support the adoption of CPIC guidelines within an EHR (69). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to

synthesize foundational knowledge that provides a common starting point for incorporating *CYP2D6* and/or *CYP2C19* genotype results in an EHR to guide SSRI dosing.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (6). 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 (70, 71). 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. 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. Guidance to achieve these objectives is provided in diagrams that illustrate how *CYP2D6* and/or *CYP2C19* pharmacogenetic test results could be entered into an EHR (**Supplemental Figure S2**) and be used for point-of-care CDS (**Supplemental Figure S3**). **Supplemental Tables S12 and S13** provide a reference to widely used nomenclature systems for the drugs and genes, respectively, relevant to this CPIC guideline.

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 phenotype (**Table 1, main manuscript**). **Supplemental Tables S14 and S15** further translate results into a coded diplotype/phenotype summary, priority result notification, and sample interpretative result text. Finally, sample point-of-care alert text that corresponds to the workflow described in **Supplemental Figure S3** is provided in **Supplemental Table S16**.

SUPPLEMENTAL TABLE S1. GENOTYPES THAT CONSTITUTE THE * ALLELES FOR CYP2D6 AND THEIR EFFECT ON CYP2D6 PROTEIN

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*1A^d	-	-	-
*1B	3828G>A	rs28371732	-
*1C	1978C>T	rs150163869	-
*1D	2575C>A	[rs28371718] ^j	-
*1E	1869T>C	rs111606937	-
*1xN	Gene duplication or multiplication		
*2A^e	-1584C>G -1235A>G -740C>T -678G>A CYP2D7 gene conversion in intron 1 1661G>C 2850C>T 4180G>C ^f	rs1080985 rs28735595 rs28624811 rs28633410 - rs1058164 rs16947 rs1135840	- - - - - - R296C S486T
*2B^{e,g}	1039C>T 1661G>C 2850C>T 4180G>C ^f	rs1081003 rs1058164 rs16947 rs1135840	- - R296C S486T
*2C^e	1661G>C 2470T>C 2850C>T 4180G>C ^f	rs1058164 - rs16947 rs1135840	- - R296C S486T
*2D^e	2850C>T 4180G>C ^f	rs16947 rs1135840	R296C S486T
*2E^e	997C>G 1661G>C 2850C>T 4180G>C ^f	rs28371705 rs1058164 rs16947 rs1135840	- - R296C S486T
*2F^e	1661G>C 1724C>T 2850C>T 4180G>C ^f	rs1058164 rs74962936 rs16947 rs1135840	- - R296C S486T
*2G^e	1661G>C 2470T>C 2575C>A 2850C>T 4180G>C ^f	rs1058164 - rs28371718 ^j rs16947 rs1135840	- - - R296C S486T

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*2H^e	1661G>C 2480C>T 2850C>T 4180G>C ^f	rs1058164 rs267608298 rs16947 rs1135840	- - R296C S486T
*2K^e	1661G>C 2850C>T 4115C>T 4180G>C ^f	rs1058164 rs16947 rs150445731 rs1135840	- R296C - S486T
*2L^e	-1298G>A -1235A>G -740C>T 310G>T 746C>G 843T>G 1513C>T 1661G>C 1757C>T 2850C>T 3384A>C 3584G>A 3790C>T 4180G>C ^f	rs59099247 rs28735595 rs28624811 rs28371699 rs28371701 - rs67497403 rs1058164 rs199849357 rs16947 rs1985842 rs28371730 rs116917064 rs1135840	- - - - - - - - - R296C - - - S486T
*2M^e	Variable number of A's in the region - 1258 to -1237 -1235A>G -750_-749delGA>del -740C>T -678G>A <i>CYP2D7</i> gene conversion in intron 1 310G>T 746C>G 843T>G 1661G>C 2850C>T 3384A>C 3584G>A 3790C>T 4180G>C ^f 4481G>A	- rs28735595 - rs28624811 rs28633410 - rs28371699 rs28371701 - rs1058164 rs16947 rs1985842 rs28371730 rs116917064 rs1135840 rs116390392	- - - - - - - - - - R296C - - - S486T -
*2xN	Gene duplication or multiplication		
*3A	2549A>del	rs35742686	Frameshift
*3B	1749A>G 2549A>del	rs1135824 rs35742686	N166D Frameshift

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*4A	100C>T 974C>A 984A>G 997C>G 1661G>C 1846G>A 4180G>C ^f	rs1065852 rs28371703 rs28371704 rs28371705 rs1058164 rs3892097 rs1135840	P34S L91M H94R - - Splicing defect [S486T]
*4B	100C>T 974C>A 984A>G 997C>G 1846G>A 4180G>C ^f	rs1065852 rs28371703 rs28371704 rs28371705 rs3892097 rs1135840	P34S L91M H94R - Splicing defect [S486T]
*4C	100C>T 1661G>C 1846G>A 3887T>C 4180G>C ^f	rs1065852 rs1058164 rs3892097 [rs72549345] ⁱ rs1135840	P34S - Splicing defect [L421P] [S486T]
*4D	100C>T 1039C>T 1661G>C 1846G>A 4180G>C ^f	rs1065852 rs1081003 rs1058164 rs3892097 rs1135840	P34S - - Splicing defect [S486T]
*4E	100C>T 1661G>C 1846G>A 4180G>C ^f	rs1065852 rs1058164 rs3892097 rs1135840	P34S - Splicing defect [S486T]
*4F	100C>T 974C>A 984A>G 997C>G 1661G>C 1846G>A 1858C>T 4180G>C ^f	rs1065852 rs28371703 rs28371704 rs28371705 rs1058164 rs3892097 rs370249680 rs1135840	P34S L91M H94R - - Splicing defect [R173C] [S486T]
*4G	100C>T 974C>A 984A>G 997C>G 1661G>C 1846G>A 2938C>T 4180G>C ^f	rs1065852 rs28371703 rs28371704 rs28371705 rs1058164 rs3892097 rs140513104 rs1135840	P34S L91M H94R - - Splicing defect [P325L] [S486T]

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*4H	100C>T 974C>A 984A>G 997C>G 1661G>C 1846G>A 3877G>C 4180G>C ^f	rs1065852 rs28371703 rs28371704 rs28371705 rs1058164 rs3892097 - rs1135840	P34S L91M H94R - - Splicing defect [E418Q] [S486T]
*4J	100C>T 974C>A 984A>G 997C>G 1661G>C 1846G>A	rs1065852 rs28371703 rs28371704 rs28371705 rs1058164 rs3892097	P34S L91M H94R - - Splicing defect
*4K	100C>T 1661G>C 1846G>A 2850C>T 4180G>C ^f	rs1065852 rs1058164 rs3892097 rs16947 rs1135840	P34S - Splicing defect [R296C] [S486T]
*4L	100C>T 997C>G 1661G>C 1846G>A 4180G>C ^f	rs1065852 rs28371705 rs1058164 rs3892097 rs1135840	P34S - - Splicing defect [S486T]
*4M	-1235A>G 746C>G 843T>G 974C>A 984A>G 997C>G 1661G>C 1846G>A 2097A>G 3384A>C 3582A>G 4401C>T	rs28735595 rs28371701 - rs28371703 rs28371704 rs28371705 rs1058164 rs3892097 [rs58440431] ^j rs1985842 rs2004511 rs28371738	- - - L91M H94R - - Splicing defect - - - -

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*4N	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	974C>A	rs28371703	L91M
	984A>G	rs28371704	H94R
	997C>G	rs28371705	-
	1661G>C	rs1058164	-
	1846G>A	rs3892097	Splicing defect
	2097A>G	[rs58440431] ^j	-
	3384A>C	rs1985842	-
	3582A>G	rs2004511	-
	gene conversion to <i>CYP2D7</i> in exon 9	-	-
	4180G>C ^f	rs1135840	[S486T]
	4401C>T	rs28371738	-
*4P	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	974C>A	rs28371703	L91M
	984A>G	rs28371704	H94R
	997C>G	rs28371705	-
	1661G>C	rs1058164	-
	1846G>A	rs3892097	Splicing defect
	2097A>G	[rs58440431] ^j	-
	2576C>T	-	[P268S]
	3384A>C	rs1985842	-
	3435C>A	rs28371729	-
	3582A>G	rs2004511	-
	4180G>C ^f	rs1135840	[S486T]
	4401C>T	rs28371738	-
*4xN	Gene duplication or multiplication		
*5	Gene deletion	N/A	Gene deletion
*6A	1707T>del	rs5030655	Frameshift
*6B	1707T>del 1976G>A	rs5030655 rs139779104	Frameshift [G212E]

Allele^a	Major Nucleotide Variation^b	dbSNP Number^c	Effect on CYP2D6 Protein
*6C	1707T>del 1976G>A 4180G>C ^f	rs5030655 rs139779104 rs1135840	Frameshift [G212E] [S486T]
*6D	1707T>del 3288G>A	rs5030655 rs150552908	Frameshift [G373S]
*6xN	Gene duplication or multiplication ^k		
*7	2935A>C	rs5030867	H324P
*8	1661G>C 1758G>T 2850C>T 4180G>C ^f	rs1058164 - rs16947 rs1135840	- G169X [R296C] [S486T]
*9	2615delAAG	rs5030656	K281 deletion
*9xN	Gene duplication or multiplication		
*10A	100C>T 1661G>C 4180G>C ^f	rs1065852 rs1058164 rs1135840	P34S - S486T
*10B	-1426C>T Variable number of A's in the region - 1258 to -1237 -1235A>G -1000G>A 100C>T 1039C>T 1661G>C 4180G>C ^f	rs28588594 - rs28735595 rs1080989 rs1065852 rs1081003 rs1058164 rs1135840	- - - - P34S - - S486T
*10D	100C>T 1039C>T 1661G>C 4180G>C ^f CYP2D7-like 3'-flanking region	rs1065852 rs1081003 rs1058164 rs1135840 -	P34S - - S486T -
*10xN	Gene duplication or multiplication		
*11	883G>C 1661G>C 2850C>T 4180G>C ^f	rs201377835 rs1058164 rs16947 rs1135840	Splicing defect - [R296C] [S486T]
*12	124G>A 1661G>C 2850C>T 4180G>C ^f	rs5030862 rs1058164 rs16947 rs1135840	G42R - R296C S486T

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*13	<i>CYP2D6</i> *13 alleles share a <i>CYP2D7/2D6</i> hybrid gene structure, with <i>CYP2D7</i> sequence in exon 1 leading to an insertion (137_138insT) and frameshift of the open reading frame.	-	Frameshift
*14A	100C>T 1758G>A 2850C>T 4180G>C ^f	rs1065852 rs5030865 rs16947 rs1135840	P34S G169R R296C S486T
*14B	intron 1 conversion with <i>CYP2D7</i> (214-245) 1661G>C 1758G>A 2850C>T 4180G>C ^f	- rs1058164 rs5030865 rs16947 rs1135840	- - G169R R296C S486T
*15	137_138insT	-	Frameshift
*16	See <i>CYP2D6</i> *13		
*17	1023C>T 1661G>C 2850C>T 4180G>C ^f	rs28371706 rs1058164 rs16947 rs1135840	T107I - R296C S486T
*17xN	Gene duplication or multiplication		
*18	4125_4133dupGTGCCCACT	-	468_470dupVPT
*19	1661G>C 2539_2542AACT>del 2850C>T 4180G>C ^f	rs1058164 [rs72549353] ⁱ rs16947 rs1135840	- Frameshift R296C S486T
*20	1661G>C 1973_1974insG 1978C>T 1979T>C 2850C>T 4180G>C ^f	rs1058164 rs72549354 rs150163869 rs199535154 rs16947 rs1135840	- Frameshift - [L213P] [R296C] [S486T]

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*21A	-1584C>G	rs1080985	-
	-1426C>T	rs28588594	-
	Variable number of A's in the region - 1258 to -1237	-	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	-678G>A	rs28633410	-
	-629A>G	-	-
	partial intron 1 conversion with <i>CYP2D7</i> (214-227)	-	-
	310G>T	rs28371699	-
	601delC	-	-
	1661G>C	rs1058164	-
	2573_2574insC	rs267608296	Frameshift [R296C]
	2850C>T	rs16947	-
	3584G>A	rs28371730	-
	4180G>C ^f	rs1135840	[S486T]
*21B	-1584C>G	rs1080985	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	-678G>A	rs28633410	-
	intron 1 conversion with <i>CYP2D7</i> (214-245)	-	-
	1661G>C	rs1058164	-
	2573_2574insC	rs267608296	Frameshift [R296C]
	2850C>T	rs16947	[S486T]
	4180G>C ^f	rs1135840	
*22	82C>T	rs138100349	R28C
*23	957C>T	rs267608310	A85V
*24	2853A>C	-	I297L
*25	3198C>G	rs267608295	R343G
*26	3277T>C	-	I369T
*27	3853G>A	[rs61737947] ⁱ	E410K
*28	19G>A	rs72549358	V7M
	1661G>C	rs1058164	-
	1704C>G	rs78482768	Q151E
	2850C>T	rs16947	R296C
	4180G>C ^f	rs1135840	S486T

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
29	1659G>A; 1661G>C 2850C>T 3183G>A 4180G>C ^f	rs61736512 (*for V136M; combined with 1661G>C to V136I) rs16947 rs59421388 rs1135840	V136I R296C V338M S486T
*29xN	Gene duplication or multiplication		
*30	1661G>C 1863_1864insTTTCGCCCC 2850C>T 4180G>C ^f	rs1058164 - rs16947 rs1135840	- 174_175insFRP R296C S486T
*31	-1770G>A -1584C>G -1235A>G -740C>T -678G>A <i>CYP2D7</i> gene conversion in intron 1 310G>T 746C>G 843T>G 1661G>C 2850C>T 3384A>C 3584G>A 3790C>T 4042G>A 4180G>C ^f 4481G>A	rs1080983 rs1080985 rs28735595 rs28624811 rs28633410 - rs28371699 rs28371701 - rs1058164 rs16947 rs1985842 rs28371730 rs116917064 rs267608319 rs1135840 rs116390392	- - - - - - - - - - R296C - - - - R440H S486T -
*32	1661G>C 2850C>T 3853G>A 4180G>C ^f	rs1058164 rs16947 [rs61737947] ⁱ rs1135840	- R296C E410K S486T
*33	2483G>T	rs28371717	A237S
*34	2850C>T	rs16947	R296C
*35A	-1584C>G 31G>A 1661G>C 2850C>T 4180G>C ^f	rs1080985 rs769258 rs1058164 rs16947 rs1135840	- V11M - R296C S486T

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*35B	-1584C>G	rs1080985	-
	<i>CYP2D7</i> conversion upstream of exon 1 (-225 to -431)	-	-
	31G>A	rs769258	V11M
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	4180G>C ^f	rs1135840	S486T
*35xN	Gene duplication or multiplication		
*36	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	2097A>G	[rs58440431] ^j	-
	3384A>C	rs1985842	-
	3582A>G	rs2004511	-
	gene conversion to <i>CYP2D7</i> in exon 9	-	P469A
		-	T470A
		-	H478S
		-	G479R
		-	F481V
		-	A482S
	4180G>C ^f	rs1135840	[S486T]
*36x2	Duplication or tandem		
*37	100C>T	rs1065852	P34S
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	1943G>A	[rs72549355] ⁱ	R201H
	4180G>C ^f	rs1135840	S486T
*38	2587_2590GACT>del	[rs72549351] ⁱ	Frameshift
*39	1661G>C	rs1058164	-
	4180G>C ^f	rs1135840	S486T
*40	1023C>T	rs28371706	T107I
	1661G>C	rs1058164	-
	1863_1864insTTTCGCCCCx2	-	174_175insFRPx2
	2850C>T	rs16947	[R296C]
	4180G>C ^f	rs1135840	[S486T]

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*41	-1235A>G -740C>T -678G>A <i>CYP2D7</i> gene conversion in intron 1 1661G>C 2850C>T 2988G>A 4180G>C ^f	rs28735595 rs28624811 rs28633410 - rs1058164 rs16947 rs28371725 rs1135840	- - - - - R296C Splicing S486T
*41xN	Gene duplication or multiplication ^k		
*42	1661G>C 2850C>T 3259_3260insGT 4180G>C ^f	rs1058164 rs16947 [rs72549346] ⁱ rs1135840	- R296C Frameshift [S486T]
*43	77G>A	rs28371696	R26H
*43xN	Gene duplication or multiplication ^k		
*44	82C>T 2950G>C	rs138100349 rs72549349	- Splicing defect
*45A	-1601_-1600GA>TT Variable number of A's in the region - 1258 to -1237 -1094_-1093insA -1011T>C 310G>T 746C>G 843T>G 1661G>C 1716G>A 2129A>C 2575C>A 2661G>A 2850C>T 3254T>C 3384A>C 3584G>A 3790C>T 4180G>C ^f	rs267608286 - - rs59360719 rs28371699 rs28371701 - rs1058164 rs28371710 rs267608290 [rs28371718] ^j rs76015180 rs16947 [rs28371726] ^j rs1985842 rs28371730 rs116917064 rs1135840	- - - - - - - E155K - - - R296C - - - - S486T

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*45B	-1543G>A	rs76210340	-
	-1298G>A	rs59099247	-
	-1235A>G	rs28735595	-
	-1094_-1093insA	-	-
	-740C>T	rs28624811	-
	-695_-692delTGTG	-	-
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	1661G>C	rs1058164	-
	1716G>A	rs28371710	E155K
	2575C>A	[rs28371718] ^j	-
	2661G>A	rs76015180	-
	2850C>T	rs16947	R296C
	3254T>C	[rs28371726] ^j	-
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
*45xN	Gene duplication or multiplication ^k		
*46	-1543G>A	rs76210340	-
	-1298G>A	rs59099247	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	77G>A	rs28371696	R26H
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	1661G>C	rs1058164	-
	1716G>A	rs28371710	E155K
	2575C>A	rs28371718j	-
	2661G>A	rs76015180	-
	2850C>T	rs16947	R296C
	3030G>G/A	rs267608291	-
	3254T>C	[rs28371726] ^j	-
	3384A>C	rs1985842	-
	3491G>A	rs267608292	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*47	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	73C>T	rs267608313	R25W
	100C>T	rs1065852	P34S
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	4180G>C ^f	rs1135840	S486T
*48	972C>T	rs267608309	A90V
*49	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	1039C>T	rs1081003	-
	1611T>A	rs1135822	F120I
	1661G>C	rs1058164	-
	4180G>C ^f	rs1135840	S486T
*50	1720A>C	rs267608302	E156A
*51	-1584C>G	rs1080985	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	-678G>A	rs28633410	-
	<i>CYP2D7</i> gene conversion in intron 1	-	-
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	3172A>C	[rs72549348] ⁱ	E334A
	4180G>C ^f	rs1135840	S486T
*52	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	3877G>A	rs149157808	E418K
	4180G>C ^f	rs1135840	S486T
	4401C>T	rs28371738	-
*53	1598A>G	rs267608305	-
	1611T>A	rs1135822	F120I
	1617G>T	rs1135823	A122S

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*54	100C>T	rs1065852	P34S
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	2556C>T	rs267608297	T261I
	4180G>C ^f	rs1135840	S486T
*55	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	3790C>T	rs116917064	-
	3835A>C	rs267608285	K404Q
	4180G>C ^f	rs1135840	S486T
*56A	-1584C>G	rs1080985	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	-678G>A	rs28633410	-
	<i>CYP2D7</i> gene conversion in intron 1	-	-
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	3201C>T	rs147960066	R344X
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	[S486T]
*56B	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	2097A>G	[rs58440431] ^j	-
	3201C>T	rs147960066	R344X
	3384A>C	rs1985842	-
	3582A>G	rs2004511	-
	4180G>C ^f	rs1135840	[S486T]

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*57	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	887C>T	rs267608311	R62W
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	3384A>C	rs1985842	-
	3582A>G	rs2004511	-
	gene conversion to <i>CYP2D7</i> in exon 9	-	P469A
		-	T470A
		-	H478S
		-	G479R
		-	F481V
		-	A482S
	4180G>C ^f	rs1135840	[S486T]
*58	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	<i>CYP2D7</i> gene conversion in intron 1	-	-
	310G>T	rs28371699	-
	843T>G	-	-
	1023C>T	rs28371706	T107I
	1661G>C	rs1058164	-
	1863_1864insTTTCGCCCC	-	174_175insFRP
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
*59	1661G>T	rs1058164	-
	2291G>A	rs267608300	-
	2850C>T	rs16947	R296C
	2939G>A	rs79292917	-
	4180G>C ^f	rs1135840	S486T
*60	1887insTA	-	S183X
	2303C>T	rs79738337	-
*61	3384A>C	rs1985842	-
	<i>CYP2D7</i> sequence from intron 7 onwards	-	-
*62	4044C>T	rs730882171	R441C

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*63	-1584C>G	rs1080985	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	-678G>A	rs28633410	-
	intron 1 conversion with <i>CYP2D7</i> (214-245)	-	-
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	<i>CYP2D7</i> sequence from exon 8 onwards	-	<i>CYP2D7</i> sequence
*64	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	1023C>T	rs28371706	T107I
	1661G>C	rs1058164	-
	2097A>G	[rs58440431] ^j	-
	3384A>C	rs1985842	-
	3582A>G	rs2004511	-
	4180G>C ^f	rs1135840	S486T
	4401C>T	rs28371738	-
*65	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
	4481G>A	rs116390392	-
*66	See <i>CYP2D6</i> *13		
*67	See <i>CYP2D6</i> *13		

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*68A	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	<i>CYP2D7</i> sequence from intron 1 onwards	-	<i>CYP2D7</i> sequence
*68B	Similar but not identical switch region compared to <i>CYP2D6</i> *68A		
*69	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S ^h
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	1062A>G	rs267608289	-
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	2988G>A	rs28371725	Splicing ^h
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
	4401C>T	rs28371738	-
	4481G>A	rs116390392	-
*70	-176G>A	rs1080993	-
	310G>T	rs28371699	-
	843T>G	-	-
	1608G>A	rs374616348	V119M
	1659G>A, 1661G>C	rs61736512*	V136I
		(*for V136M; combined with 1661G>C to V136I)	
	3183G>A	rs59421388	V338M
	3384A>C	rs1985842	-
	4180G>C ^f	rs1135840	S486T
*71	-1584C>G	rs1080985	-
	125G>A	rs118203758	G42E
	1494T>C	rs267608306	-

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*72	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	2097A>G	[rs58440431] ^j	-
	3318G>A	rs75386357	E383K
	3384A>C	rs1985842	-
	3582A>G	rs2004511	-
	4180G>C	rs1135840	S486T
	4401C>T	rs28371738	-
*73	-740C>T	rs28624811	-
	<i>CYP2D7</i> gene conversion intron 1 (214-245)	-	-
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	1013G>A	rs267608308	V104M
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
	4535insT	rs372465406	-
*74	974C>A	rs28371703	L91M
	3609G>T	rs267608322	-
*75	4045G>A	[rs113940699] ⁱ	R441H
*76	See <i>CYP2D6</i> *13		
*77	See <i>CYP2D6</i> *13		
*78	See <i>CYP2D6</i> *13		
*79	See <i>CYP2D6</i> *13		
*80	See <i>CYP2D6</i> *13		
*81	2579C>T	rs367543000	R269X
	2606G>A	[rs77913725] ⁱ	E278K
	2610T>A	rs201830078	M279K

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*82	<i>CYP2D7</i> gene conversion in exon 2	-	-
	974C>A	rs28371703	L91M
	984A>G	rs28371704	H94R
	997C>G	rs28371705	-
	1014T>C	rs76187628	V104A
	1022A>T; 1023C>A	-	T107Y
	1028A>G	rs78459009	I109V
	1036T>C	[rs1135821] ^j	-
*83	843T>G	-	-
	gene conversion to <i>CYP2D7</i> in exon 9	-	P469A
		-	T470A
		-	H478S
		-	G479R
		-	F481V
		-	A482S
	4180G>C ^f	rs1135840	[S486T]
*84	-1740C>T	rs58188898	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	-678A>G	rs28633410	-
	18G>A	rs148382141	-
	intron 1 conversion with <i>CYP2D7</i> (214-245)	-	-
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	1661G>C	rs1058164	-
	2574C>A	rs148769737	P267H
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3491G>A	rs267608292	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
	4481G>A	rs116390392	-

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*85	-1740C>T	rs58188898	-
	-1298G>A	rs59099247	-
	-1235A>G	rs28735595	-
	-740C>T	rs28624811	-
	102A>G	rs151226748	-
	310G>T	rs28371699	-
	607G>A	-	-
	746C>G	rs28371701	-
	843T>G	-	-
	1513C>T	rs67497403	-
	1661G>C	rs1058164	-
	2308G>A	-	-
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
	4157T>G	-	H478Q
	4180G>C ^f	rs1135840	S486T
*86	2606G>A	[rs77913725] ¹	E278K
	2610T>A	rs201830078	M279K
*87	14C>T	-	A5V
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	4180G>C ^f	rs1135840	S486T
*88	746C>G	rs28371701	-
	intron 1 conversion with <i>CYP2D7</i> (214-247)	-	-
	843T>G	-	-
	1014T>C	rs76187628	V104A
	1661G>C	rs1058164	-
	3384A>C	rs1985842	-
	3584G>A	rs28371730	-
	3790C>T	rs116917064	-
*89	4180G>C ^f	rs1135840	S486T
	1678T>C	rs375135093	L142S
*90	1693A>G	-	K147R
*91	1735G>C	-	C161S
	2850C>T	rs16947	R296C
	2988G>A	rs28371725	Splicing

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*92	1995delC	-	Frameshift
*93	2519A>C	-	T249P
*94A	100C>T 310G>T 843T>G 1039C>T 1661G>C 3181A>G 4180G>C ^f	rs1065852 rs28371699 - rs1081003 rs1058164 - rs1135840	P34S - - - - D337G S486T
*94B	100C>T 843T>G 1039C>T 1661G>C 3181A>G 3384A>C 4180G>C ^f	rs1065852 - rs1081003 rs1058164 - rs1985842 rs1135840	P34S - - - D337G - S486T
*95	100C>T 843T>G 1039C>T 1661G>C 3334G>A 3384A>C 4180G>C ^f	rs1065852 - rs1081003 rs1058164 rs77312092 rs1985842 rs1135840	P34S - - - R388H - S486T
*96	3895C>T	-	Q424X
*97	4094C>A	-	F457L
*98	746C>G 843T>G intron 1 conversion with <i>CYP2D7</i> (214-247) 1661G>C 2850C>T 3384A>C 3584G>A 3790C>T 4110C>G 4180G>C ^f	rs28371701 - - rs1058164 rs16947 rs1985842 rs28371730 rs116917064 - rs1135840	- - - - R296C - - - H463D S486T

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*100	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1109C>T	rs267608271	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	2097A>G	[rs58440431] ^j	-
	2828C>del	rs267608279	Frameshift
	3384A>C	rs1985842	-
	3582A>G	rs2004511	-
	4180G>C ^f	rs1135840	[S486T]
	4401C>T	rs28371738	-
*101	-1426C>T	rs28588594	-
	-1235A>G	rs28735595	-
	-1000G>A	rs1080989	-
	100C>T	rs1065852	P34S
	310G>T	rs28371699	-
	843T>G	-	-
	1039C>T	rs1081003	-
	1661G>C	rs1058164	-
	2097A>G	[rs58440431] ^j	-
	2927_2945GATCCTACATCCGGATGT G>del	rs730882170	Frameshift
	3384A>C	rs1985842	-
	3582A>G	rs2004511	-
	4180G>C ^f	rs1135840	[S486T]
	4401C>T	rs28371738	-
*102	Intron 1 conversion with <i>CYP2D7</i> (214- 245)	-	-
	310G>T	rs28371699	-
	972C>T	rs267608309	A90V
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
	4481G>A	rs116390392	-

Allele ^a	Major Nucleotide Variation ^b	dbSNP Number ^c	Effect on CYP2D6 Protein
*103	Intron 1 conversion with <i>CYP2D7</i> (214-245)	-	-
	310G>T	rs28371699	-
	972C>T	rs267608309	A90V
	1661G>C	rs1058164	-
	1749A>G	rs1135824	N166D
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
	4481G>A	rs116390392	-
*104	Intron 1 conversion with <i>CYP2D7</i> (214-245)	-	-
	310G>T	rs28371699	-
	843T>G	-	-
	1661G>C	rs1058164	-
	1720A>T	-	E156V
	2850C>T	rs16947	R296C
	3384A>C	rs1985842	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
	4481G>A	rs116390392	-
*105	Intron 1 conversion with <i>CYP2D7</i> (214-245)	-	-
	310G>T	rs28371699	-
	746C>G	rs28371701	-
	843T>G	-	-
	1661G>C	rs1058164	-
	2850C>T	rs16947	R296C
	3268T>C	-	F366S
	3384A>C	rs1985842	-
	3790C>T	rs116917064	-
	4180G>C ^f	rs1135840	S486T
	4481G>A	rs116390392	-

^aSee Human Cytochrome P450 Allele Nomenclature Committee website

(<http://www.cypalleles.ki.se>) for updated allele information.

^bAll coordinates refer to accession #M33388 as detailed at <http://www.cypalleles.ki.se/cyp2d6.htm>.

All variants are annotated to the negative DNA strand.

^cRefSNP accession ID number (<http://www.ncbi.nlm.nih.gov/snp/>).

^dThe *CYP2D6**1 allele is characterized by the absence of any sequence variations. Consequently, this allele cannot be identified by a SNP; rather *CYP2D6**1 is assigned by default when no SNPs are detected during testing.

^eThe *CYP2D6**2 allele is typically characterized by two amino acid changes; both, however also occur in many other *CYP2D6* alleles. Therefore, if an allele carries these two SNPs exclusively, it is designated *CYP2D6**2. Interrogating for additional SNPs is the only way to distinguish *CYP2D6**2 from other alleles (e.g., *CYP2D6**17 and *41).

^fThis SNP is present on many allelic variants including functional and non-functional variants. Specifically, it has been found on some *CYP2D6**4 subvariants. While some tests include this SNP, it cannot be utilized to identify an allelic variant with certainty.

^g*CYP2D6**2B and some other alleles have been defined based on exon sequence only. There may be additional SNPs in introns or flanking regions that are not listed.

^hBoth SNPs in concert have been shown to cause poor metabolizer status in vivo (72).

ⁱrs number has no locus information in dbSNP (dbSNP accessed January 2015).

^jrs number marked as “Suspected” by dbSNP (dbSNP accessed January 2015).

^kThese duplications have been observed (73) but are currently not listed by the nomenclature database.

SUPPLEMENTAL TABLE S2. ASSOCIATION BETWEEN ALLELIC VARIANTS^A AND CYP2D6 ENZYME ACTIVITY

Functional Status (2, 7)	Activity Value ^{c,d}	Alleles
Increased function	>1	*1xN, *2xN, *35xN, *45 ^g xN
Normal or Increased function	1 or >1 ^h	*9xN, *10xN, *17xN, *29xN, *41xN
Normal function ^b	1	*1 ^e , *2, *27, *33, *34 ^f , *35, *39 ^f , *45 ^g , *46 ^g , *48, *53
Decreased function	0.5	*9, *10, *14B, *17, *29, *41, *49, *50, *54, *55, *59, *72
No-function	0	*3, *3xN, *4, *4xN, *5, *6, *6xN, *7, *8, *11, *12, *13, *14A, *15, *18, *19, *20, *21, *31, *36, *36xN, *38, *40, *42, *44, *47, *51, *56, *57, *62, *68, *69, *92, *100, *101
Unknown	N/A	*22, *23, *24, *25, *26, *28, *30, *32, *37, *43, *43xN, *52, *58, *60, *61, *63, *64, *65, *70, *71, *73, *74, *75, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *93, *94, *95, *96, *97, *98, *102, *103, *104, *105

^aSee <http://www.cypalleles.ki.se/cyp2d6.htm> for updates on *CYP2D6* allelic variants and nomenclature.

^bAn important caveat for all genotyping tests is that the decision to assign an allele a wild-type status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. It is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation is defaulted to a functional allele assignment

(wild-type). There is a rare possibility that such variation confers reduced or no activity in an individual and that the person's CYP2D6 function is not accurately predicted.

^cFor some allelic variants there is no or sparse information regarding their activity; therefore no value can be assigned and no CYP2D6 activity score can be calculated. In such cases, the activity score may be estimated based on the second/known allele. A recent in vitro investigation using tamoxifen as substrate provides preliminary information for alleles listed here as unknown (74).

^dFor certain *CYP2D6* alleles *in vivo* data are lacking to unambiguously assign an activity value. For instance, the *CYP2D6**10 and *17 activity values may be substrate dependent, and for particular drugs the activity value could be closer to 1 (normal function) or 0 (no function). It should be noted that the CYP2D6 activity score is a nominal scale. An allele with an activity score of 0.5 does not necessarily have half the metabolic activity of an allele with an activity score of 1. Rather the score of 0.5 indicates the allele has decreased metabolic activity when compared to the *CYP2D6**1 reference allele.

^e*CYP2D6**1 serves as reference and is defined as wild-type.

^fFunction of *CYP2D6**34 and *39 is extrapolated from *2. Both star alleles have SNP(s) that are part of the *2 haplotype.

^gLimited data are available to determine the predicted activity value of *CYP2D6**45 and *46. Although an activity value of 1 (functional) is assigned to *CYP2D6**45 and *46 in this guideline, others may assign an activity value of 0.5 (reduced function).

^hActivity value is dependent on the number of duplications/multiplications present.

SUPPLEMENTAL TABLE S3. FREQUENCIES^a OF *CYP2D6* ALLELES (IN %) IN MAJOR RACE/ETHNIC GROUPS^b

Allele	African	African American	Caucasian (European + North American)	Middle Eastern	East Asian	South/Central Asian	Americas	Oceanian
*1^c	32.8	34.0	39	40.7	34.7	45.6	52.0	73.0
*2^d	20.1	14.2	28.1	21.7	13.1	32.4	22.9	1.2
*3	0.03	0.3	1.3	0.1	0	0.03	0.6	0
*4	3.4	6.2	18.0	7.8	0.5	7.8	10.7	1.1
*5	6.1	6.1	2.8	2.3	5.2	3.5	1.9	5.0
*6	0	0.2	0.9	0.6	0.02	0	0.4	0
*7	0	0	0.1	0	0	ND	0	0
*8	0	0	0.02	0	0	ND	0.1	0
*9	0.1	0.5	2.1	0	0.1	1.1	1.2	0
*10^e	6.8	4.2	2.9	3.5	42.7	14.0	2.8	1.6
*14	0.3	0	0	0.2	0.8	0	0.3	0
*17^f	20.0	18.2	0.4	1.6	0.01	0.2	2.3	0.1
*29	10.3	6.5	0.1	0.8	0	0.1	1.4	0
*36	0	0.6	0	0	1.5	ND	0.3	0
*41^g	10.9	9.4	7.7	19.9	2.2	12.0	3.9	0

Allele	African	African American	Caucasian (European + North American)	Middle Eastern	East Asian	South/Central Asian	Americas	Oceanian
xN^h	7.6	4.4	2.7	6.7	1.5	1.6	3.83	8.9
$*1xN^i$	1.5	0.4	0.9	3.1	0.3	0.6	0.79	11.8
$*2xN^i$	1.6	1.6	1.2	3.9	0.4	1.1	1.84	0
$*4xN^i$	1.4	2.1	0.2	0	0	0.2	0.47	0

Abbreviations are as follows: ND = not determined

^aAverage frequencies are based on the actual number of subjects with each allele reported in multiple studies. For full details and references please see http://www.pharmgkb.org/download.action?filename=CYP2D6_Frequency_Table_and_Legend_R3.pdf.

^bWorldwide race/ethnic designations correspond to the Human Genome Diversity Project- Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) (75, 76).

^cBecause *CYP2D6*1* is not genotyped directly, all alleles that are negative for a sequence variation are defaulted to a *CYP2D6*1* assignment. Likewise, sequence variations of alleles that are not tested may default to a *CYP2D6*1* assignment and hence contribute to the frequencies reported for this allele. Therefore, the inferred frequency for *CYP2D6*1* was calculated as an average from studies describing allele frequencies for the most common alleles found in a particular ethnic group. Studies not describing a frequency for *2 or few allelic variants (*4 and *5 only, or *10 only, for example) were omitted for the estimation of *1.

^d*CYP2D6*2* is a 'default' assignment and, unless tested and discriminated for *CYP2D6*8*, *11, *17, *35, *41 and other variants, will default to a *CYP2D6*2* assignment. The frequencies shown here may therefore be over-estimated.

^e*CYP2D6*10* is a 'default' assignment and, unless tested and discriminated for, *CYP2D6*14* and *36 and other variants, will default to a *CYP2D6*10* assignment. The frequencies shown here may therefore be over-estimated.

^f*CYP2D6*17* is a 'default' assignment and, unless tested and discriminated for, *CYP2D6*40* and *58 will default to a *CYP2D6*17*

assignment. The frequencies shown here may therefore be over-estimated.

^g*CYP2D6**41 has not consistently been determined by its defining SNP (2988G>A) across studies; some platforms still use the -1584C>G SNP to discriminate between *CYP2D6**2 and *41. This may lead to an overestimation of the *CYP2D6**41 frequency, especially in those of African ancestry (77).

^h*xN* denotes all gene duplications regardless of their nature. Alleles reported as *CYP2D6**2*xN*, but not specifically discriminated from other duplications such as *CYP2D6**1*xN* or *4*xN* were tabulated as *xN*.

ⁱFrequencies calculated only from those studies which discriminated between gene duplications, that is studies that specified duplications such as *CYP2D6**1*xN*, *2*xN*, or *4*xN* were present. Because there may have been other duplications present and fewer studies had data for differentiated gene duplications, the sum of *CYP2D6**1*xN*, *2*xN*, and *4*xN* is less than the sum shown for *xN*. *xN* may also contain other alleles with gene rearrangements that test positive in a duplication assay, but do not carry duplications of identical gene units.

Note: Diplotype frequencies of interest can be estimated using the equation describing Hardy Weinberg equilibrium. For example, the probability of observing an African American individual with a homozygous *CYP2D6**1/*1 diplotype is p^2 ($0.3397 \times 0.3397 = 0.115$ or 11.5%). The probability for subjects to be heterozygous for the *CYP2D6**1/*5 diplotype is $2pq$ ($2 \times 0.3397 \times 0.0614 = 0.042$ or 4.2%) and subjects to be homozygous for *CYP2D6**5/*5 is q^2 ($0.0614 \times 0.0614 = 0.0038$ or 0.38%). To translate respective diplotypes into its phenotype, see the translation table available at PharmGKB (<https://www.pharmgkb.org/guideline/PA166127636> or <https://www.pharmgkb.org/guideline/PA166127637>).

SUPPLEMENTAL TABLE S4. GENOTYPES THAT MAINLY CONSTITUTE THE STAR (*) ALLELES FOR *CYP2C19* AND THEIR EFFECT ON CYP2C19 PROTEIN

Allele ^a	Major Nucleotide Variation ^{b,c}	dbSNP Number ^d	Effect on CYP2C19 Protein
*1	-	-	-
*2	19154G>A	rs4244285	Splicing defect
*3	17948G>A	rs4986893	W212X
*4A^e	1A>G	rs28399504	M1V
*4B^e	-806C>T	rs12248560	-
	1A>G	rs28399504	M1V
*5	90033C>T	rs56337013	R433W
*6	12748G>A	rs72552267	R132Q
*7	19294T>A	rs72558186	Splicing defect
*8	12711T>C	rs41291556	W120R
*9	12784G>A	rs17884712	R144H
*10	19153C>T	rs6413438	P227L
*11	12802G>A	rs58973490	R150H
*12	90209A>C	rs55640102	X491C (26 extra aa)
*13	87290C>T	rs17879685	R410C
*14	50T>C	rs55752064	L17P
*15	55A>C	rs17882687	I19L
*16	90060C>T	rs192154563	R442C
*17^e	-806C>T	rs12248560	-
n/a^f	-806C>T	rs12248560	-
	c.463G>T	rs374036992	E155X
*18	80156G>A	rs138142612	R329H
	87106T>C	rs4917623	-
*19	151A>G	-	S51G
	87106T>C	rs4917623	-
*22	17869G>C	rs140278421	R186P
*23	12455G>C	rs118203756	G91R
*24	80174G>A	rs118203757	R335Q
	87259A>G	-	-

Allele ^a	Major Nucleotide Variation ^{b,c}	dbSNP Number ^d	Effect on CYP2C19 Protein
*25	90080C>G	rs118203759	F448L
*26	19239G>A	-	D256N
*27	-1041G>A	-	-
*28	-2030C>T	rs113164681	-
	-2020C>A	rs111490789	-
	-1439T>C	rs17878739	-
	55A>C	rs17882687	I19L
	80290G>A	rs113934938	V374I
*29	83A>T	-	K28I
*30	12401C>T ^g	rs145328984	R73C
*31	12416C>T	-	H78Y
*32	12480A>G	-	H99R
*33	17874G>A	rs370803989	D188N
*34	-13G>A	-	-
	7C>T	rs367543002	P3S
	10T>C	rs367543003	F4L

^aSee Human Cytochrome P450 Allele Nomenclature Committee website

(<http://www.cypalleles.ki.se>) for comprehensive haplotype definitions of *CYP2C19* variant alleles and updated allele information.

^bAll coordinates refer to GenBank *CYP2C19* sequence NT_030059.13⁺ as detailed at <http://www.cypalleles.ki.se/cyp2c19.htm>. All variants are annotated to the positive DNA strand. (⁺To be considered *CYP2C19**1A, the genomic reference sequence must be changed to -1041G, 99C and 80161A).

^cSome of the alleles may carry multiple nucleotide variations. More specific details on the combinations of SNPs present in each allele can be found at <http://www.cypalleles.ki.se>. In addition, the specific SNPs included in the genotyping assays can be found in the assays' product inserts.

^dRefSNP accession ID number (<http://www.ncbi.nlm.nih.gov/snp/>).

^eThe detrimental *CYP2C19**4-defining SNP (rs28399504) has been identified to be linked (i.e. on the same chromosome) with *17 (-806C>T; rs12248560) in certain ethnic subpopulations. This haplotype is designated *CYP2C19**4B (1, 40). To distinguish the *4 (no function) and *17

(increased function) alleles, both rs28399504 and rs12248560 should be genotyped (40, 42)).

^fA novel SNP (c.463G>T) has been identified to occur in linkage with the *17-defining SNP (-806C>T; rs12248560). This allele has not been assigned a separate star (*) designation by the Nomenclature Committee. To distinguish *17 from this novel haplotype, c.463G>T needs to be genotyped (41).

SUPPLEMENTAL TABLE S5. ASSOCIATION BETWEEN ALLELIC VARIANTS AND CYP2C19 ENZYME ACTIVITY

Functional Status	Alleles
Increased function	*17
Normal function ^a	*1, *11, *13, *15, *18, *28
Decreased function	*9, *10, *16, *19, *25, *26
No function	*2, *3, *4, *5, *6, *7, *8, *22, *24
Unknown	*12, *14, *23, *27, *29, *30, *31, *32, *33, *34

^aAn important caveat for all genotyping tests is that the decision to assign an allele a wild-type status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. It is always possible that a novel, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as wild-type.

SUPPLEMENTAL TABLE S6. FREQUENCIES^a OF *CYP2C19* ALLELES (IN %) IN MAJOR RACE/ETHNIC GROUPS^b

Allele	African	African American	Caucasian (European + North American)	Middle Eastern	East Asian	South/Central Asian	Americas	Oceanian
*1^c	36.4	58.1	62.1	84.2	58.0	47.4	69.0	28.6
*2	14.2	18.3	14.6	13.2	29.0	34.4	13.1	54.9
*3	0.8	0.3	0.6	2.6	8.5	1.7	0.3	13.9
*4^d	0	0	0.4	ND	0.1	0	0.03	ND
*5	0	0	0	ND	0	0	0	ND
*6	0	0	0.1	ND	0.03	0	0	ND
*8	0	0.2	0.3	ND	0	0	0.1	ND
*17	15.1	19.4	21.5	ND	1.6	16.5	16.3	2.5

Abbreviations are as follows: ND = not determined

For full details and references please

http://www.pharmgkb.org/download.action?filename=CYP2C19_Frequency_Table_and_Legend_V1.pdf.

^aAverage frequencies are based on the actual number of subjects with each allele as reported in one or multiple studies.

^bWorldwide race/ethnic designations correspond to the Human Genome Diversity Project- Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) (75, 76).

^cBecause *CYP2C19**1 is not genotyped directly, all alleles that are negative for a sequence variation are defaulted to a *CYP2C19**1 assignment. The inferred frequency for *CYP2C19**1 is calculated as: 100 - (sum of averaged variant allele frequencies).

^d*CYP2C19**4A and *4B allele frequencies were combined.

Note: Diplotype frequencies of interest can be estimated using the equation describing Hardy Weinberg equilibrium. For example, the probability of observing an African American individual with a homozygous *CYP2C19**1/*1 diplotype is p^2 ($0.5809 \times 0.5809 = 0.337$ or 33.7%). The probability for subjects to be heterozygous for the *CYP2C19**1/*2 diplotype is $2pq$ ($2 \times 0.5809 \times 0.1833 = 0.213$ or 21.3%) and subjects to be homozygous for *CYP2C19**2/*2 is q^2 ($0.1833 \times 0.1833 = 0.034$ or 3.4%). To translate respective diplotypes into its phenotype, see the translation table available at PharmGKB (link will be added once/if manuscript accepted).

SUPPLEMENTAL TABLE S7. EVIDENCE LINKING *CYP2D6* GENOTYPE TO FLUVOXAMINE PHENOTYPE

CYP2D6 -Fluvoxamine			
Experimental model	Major Findings	References	Level of Evidence
Clinical	Higher risk of developing gastrointestinal side effects in patients with reduced CYP2D6 activity (*1/*5; *10/*10; *5/*10) compared to normal metabolizers (*1/*1; *1/*10).	Suzuki <i>et al.</i> 2006 (78)	Moderate
Clinical	Patients with two variant <i>CYP2D6</i> alleles (<i>CYP2D6</i> *5/ <i>CYP2D6</i> *10 and <i>CYP2D6</i> *10/ <i>CYP2D6</i> *10) had significantly higher fluvoxamine plasma concentrations compared to patients with no variant alleles.	Suzuki <i>et al.</i> 2011 (79)	Moderate
Clinical	Phenotypic CYP2D6 PMs (healthy volunteers (80) and patients (81) had significantly different fluvoxamine pharmacokinetic parameters (higher maximum plasma concentration, longer half-life, or lower oral clearance of fluvoxamine) following a single dose as compared to EMs.	Carrillo <i>et al.</i> 1996 (80) Spigset <i>et al.</i> 1997 (81)	Moderate
Clinical	Phenotypic CYP2D6 PMs (healthy volunteers) had a lower clearance than EMs following a single dose of fluvoxamine.	Spigset <i>et al.</i> 2001 (82)	Weak
Clinical	Patients with at least one variant <i>CYP2D6</i> allele had significantly higher fluvoxamine plasma levels than CYP2D6 wild-type patients under steady state conditions with lower doses of fluvoxamine (50mg) but not higher doses (100-200mg).	Watanabe <i>et al.</i> 2008 (83)	Weak

SUPPLEMENTAL TABLE S8. EVIDENCE LINKING *CYP2D6* GENOTYPE TO PAROXETINE PHENOTYPE

CYP2D6 -Paroxetine			
Experimental model	Major findings	Reference	Level of evidence
Clinical	Genotypic CYP2D6 UMs (patients (58, 59, 84) and health volunteers (57)) had significantly lower, or undetectable, paroxetine plasma concentrations at steady state when compared to genotypic EMs.	Güzey <i>et al.</i> 2006 (59) Lam <i>et al.</i> 2002 (57) Charlier <i>et al.</i> 2003 (84) Gex-Fabry <i>et al.</i> 2008 (58)	High
Clinical	Genotypic CYP2D6 UMs (patients) did not have an antidepressant response to paroxetine.	Güzey <i>et al.</i> 2006 (59) Gex-Fabry <i>et al.</i> 2008 (58)	Weak
Clinical	A subset of individuals determined to be CYP2D6 EMs by genotyping/phenotyping may phenocopy after prolonged paroxetine treatment.	Sindrup <i>et al.</i> 1992 (85) Zourková <i>et al.</i> 2003 (86) Lam <i>et al.</i> 2002 (57) Solai <i>et al.</i> 2002 (87)	Moderate
Clinical	CYP2D6 UMs may not phenocopy (convert to a PM phenotype) when administered paroxetine.	Lam <i>et al.</i> 2002 (57)	Weak
Clinical	Healthy volunteers determined to be CYP2D6 PMs by genotyping or phenotyping had significantly higher paroxetine plasma concentrations at steady state compared to EMs.	Charlier <i>et al.</i> 2003 (84) Sindrup <i>et al.</i> 1992 (85)	High
Clinical	Individuals (healthy volunteers (85) and patients (88)) determined to be CYP2D6 PMs by genotyping/phenotyping had significantly different pharmacokinetic parameters (e.g., lower clearance, greater AUC and half-life) of paroxetine versus EMs.	Findling <i>et al.</i> 1999 (88) Sindrup <i>et al.</i> 1992 (85)	Moderate
Clinical	Pharmacokinetic parameters at steady state were significantly different among those with 0, 1, 2, or >2 active <i>CYP2D6</i> alleles. Those with the most active alleles had the lowest paroxetine concentrations and those with no active alleles had the highest paroxetine concentrations.	Feng <i>et al.</i> 2006 (89) Findling <i>et al.</i> 2006 (90) Sawamura <i>et al.</i> 2004 (91) Van Nieuwerburgh <i>et al.</i> 2009 (92) Saruwatari <i>et al.</i> (93)	High
Clinical	Significant relationship between paroxetine-induced adverse drug reactions observed when female CYP2D6 PMs were compared to female EMs.	Zourkova <i>et al.</i> 2007 (94)	Weak
Clinical	Suspected adverse effects due to paroxetine intoxication in a genotypic CYP2D6 IM.	Sato <i>et al.</i> 2004 (95)	Weak
Clinical	No significant relationship between paroxetine-induced adverse drug reactions was observed when genotypic CYP2D6 PMs and/or IMs were compared to EMs.	Murphy <i>et al.</i> 2003 (96) Stedman <i>et al.</i> 2002 (97) Sugai <i>et al.</i> 2006(98)	Weak

SUPPLEMENTAL TABLE S9. EVIDENCE LINKING *CYP2C19* AND *CYP2D6* GENOTYPE TO CITALOPRAM/ESCITALOPRAM PHENOTYPE

CYP2C19 and CYP2D6-Citalopram/Escitalopram			
Experimental model	Major findings	Reference	Level of Evidence
Clinical	Genotypic CYP2C19 PMs (patients) had significantly higher racemic citalopram or escitalopram plasma concentrations at steady state as compared to the median dose-corrected plasma concentrations of all study participants.	Grasmader <i>et al.</i> 2004 (99) de Vos <i>et al.</i> 2011 (15) Huezo-Diaz <i>et al.</i> 2012 (100) Rudberg <i>et al.</i> 2008 (101) Tsai <i>et al.</i> 2010 (102)	High
Clinical	Individuals (healthy volunteers (103, 104) and patients (105))determined to be CYP2C19 PMs by genotyping or phenotyping had significantly different pharmacokinetic parameters (higher citalopram or escitalopram plasma concentrations, higher AUC, longer half-life, or slower clearance) at steady state as compared to EMs.	Herrlin <i>et al.</i> 2003 (103) Noehr-Jensen <i>et al.</i> 2009 (104) Yin <i>et al.</i> 2006 (105)	High
Clinical	Healthy volunteers determined to be CYP2C19 PMs by genotyping or phenotyping had significantly higher escitalopram AUC, half-life, or lower clearance after a single dose of escitalopram as compared to EMs.	Noehr-Jensen <i>et al.</i> 2009 (104) Fudio <i>et al.</i> 2010 (106) Yu <i>et al.</i> 2003 (107)	Moderate
Clinical	Genotypic CYP2C19 IMs (patients (101) and healthy volunteers (106, 108) had significantly higher citalopram or escitalopram plasma concentrations or AUC when compared to EMs.	Rudberg <i>et al.</i> 2008 (101) Fudio <i>et al.</i> 2010 (106) Chen <i>et al.</i> 2013 (108)	High
Clinical	Patients carrying a <i>CYP2C19</i> *17 allele had significantly lower levels of citalopram or escitalopram.	Rudberg <i>et al.</i> 2008 (101) Hodgson <i>et al.</i> 2014 (109) de Vos <i>et al.</i> 2011 (15) Huezo-Diaz <i>et al.</i> 2012 (100)	Moderate
Clinical	Patients with a <i>CYP2C19</i> *17/*17 genotype had significantly lower citalopram or escitalopram plasma concentrations at steady state when compared to EMs.	Huezo-Diaz <i>et al.</i> 2012 (100) Rudberg <i>et al.</i> 2008 (101) Hodgson <i>et al.</i> 2014 (109) Rosenborg <i>et al.</i> 2008 (110)	High

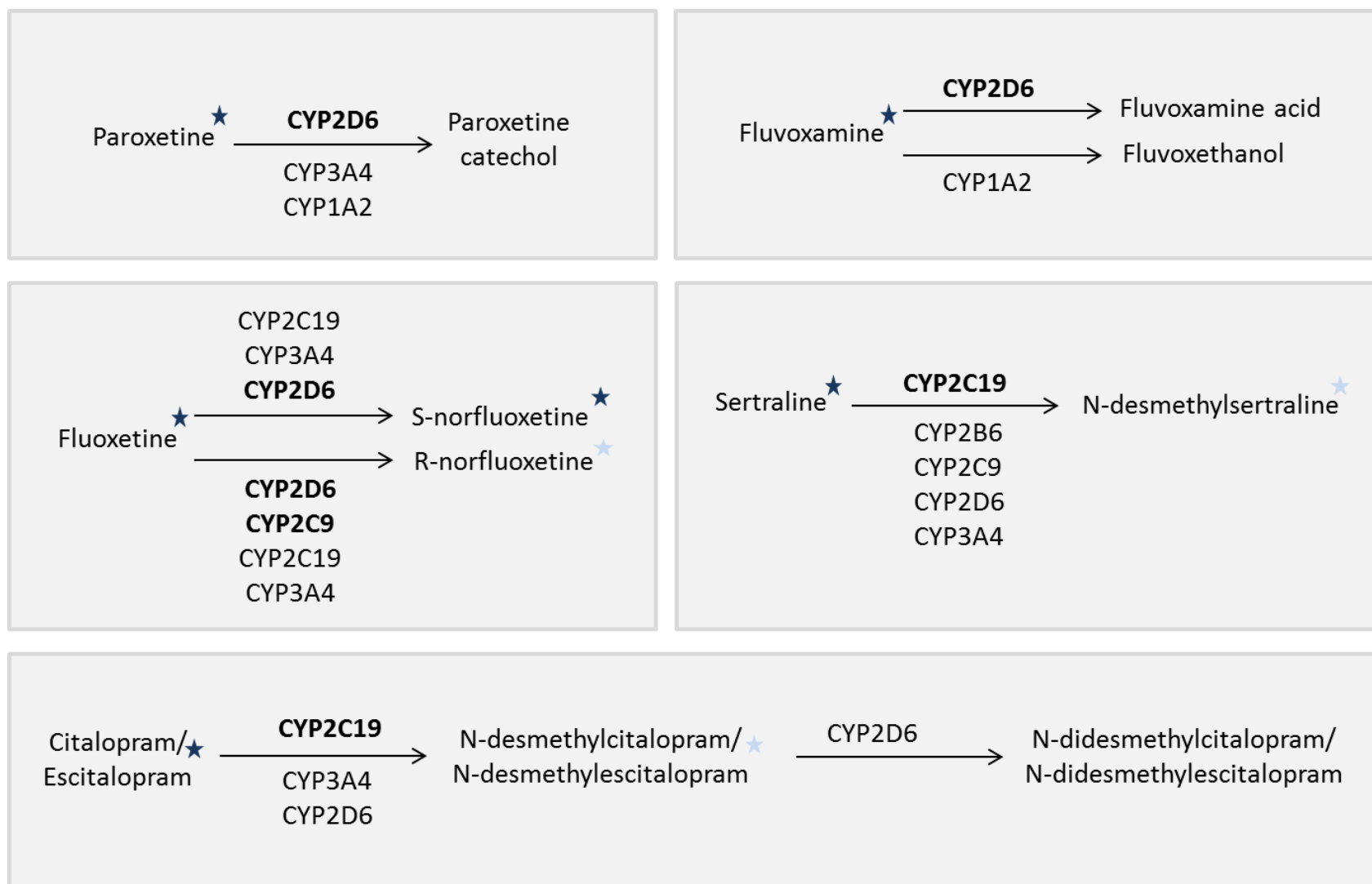
Experimental model	Major findings	Reference	Level of Evidence
Clinical	CYP2C19 PMs and IMs may be at greater risk of citalopram-induced prolonged QT interval. No association between escitalopram-induced prolonged QT interval and CYP2D6 phenotype.	Kumar <i>et al.</i> 2014(111)	Moderate
Clinical	CYP2C19 PM (determined by genotyping or phenotyping) associated with decreased tolerance.	Mrazek <i>et al.</i> 2011 (112) Herrlin <i>et al.</i> 2003 (103) Yin <i>et al.</i> 2006 (105)	Weak
Clinical	CYP2C19 PM (determined by genotyping) associated with better response or remission.	Mrazek <i>et al.</i> 2011 (112) Hodgson <i>et al.</i> 2014 (113)	Weak
Clinical	CYP2C19 PM (determined by genotyping) not associated with better response or remission.	Hodgson <i>et al.</i> 2014 (109) Peters <i>et al.</i> 2008 (114) Tsai <i>et al.</i> 2010 (102)	
Clinical	Side effects observed in a patient determined by phenotyping to be both a CYP2D6 PM and CYP2C19 PM.	Herrlin <i>et al.</i> 2003 (103)	Weak
Clinical	Genotypic CYP2D6 PMs (patients) had significantly higher citalopram or escitalopram plasma concentrations at steady state when compared to EMs.	Grasmader <i>et al.</i> 2004 (99) Herrlin <i>et al.</i> 2003 (103) Huezo-Diaz <i>et al.</i> 2012 (100) Tsai <i>et al.</i> 2010 (102)	Weak
Clinical	Genotypic CYP2D6 IMs (patients) had significantly higher citalopram or escitalopram plasma concentrations at steady state when compared to EMs.	Huezo-Diaz <i>et al.</i> 2012 (100)	Weak
Clinical	Relationship between genotypic CYP2D6 IM/PM status and better/faster response (tolerance and remission).	Mrazek <i>et al.</i> 2011 (112) Tsai <i>et al.</i> 2010 (102) Han <i>et al.</i> 2013(115)	Weak
Meta-analysis	Meta-analysis included a total 847 patients from psychiatric patient trials and 140 healthy subjects from pharmacokinetic studies. CYP2C19 PMs (*2 or *3/*2 or *3) had increased exposure to (es)citalopram by 95 %, IMs (*1/*2 or *3) by 30 % , IMs (*17/*2 or *3) by 25 % compared to EMs (*1/*1). Subjects with CYP2C19*17/*17 had decreased exposure by 36 % and CYP2C19*17/*1 by 14 % compared to EM (*1/*1).	Chang <i>et al.</i> 2014 (116)	High

SUPPLEMENTAL TABLE S10. EVIDENCE LINKING *CYP2D6* GENOTYPE TO FLUOXETINE PHENOTYPE

CYP2D6 -Fluoxetine			
Type of experimental model	Major findings	Reference	Level of Evidence
Clinical	Patients determined to be CYP2D6 PMs by genotyping or phenotyping had significantly higher fluoxetine plasma concentrations at steady as compared to EMs.	Charlier <i>et al.</i> 2003 (84) Eap <i>et al.</i> 2001 (117)	High
Clinical	Phenotypic CYP2D6 PMs (healthy volunteers) had significantly different fluoxetine pharmacokinetic parameters (lower clearance, greater AUC and half-life) following a single dose as compared to EMs.	Fjordside <i>et al.</i> 1999 (52) Hamelin <i>et al.</i> 1996 (118)	High
Clinical	Steady-state fluoxetine dose-corrected plasma concentrations were significantly different among patients with 0, 1, 2, or >2 active <i>CYP2D6</i> alleles. Subjects with the most active alleles had the lowest fluoxetine concentrations and those with no active alleles had the highest fluoxetine concentrations.	Llerena <i>et al.</i> 2004 (8)	High
Clinical	Fluoxetine/(S)-norfluoxetine ratio is negatively correlated with the number of normal function CYP2D6 alleles	Gasso <i>et al.</i> 2014 (119)	Moderate
Clinical	Suspected adverse effects and eventual death due to fluoxetine intoxication in a genotypic <i>CYP2D6</i> PM.	Sallee <i>et al.</i> 2000 (120)	Weak
Clinical	No significant relationship between fluoxetine-induced adverse drug reactions and CYP2D6 PMs and EMs determined by genotyping.	Roberts <i>et al.</i> 2004 (121)	Moderate

SUPPLEMENTAL TABLE S11. EVIDENCE LINKING *CYP2C19* GENOTYPE TO SERTRALINE PHENOTYPE

CYP2C19 -Sertraline			
Type of experimental model	Major findings	Reference	Level of Evidence
Clinical	Genotypic CYP2C19 PMs (patients carrying two defective <i>CYP2C19</i> alleles) had higher sertraline plasma concentrations at steady state compared to EM patients with a <i>CYP2C19</i> *1/*1 Genotype.	Rudberg <i>et al.</i> 2008 (122)	Moderate
Clinical	Healthy volunteers determined to be CYP2C19 PMs by phenotyping and genotyping had significantly different sertraline pharmacokinetic parameters (<i>i.e.</i> higher area under the plasma concentration versus time curve and longer half-life, lower clearance) after one dose of sertraline compared to EMs (<i>CYP2C19</i> *1/*1 and *1/null).	Wang <i>et al.</i> 2001 (123)	Moderate
Clinical	Sertraline-induced adverse effects observed in CYP2C19 PMs (determined by phenotyping).	Wang <i>et al.</i> 2001 (123)	Weak



SUPPLEMENTAL FIGURE S1. METABOLISM OF SSRIs, WHERE BOLDEN ENZYMES REPRESENT A MAJOR METABOLIC PATHWAY.

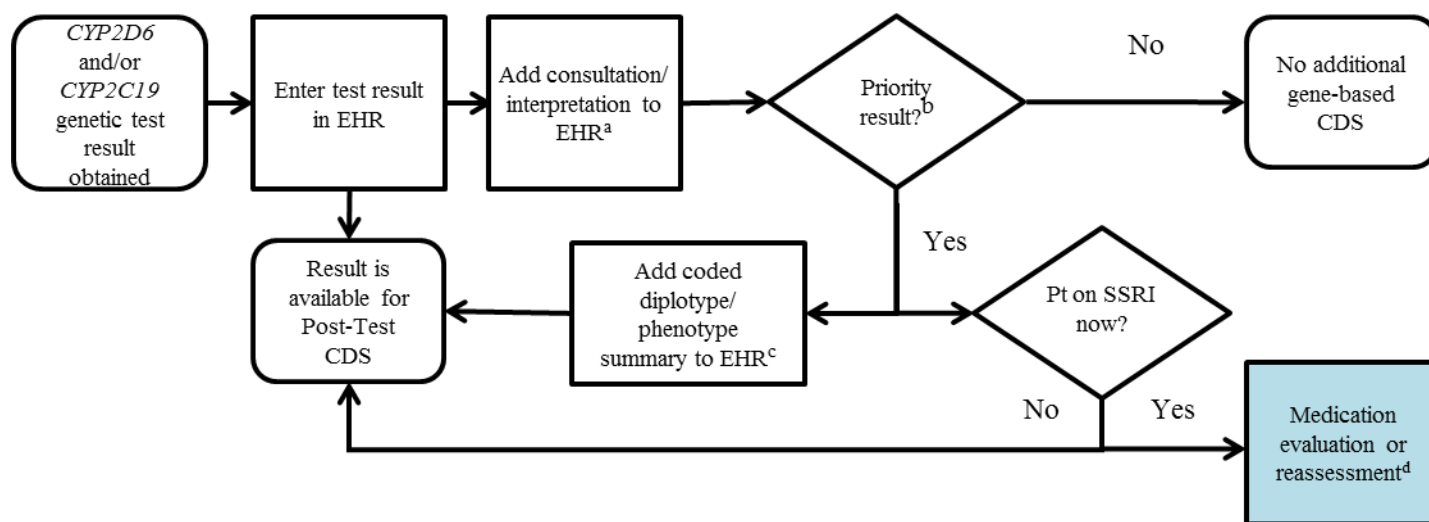
★ Active ★ Less active metabolite

SUPPLEMENTAL TABLE S12. DRUGS ASSOCIATED WITH GENE-BASED DOSING RECOMMENDATIONS IN THIS GUIDELINE.

Drug or Ingredient	Source	Code Type	Code
Citalopram	RxNorm	RxCUI	C0008845
Citalopram	DrugBank	Accession Number	DB00215
Citalopram	ATC	ATC Code	N06AB04
Citalopram	PharmGKB	PharmGKB ID	PA449015
Escitalopram	RxNorm	RxCUI	C1099456
Escitalopram	DrugBank	Accession Number	DB01175
Escitalopram	ATC	ATC Code	N06AB10
Escitalopram	PharmGKB	PharmGKB ID	PA10074
Fluvoxamine	RxNorm	RxCUI	C0085228
Fluvoxamine	DrugBank	Accession Number	DB00176
Fluvoxamine	ATC	ATC Code	N06AB08
Fluvoxamine	PharmGKB	PharmGKB ID	PA449690
Paroxetine	RxNorm	RxCUI	C0070122
Paroxetine	DrugBank	Accession Number	DB00715
Paroxetine	ATC	ATC Code	N06AB05
Paroxetine	PharmGKB	PharmGKB ID	PA450801
Sertraline	RxNorm	RxCUI	C0074393
Sertraline	DrugBank	Accession Number	DB01104
Sertraline	ATC	ATC Code	N06AB06
Sertraline	PharmGKB	PharmGKB ID	PA451333

SUPPLEMENTAL TABLE S13. GENES THAT PERTAIN TO THIS GUIDELINE

Gene Symbol	Source	Code Type	Code
<i>CYP2C19</i>	HGNC	Symbol	CYP2C19
<i>CYP2C19</i>	HGNC	HGNC ID	HGNC:2621
<i>CYP2C19</i>	NCBI	Gene ID	1557
<i>CYP2C19</i>	Ensembl	Ensembl ID	ENSG00000165841
<i>CYP2C19</i>	PharmGKB	PharmGKB ID	PA124
<i>CYP2D6</i>	HGNC	Symbol	CYP2D6
<i>CYP2D6</i>	HGNC	HGNC ID	HGNC:2625
<i>CYP2D6</i>	NCBI	Gene ID	1565
<i>CYP2D6</i>	Ensembl	Ensembl ID	ENSG00000100197
<i>CYP2D6</i>	PharmGKB	PharmGKB ID	PA128



Blue shading indicates interaction with provider

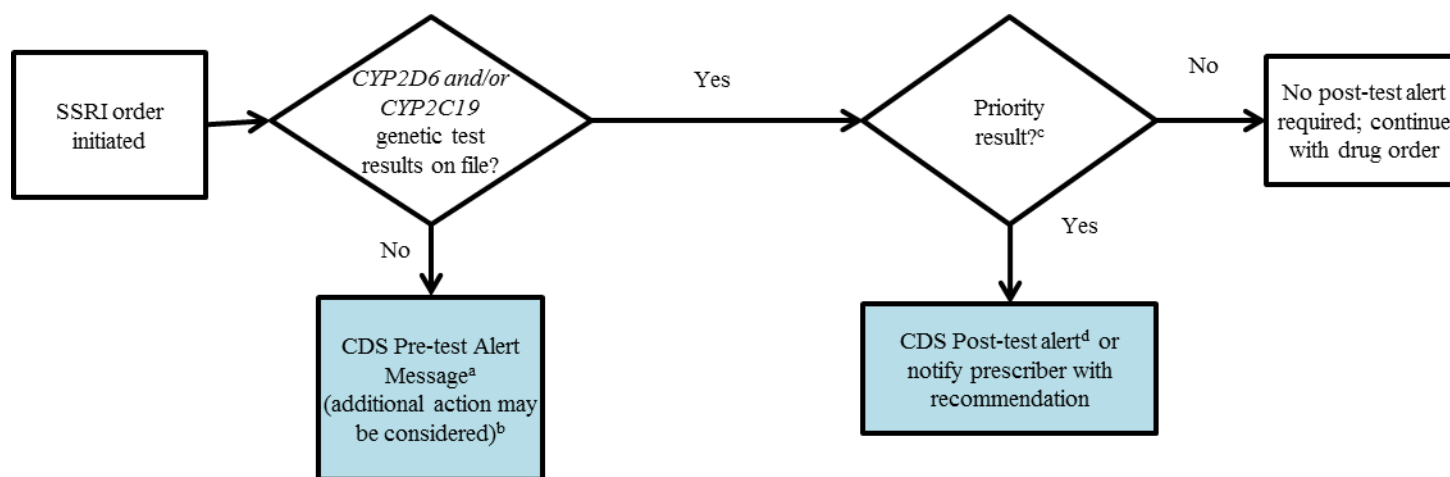
SUPPLEMENTAL FIGURE S2. *CYP2D6/CYP2C19* PHARMACOGENETIC TEST RESULT: CLINICAL IMPLEMENTATION WORKFLOW FOR EHR

^aSee **Supplementary Table S14** (*CYP2D6*) and **S15** (for *CYP2C19*) for diplotype/phenotype specific examples

^bPriority result is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.

^cDocumentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently inform prescribing decisions. See **Supplementary Tables S14** (*CYP2D6*) and **S15** (for *CYP2C19*) for genotype/phenotype-specific summaries.

^d*CYP2D6/CYP2C19* genetic testing is most helpful prior to initiation of the drug. However, in some cases (e.g., patient experiencing side effects, current drug therapy ineffective) *CYP2D6/CYP2C19* genetic results might be useful in choosing alternative therapy.



SUPPLEMENTAL FIGURE S3. *CYP2D6/CYP2C19* GENOTYPE AND SSRI: POINT OF CARE CLINICAL DECISION SUPPORT

^a See **Supplementary Table S16** for diplotype/phenotype specific pre-test alert examples.

^b Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.

^c Priority result is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.

^d See **Supplementary Table S16** for diplotype/phenotype specific post-test alert examples.

SUPPLEMENTAL TABLE S14. EXAMPLE IMPLEMENTATION OF THIS GUIDELINE FOR CYP2D6:

PHARMACOGENETIC DIPOTYPE/PHENOTYPE SUMMARY ENTRIES^a

Allele definition	CYP2D6 Activity Score	Coded Diploype/Phenotype Summary^b	EHR Priority Result Notation^c	Consultation (Interpretation) Text Provided with Test Result^d
An individual carrying duplications of normal function alleles	> 2	CYP2D6 Ultrarapid Metabolizer	Abnormal/Priority/High Risk	This result signifies that this patient has more than two copies of a normal function allele. Based on the genotype result this patient is predicted to be an ultrarapid metabolizer of CYP2D6 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.
An individual carrying a duplicated normal function allele and a decreased function allele	> 2	CYP2D6 Ultrarapid Metabolizer	Abnormal/Priority/High Risk	This result signifies that this patient has two copies of normal function allele (* _x N) ^e and one copy of a reduced function allele (* _r). Based on the genotype result this patient is predicted to be an ultrarapid metabolizer of CYP2D6 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.

Allele definition	CYP2D6 Activity Score	Coded Diplotype/Phenotype Summary^b	EHR Priority Result Notation^c	Consultation (Interpretation) Text Provided with Test Result^d
An individual carrying two normal function alleles	2.0	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a normal function allele. Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates. There is no reason to selectively adjust the dose of most medications that are metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.
An individual carrying one normal function allele and a duplicated decreased function allele	2.0	None	Normal/Routine/ Low Risk	This result signifies that this patient has one copy of a normal function allele (*_) and two copies of a reduced function allele (*_xN) ^e . Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates. There is no reason to selectively adjust the dose of most medications that are metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.
An individual carrying one normal function and one decreased function allele	1.5	None	Normal/Routine/ Low Risk	This result signifies that the patient has one copy of a normal function allele (*_) and one copy of a decreased function allele (*_). Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates. There is no reason to selectively adjust the dose of most medications that are metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.

Allele definition	CYP2D6 Activity Score	Coded Diplotype/Phenotype Summary^b	EHR Priority Result Notation^c	Consultation (Interpretation) Text Provided with Test Result^d
An individual carrying one duplicated decreased function allele and one decreased function allele	1.5	None	Normal/Routine/ Low Risk	This result signifies that this patient two copies of a decreased function allele (* _x N) ^e and one copy of a reduced function allele (* ₁). Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates. There is no reason to selectively adjust the dose of most medications that are metabolized by CYP2D6Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.
An individual carrying two decreased function alleles	1.0	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a decreased function allele. Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates. There is no reason to selectively adjust the dose of most medications that are metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.
An individual carrying one normal function and one no function allele	1.0	None		This result signifies that the patient has one copy of a normal function allele (* ₁) and one copy of a no function allele (* ₀). Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates. There is no reason to selectively adjust the dose of most medications that are metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.

Allele definition	CYP2D6 Activity Score	Coded Diplotype/Phenotype Summary^b	EHR Priority Result Notation^c	Consultation (Interpretation) Text Provided with Test Result^d
An individual carrying one no function allele and a duplicated decreased function allele	1.0	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a reduced function allele (* _x N) ^e and one copy of a no function allele (* ₋). Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates. There is no reason to selectively adjust the dose of most medications that are metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.
An individual carrying one decreased function and one no function allele	0.5	CYP2D6 Intermediate Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of a decreased function allele (* ₋) and one copy of a no function allele (* ₋). Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2D6 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.

Allele definition	CYP2D6 Activity Score	Coded Diplotype/Phenotype Summary^b	EHR Priority Result Notation^c	Consultation (Interpretation) Text Provided with Test Result^d
An individual carrying only no functional alleles	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a no function allele. Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2D6 substrates. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2D6. Please consult a clinical pharmacist for more information about how CYP2D6 metabolic status influences drug selection and dosing.

This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarizes the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. Because various EHRs or organizations may require different terms different options are provided.

^aA more comprehensive table of genotype/phenotype EHR entries for possible diplotype combinations of all variants listed in **Supplemental Table S2** is available at PharmGKB (<https://www.pharmgkb.org/guideline/PA166127636> or <https://www.pharmgkb.org/guideline/PA166127637>).

^bThe coded diplotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites. Assignment of all Genotype/Phenotype Summaries based on diplotype is available at (<https://www.pharmgkb.org/guideline/PA166127636> or <https://www.pharmgkb.org/guideline/PA166127637>).

^cFor this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

^dThe specific wording of the interpretive text may differ among sites.

^cInterpretation examples for *CYP2D6* duplications are provided. Interpretations will need to be modified for instances when *CYP2D6* multiplications are present.

**SUPPLEMENTAL TABLE S15. EXAMPLE IMPLEMENTATION OF THIS GUIDELINE FOR CYP2C19:
PHARMACOGENETIC DIPLTYPE/PHENOTYPE SUMMARY ENTRIES^A**

Diplotype Test Result for <i>CYP2C19</i>	Coded Genotype/Phenotype Summary^b	EHR Priority Result Notation^b	Consultation (Interpretation) Text Provided with Test Result^d
<i>*17/*17</i>	CYP2C19 Ultrarapid Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of an increased function allele (<i>*17/*17</i>). Based on the genotype result this patient is predicted to be an ultrarapid metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
<i>*1/*17</i>	CYP2C19 Ultrarapid Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of a normal function allele (<i>*1</i>) and one copy of an increased function allele (<i>*17</i>). Based on the genotype result this patient is predicted to be an ultrarapid metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.

Diplotype Test Result for CYP2C19	Coded Genotype/Phenotype Summary^b	EHR Priority Result Notation^b	Consultation (Interpretation) Text Provided with Test Result^d
<i>*1/*1</i>	None	Normal/Routine/Low Risk	This result signifies that the patient has two copies of a normal function allele (<i>*1/*1</i>). Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2C19 substrates. There is no reason to selectively adjust the dose of most medications that are metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
<i>*1/*2</i>	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of a normal function allele (<i>*1</i>) and one copy of a no function allele (<i>*2</i>). Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
<i>*1/*3</i>	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of a normal function allele (<i>*1</i>) and one copy of a no function allele (<i>*3</i>). Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.

Diplotype Test Result for CYP2C19	Coded Genotype/Phenotype Summary^b	EHR Priority Result Notation^b	Consultation (Interpretation) Text Provided with Test Result^d
*2/*17	CYP2C19 Intermediate Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has one copy of an increased function allele (*17) and one copy of a no function allele (*2). Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
*2/*2	CYP2C19 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a no function allele (*2). Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2C19 substrates. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.
*2/*3	CYP2C19 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a no function allele (*2/*3). Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2C19 substrates. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.

Diplotype Test Result for CYP2C19	Coded Genotype/Phenotype Summary^b	EHR Priority Result Notation^b	Consultation (Interpretation) Text Provided with Test Result^d
*3/*3	CYP2C19 Poor Metabolizer	Abnormal/Priority/High Risk	This result signifies that the patient has two copies of a no function allele (*3). Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2C19 substrates. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2C19. Please consult a clinical pharmacist for more information about how CYP2C19 metabolic status influences drug selection and dosing.

This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarizes the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. Because various EHRs or organizations may require different terms different options are provided.

^aA more comprehensive table of genotype/phenotype EHR entries for possible diplotype combinations of all variants listed in **Supplemental Table S2** is available at PharmGKB (<https://preview.pharmgkb.org/guideline/PA166127638> or <https://preview.pharmgkb.org/guideline/PA166127639>)

^bThe coded diplotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites. Assignment of all Genotype/Phenotype Summaries based on diplotype is available at (<https://preview.pharmgkb.org/guideline/PA166127638> or <https://preview.pharmgkb.org/guideline/PA166127639>)

^cFor this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

^dThe specific wording of the interpretive text may differ among sites.

SUPPLEMENTAL TABLE S16. EXAMPLE IMPLEMENTATION OF THIS GUIDELINE: POINT OF CARE CLINICAL DECISION SUPPORT

CDS Alert trigger condition	CDS Context, relative to genetic testing	CDS Alert Text ^a
CYP2D6 and paroxetine		
No <i>CYP2D6</i> test on file and paroxetine ordered	Pre-Test	<i>CYP2D6</i> genetic status may be predictive of an adverse reaction or poor response to this medication. A <i>CYP2D6</i> genotype does not appear to have been ordered for this patient. Use of an alternative drug or dose may be recommended. Please consult a clinical pharmacist ^b for more information.
CYP2D6 UM and paroxetine ordered	Post-Test	This patient is predicted to be a CYP2D6 ultrarapid metabolizer and may be at an increased risk of a poor response due to low plasma concentrations of paroxetine. Consider selecting an alternative SSRI not extensively metabolized by CYP2D6. Please consult a clinical pharmacist for more information.
CYP2D6 EM or IM and paroxetine ordered	Post-Test	No CDS
CYP2D6 PM and paroxetine ordered	Post-Test	This patient is predicted to be a CYP2D6 poor metabolizer and may be at an increased risk of an adverse reaction due to elevated paroxetine plasma concentrations. Select an alternative SSRI not extensively metabolized by CYP2D6. If paroxetine is warranted, consider a 50% decrease of the initial dose and titrate to response. Please consult a clinical pharmacist for more information.

CDS Alert trigger condition	CDS Context, relative to genetic testing	CDS Alert Text ^a
CYP2D6 and fluvoxamine		
No <i>CYP2D6</i> test on file and fluvoxamine ordered	Pre-Test	<i>CYP2D6</i> genetic status may be predictive of an adverse reaction or poor response to this medication. A <i>CYP2D6</i> genotype does not appear to have been ordered for this patient. Use of an alternative drug or dose may be recommended. Please consult a clinical pharmacist ^b for more information.
CYP2D6 UM, EM, or IM	Post-Test	No CDS
CYP2D6 PM and fluvoxamine ordered	Post-Test	This patient is predicted to be a CYP2D6 poor metabolizer and may be at an increased risk of an adverse reaction due to elevated fluvoxamine plasma concentrations. Consider a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6. Please consult a clinical pharmacist for more information.
CYP2C19 and citalopram		
No <i>CYP2C19</i> test on file and citalopram ordered	Pre-Test	<i>CYP2C19</i> genetic status may be predictive of an adverse reaction or poor response to this medication. A <i>CYP2C19</i> genotype does not appear to have been ordered for this patient. Use of an alternative drug or dose may be recommended. Please consult a clinical pharmacist for more information.
CYP2C19 UM and citalopram ordered	Post-Test	This patient is predicted to be a CYP2C19 ultrarapid metabolizer and may be at an increased risk of a poor response due to low plasma concentrations of citalopram. Consider selecting an alternative SSRI not extensively metabolized by CYP2C19. Please consult a clinical pharmacist for more information.
CYP2C19 EM or IM and citalopram ordered	Post-Test	No CDS
CYP2C19 PM and citalopram ordered	Post-Test	This patient is predicted to be a CYP2C19 poor metabolizer and may be at an increased risk of an adverse reaction due to elevated citalopram plasma concentrations. Consider a 50% reduction of the recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19. Please consult a clinical pharmacist for more information.

CDS Alert trigger condition	CDS Context, relative to genetic testing	CDS Alert Text ^a
CYP2C19 and escitalopram		
No <i>CYP2C19</i> test on file and escitalopram ordered	Pre-Test	<i>CYP2C19</i> genetic status may be predictive of an adverse reaction or poor response to this medication. A <i>CYP2C19</i> genotype does not appear to have been ordered for this patient. Use of an alternative drug or dose may be recommended. Please consult a clinical pharmacist for more information.
CYP2C19 UM and escitalopram ordered	Post-Test	This patient is predicted to be a CYP2C19 ultrarapid metabolizer and may be at an increased risk of a poor response due to low plasma concentrations of escitalopram. Consider selecting an alternative SSRI not extensively metabolized by CYP2C19. Please consult a clinical pharmacist for more information.
CYP2C19 EM or IM and escitalopram ordered	Post-Test	No CDS
CYP2C19 PM and escitalopram ordered	Post-Test	This patient is predicted to be a CYP2C19 poor metabolizer and may be at an increased risk of an adverse reaction due to elevated escitalopram plasma concentrations. Consider a 50% reduction of the recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19. Please consult a clinical pharmacist for more information.
CYP2C19 and sertraline		
No CYP2C19 test on file and sertraline ordered	Pre-Test	CYP2C19 genetic status may be predictive of an adverse reaction or poor response to this medication. A CYP2C19 genotype does not appear to have been ordered for this patient. Use of an alternative drug or dose may be recommended. Please consult a clinical pharmacist for more information.
CYP2C19 UM, EM or IM and sertraline ordered	Post-Test	No CDS
CYP2C19 PM and sertraline ordered	Post-Test	This patient is predicted to be a CYP2C19 poor metabolizer and may be at an increased risk of an adverse reaction due to elevated sertraline plasma concentrations. Consider a 50% reduction of the recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19. Please consult a clinical pharmacist for more information.

^aThe specific wording of the alert text may differ among sites.

^bPharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

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