Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for *CYP2D6*, *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, and *GRK5* Genotypes and Beta-Blocker Therapy

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Beta-blockers are widely used medications for a variety of indications, including heart failure, myocardial infarction, cardiac arrhythmias, and hypertension. Genetic variability in pharmacokinetic (e.g., *CYP2D6*) and pharmacodynamic (e.g., *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, *GRK5*) genes have been studied in relation to beta-blocker exposure and response. We searched and summarized the strength of the evidence linking beta-blocker exposure and response with the six genes listed above. The level of evidence was high for associations between *CYP2D6* genetic variation and both metoprolol exposure and heart rate response. Evidence indicates that CYP2D6 poor metabolizers experience clinically significant greater exposure and lower heart rate in response to metoprolol compared with those who are not poor metabolizers. Therefore, we provide therapeutic recommendations regarding genetically predicted CYP2D6 metabolizer status and metoprolol therapy. However, there was insufficient evidence to make therapeutic recommendations for *CYP2D6* and other beta-blockers or for any beta-blocker and the other five genes evaluated (updates at www.cpicpgx.org).

Beta-blockers are widely used medications for the treatment of a variety of cardiovascular and non-cardiovascular indications, such as heart failure, ischemic heart disease, hypertension, cardiac arrhythmias, anxiety, and glaucoma. Certain beta-blockers are extensively metabolized by the cytochrome P450 2D6 (CYP2D6) enzyme to mostly inactive metabolites (except for carvedilol, which is metabolized by CYP2D6 into both pharmacologically active and inactive metabolites; **Table S1**). Some *CYP2D6* genotypes have been associated with higher plasma concentrations of some beta-blockers, potentially leading to more pronounced effects on vital signs such as heart rate and blood pressure. In addition, genetic variation in the pharmacodynamic genes *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, and *GRK5* have also been studied in relation to beta-blocker pharmacodynamics and clinical response, though the clinical implications of such variation are unclear. The purpose of this guideline is to provide clinicians with information that facilitates the interpretation of clinical genotype test results to guide beta-blocker prescribing and to discuss the evidence linking genetics to beta-blocker exposure and response. Detailed guidelines for the use of beta-blockers, reflections on

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Received March 8, 2024; accepted May 30, 2024. doi:10.1002/cpt.3351

the cost-effectiveness of genotyping, or whether to order a genotype test prior to beta-blocker prescribing are beyond the scope of this document. Clinical Pharmacogenetics Implementation Consortium (CPIC®) guidelines are periodically updated at www.cpicpgx.org/guidelines/.

FOCUSED LITERATURE REVIEW

Surveys periodically distributed among the CPIC membership indicated that guidelines to inform beta-blocker dosing were a high priority. Thus, a systematic literature review focused on associations between *CYP2D6*, *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, and *GRK5* genotypes and beta-blocker exposure and response was conducted (details in **Supplemental Material**). The literature search included variations of the drug class name as well as the following specific beta-blocker names: acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, celiprolol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, and sotalol (**Table S1**). The evidence for all six genes and all beta-blockers evaluated are summarized in **Tables S2–S7**.

GENES: *CYP2D6*, *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, AND *GRK5*

Background

CYP2D6. *CYP2D6* is a highly polymorphic gene,[1] with over 160 haplotypes (or star [*] alleles) defined by the Pharmacogene Variation (PharmVar) Consortium to date[2] (see ***CYP2D6* Allele Definition Table online**[3,4]). The frequencies of these star alleles differ significantly across ancestrally diverse populations (see ***CYP2D6* Allele Frequency Table online**[3,4]). Alleles are categorized into predicted enzyme function groups with activity values ranging from 0 to 1 and are listed in **Table 1** as follows: normal function (activity value 1; e.g., *CYP2D6*1* and **2*), decreased function (activity value 0.5; e.g., **17* and **29* or 0.25; e.g., *CYP2D6*9*, **10*, and **41*), and no function (activity value 0; e.g., *CYP2D6*3*, **4*, **5*, or **6*). Given that *CYP2D6* is prone to structural variation, including gene deletions, duplications, multiplications, and rearrangements with the pseudogene *CYP2D7*, clinical laboratories often report on *CYP2D6* copy number variation. Notably, *CYP2D6*5* represents a gene deletion, whereas gene duplications and multiplications may be denoted as *CYP2D6*1x2*, indicating the presence of two gene copies, while *CYP2D6*1xN* denotes the presence of two or more gene copies.[5] Clinical allele function, as described in the ***CYP2D6* Allele Functionality Table**, was determined based on reported *in vitro* and/or *in vivo* data when available.[3,4]

ADRB1. *ADRB1* encodes the beta-1 adrenoreceptor, which is antagonized by both "beta-1 selective" (e.g., metoprolol, atenolol) and "non-selective" (e.g., carvedilol, labetalol, propranolol) beta-blockers. The beta-1 adrenoreceptor is a G-protein-coupled receptor that stimulates intracellular cyclic adenylyl monophosphate (cAMP) generation in response to catecholamines (e.g., epinephrine, norepinephrine). Beta-1 adrenoreceptors are primarily expressed in cardiac tissue and thus mediate chronotropic, dromotropic, and inotropic effects from sympathetic nervous system activation in the heart.[6] In the heart, endogenous catecholamine-induced receptor activation (and the subsequent cAMP generation) initiates a calcium-mediated signaling cascade that results in increased cardiac contractility and rate of contraction.[7] Beta-1 adrenoreceptor activation in renal, vascular, and adipose tissues also mediates important physiological events, including renin release, vasodilation, and lipolysis.[8–10] Sustained beta-1 receptor stimulation, which results in receptor desensitization and down-regulation, plays a key role in the development and progression of cardiovascular disease.[11,12] The two most extensively studied ADRB1 variants include the missense variants rs1801252 (c.145A>G; p.Ser49Gly) and rs1801253 (c.1165G>C; p.Gly389Arg). The Gly49 allele increases agonist-promoted desensitization of the beta-1 adrenoreceptor, while Gly389 decreases the efficiency of G-protein coupling.[11] Both alleles produce the net effect of decreasing adenylyl cyclase activity, which results in decreased cAMP production.

ADRB2. *ADRB2* encodes the beta-2 adrenoreceptor, another G-protein-coupled receptor that functions via a similar mechanism as

Table 1 Assignment of predicted CYP2D6 phenotype based on genotype

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

n/a, not applicable.
[a]See the ***CYP2D6* Allele Frequency Table** for ancestry-specific allele and phenotype frequencies.[3,4] [b]Assignment of allele function and allele activity values, including citations for allele function, can be found in the ***CYP2D6* Allele Definition Table** and the ***CYP2D6* Allele Functionality Table**. For a complete list of *CYP2D6* diplotypes and predicted phenotypes, see the ***CYP2D6* Diplotype to Phenotype Table.**[3,4] [c]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see the **Supplemental Material** for additional information on how to translate diplotypes into phenotypes.

the beta-1 receptor. The beta-2 receptor is antagonized at clinically used doses by "non-selective" beta-blockers, such as carvedilol, labetalol, and propranolol. This receptor is primarily expressed in bronchial smooth muscle cells but is also expressed in cardiomyocytes and vascular smooth muscle cells. Like the beta-1 adrenoreceptor, activation of the beta-2 adrenoreceptor by catecholamines stimulates intracellular signaling of adenylyl cyclase to produce cAMP. Activation of beta-2 adrenoreceptors in bronchial smooth muscle results in bronchodilation, and activation in cardiomyocytes also potentiates chronotropic, dromotropic, and inotropic effects. The two frequent and most studied ADRB2 variants are rs1042713 (c.46G>A; p.Gly16Arg) and rs1042714 (c.79G>C; p.Glu27Gln). The Gly16 allele potentiates agonist-promoted receptor downregulation (decreasing cAMP production), while Glu27 produces resistance to agonist-promoted downregulation (increasing cAMP production).[13–15]

ADRA2C. *ADRA2C* encodes the alpha-2c adrenoreceptor, a pre-synaptic G-protein-coupled receptor that decreases norepinephrine release from sympathetic nerves when activated. When stimulated by endogenous catecholamines, alpha-2 adrenoreceptors inhibit adenylyl cyclase to decrease cAMP levels and cause hyperpolarization of noradrenergic neurons.[16] The in-frame deletion rs61767072 (c.971_982del) results in the loss of four amino acids (p.Gly324_Ala327del; also commonly referred to as $Del_{322\text{-}325}$) is most commonly found in individuals of African descent and is associated with decreased receptor function.[17] This leads to increased sympathetic nervous activity and increased catecholamine response to the alpha-2 adrenoreceptor antagonist yohimbine.[18]

GRK4. G protein-coupled receptor kinases (GRK) desensitize activated G protein-coupled receptors, including the beta-1 and beta-2 adrenoreceptors, ultimately leading to receptor downregulation.[19] Agonist-occupied G protein-coupled receptors are deactivated via intracellular phosphorylation by GRKs, leading to beta-arrestin-mediated receptor desensitization.[19] There are seven known GRK isoforms, and GRK4 and GRK5 are the most studied with regard to beta-blocker pharmacogenetics. *GRK4* encodes the G protein-coupled receptor kinase 4 and is primarily expressed in the testes and brain. The two most commonly studied variants in *GRK4*, rs1024323 (c.425C>T; p.Ala142Val) and rs1801058 (c.1457T>C; p.Val486Ala), enhance agonist-promoted desensitization of beta-adrenoreceptors, leading to decreased intracellular cAMP production.[20]

GRK5. *GRK5* encodes the G protein-coupled receptor kinase 5, and it is expressed in cardiovascular tissues.[21] The rs2230345 (c.122A>T; p.Gln41Leu) variant potentiates agonist-promoted beta-receptor desensitization, ultimately decreasing the production of cAMP.[22]

Genetic test interpretation

CYP2D6. Clinical laboratories typically interrogate *CYP2D6* genetic variants of known functional consequences in the general population. Genotypes are assigned using star (*) allele nomenclature, which can be found at the PharmVar website (https://www.pharmvar.org/gene/CYP2D6). Each star allele (or haplotype) represents a specific combination of variants identified by the gene test. The combination of inherited alleles (maternal and paternal) determines a person's diplotype, also referred to as genotype (e.g., *CYP2D6*1/*4*). Tables on the CPIC and PharmGKB websites contain lists of known *CYP2D6* alleles, the combinations of variants that define each allele, their associated functions, and reported allele frequencies across major ancestral populations.[3,4] Unlike many other pharmacogenes, discerning gene copy number is essential for the accurate genetic prediction of an individual's CYP2D6 phenotype. Table 1 defines each predicted phenotype based on CYP2D6 activity score and provides example diplotypes. See the ***CYP2D6* Diplotype-Phenotype Table online** for a complete list of possible diplotypes and the corresponding predicted metabolizer phenotype assignments.[3,4] *CYP2D6* genotype to phenotype translation has been standardized by CPIC and the Dutch Pharmacogenetics Working Group.[23] For more details on interpreting *CYP2D6* test results, including activity score calculations, please see the **Supplemental Material** Genetic Test Interpretation Section.

ADRB1, *ADRB2*, *ADRA2C*, *GRK4*, and *GRK5*. To date, no standardized genotype to phenotype translation or phenotype terms have been adopted for *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, or *GRK5*. Rather, variants are denoted by either their unique rs number and the bases at that location defining the genotype (e.g., C/C), the position on their respective transcript reference sequences (e.g., c.145A > G), or the corresponding amino acid that is associated with missense variations (e.g., p.389Arg/Gly). Clinical testing of these five genes is available commercially both as individual tests and as part of larger test panels.

Available genetic test options

See the **Supplemental Material** and the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/) for more information on commercially available clinical testing options.

Incidental findings

Currently, there are no diseases or conditions that have been consistently linked to variation in the *CYP2D6* gene independent of drug metabolism or drug response. *CYP2D6* variation may affect a patient's response to several drugs, many of which are discussed in CPIC guidelines (www.cpicpgx.org/guidelines/). Likewise, there are no diseases or conditions that have been consistently linked to the aforementioned variants in *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, or *GRK5*. Studies have reported associations between *ADRB2* genotype and response to long-acting beta-2 adrenoreceptor agonists in patients with asthma.[24]

Other considerations

Consistent with the approach used in most of the available studies, the evidence review primarily assessed the independent effects of each individual genetic variant. Some studies analyzed the associations for haplotypes containing two or more genetic variants or the additive effects of multiple genetic variants together (**Table S7**). While early evidence from patients with heart failure suggests that a polygenic score may help predict beta-blocker response,[25,26] the authors felt there was insufficient evidence to guide any clinical recommendations related to such scores at this time. Once additional evidence related to

polygenic effects on beta-blocker response becomes available, these scores may be evaluated in future guidelines. Other types of higher order interactions, such as multi-gene, drug–drug-gene, gene–environment interactions, and epigenetics, were not assessed in most of the studies evaluated, and hence, were also not evaluated in this guideline.

DRUGS: BETA-BLOCKERS

Background

Beta-blockers, also known as beta adrenoreceptor antagonists, are a class of drugs used for both cardiac (e.g., angina pectoris, cardiac arrhythmias, hypertension, myocardial infarction, heart failure) and non-cardiac indications (e.g., anxiety, essential tremor, glaucoma, migraine prophylaxis). Metoprolol was the sixth most prescribed drug overall in the United States, with 65.5 million prescriptions in 2021.[27] Four other beta-blockers (carvedilol, atenolol, propranolol, and timolol) were also among the top 200 drugs prescribed in the United States in 2021. Beta-blockers are classified as beta-1 selective, or "cardioselective," if they predominantly antagonize beta-1 receptors (primarily located in cardiac tissue) at clinically used doses, or they are classified as "non-selective" if they antagonize both the beta-1 and beta-2 receptors (primarily located not only in smooth muscle tissue but also expressed in the heart). Examples of "non-selective" beta-blockers include carvedilol, labetalol, and propranolol; "beta-1 selective" agents include atenolol, betaxolol, bisoprolol, metoprolol, and nebivolol (**Table S1**). Notable adverse effects caused by beta-adrenoreceptor blockade include bradycardia, hypotension, fatigue, insomnia, dizziness, depression, erectile dysfunction, and acute bronchospasm.

Linking genetic variability to variability in drug-related phenotypes

The guideline writing committee conducted a systematic evaluation of the data linking genetic variation with beta-blocker exposure and response. Beta-blockers with applicable evidence available for evaluation included acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, and sotalol. The committee reviewed and graded the evidence related to associations with response to these drugs and the following genes: *CYP2D6*, *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, and *GRK5* (**Tables S2–S7**). This evidence was used to support the therapeutic recommendations provided below. Much of the available evidence was from older studies using older genotyping and analytical techniques. However, the guideline writing committee felt sufficient evidence exists to support clinical recommendations related to *CYP2D6* and metoprolol.

CYP2D6 appears to play a major role in the hepatic metabolism and elimination of several beta-blockers, most notably, metoprolol, carvedilol, nebivolol, and propranolol (**Table S1**). CYP2D6 poor metabolizers can experience several-fold higher plasma metoprolol, carvedilol, and nebivolol concentrations following oral administration, compared with those who are not poor metabolizers.[28–30] Insufficient evidence exists to indicate whether propranolol systemic exposure is similarly increased in CYP2D6 poor metabolizers. The greatest magnitude of pharmacogenetic effects, coupled with the most extensive pharmacokinetic data, relate to metoprolol, which is metabolized by CYP2D6 to mostly inactive metabolites. Compared with CYP2D6 normal metabolizers, poor metabolizers given the same dose of metoprolol experience more than a two-fold longer elimination half-life, with a nearly five-fold increase in area under the plasma concentration–time curve (AUC).[28] Of note, beta-blockers exhibit a sigmoid dose–response relationship. Thus, increasing beta-blocker plasma concentrations beyond a certain threshold does not result in further increases in drug response.[31]

Despite the observed pharmacokinetic differences in the above-listed beta-blockers, *CYP2D6* genotype-associated differences in clinical response have only been consistently reported for metoprolol—primarily related to heart rate and blood pressure response.[32–35] Evidence suggests that the markedly increased metoprolol exposure experienced by CYP2D6 poor metabolizers also leads to a greater metoprolol-associated decrease in blood pressure (approximately 3–6 mmHg systolic; 2–6 mmHg diastolic) and heart rate (approximately 3–8 beats/min). This exaggerated heart rate response to metoprolol in poor metabolizers may increase the risk of bradycardia, but few well-powered studies have assessed this risk.[32,33] Given that beta-blockers are often started at low doses and titrated up based on response (usually as indicated by heart rate and blood pressure), the risk of bradycardia is less likely to occur than if beta-blockers were initially prescribed at target doses for guideline-directed therapy. Thus, additional caution in CYP2D6 poor metabolizers may be warranted in circumstances where metoprolol dosing may not undergo up-titration.

In *ADRB1*, p.Ser49Gly and p.Gly389Arg are among the most studied variants, with the "Gly" allele at both locations leading to decreased cAMP production after beta-1 receptor stimulation *in vitro*—somewhat endogenously mimicking the effect of beta-blockers. Thus, patients with the p.Ser49 or p.Arg389 alleles would be expected to exhibit a greater pharmacologic response to beta-blockers. Nevertheless, the current evidence does not consistently support that these variants affect either beta-blocker dosage requirements or response as indicated by heart rate, blood pressure, or echocardiographic measures in patients.[36–40] The data related to *ADRB1* and the clinical outcomes of beta-blocker treated patients are more conflicting, particularly in heart failure (the patient population most studied). However, the writing committee noted a trend in the clinical outcomes evidence, depending on whether the studies evaluated beta-blocker response by dose level vs. as a binary variable (i.e., receiving beta-blocker treatment or not). Of the studies that reported significant associations between p.Gly389Arg and cardiovascular outcomes, nearly all of them analyzed beta-blocker response by dose level in their analyses. When treated with low-dose beta-blockers, patients with the p.389Arg/Arg genotype experienced significantly worse outcomes than those with other genotypes, but no similar associations were observed at higher doses.[41–43] On the other hand, almost no studies that analyzed beta-blocker use as a binary variable (yes/no) reported p.Gly389Arg associations with clinical outcomes.[40,44–46] Thus it is possible that, if beta-blocker-mediated cardiovascular outcomes differ by p.Arg389Gly genotype, titration to goal beta-blocker doses could abrogate the effect. However, this dose-related trend

was primarily observed in *post hoc* analyses of non-randomized studies. Given the current available evidence, the writing committee concluded that additional research is needed to further confirm or refute this dose-related observation before any clinical recommendations could be made (CPIC level C-no recommendation).

The committee found insufficient evidence to support recommendations between beta-blocker response and *ADRB2* genotype. However, fewer analyses of *ADRB2* variants are available in the literature compared with *ADRB1*, and pharmacogenetic interactions with *ADRB2* may depend on whether the beta-blocker in question is non-selective (and therefore likely to inhibit the beta-2 receptor at clinically used doses). Even fewer studies were available related to individual variants in *ADRA2C*, *GRK4*, and *GRK5* and their associations with beta-blocker response. Thus, no clinical recommendations were provided for individual variants in *ADRB2*, *ADRA2C, GRK4*, or *GRK5* (CPIC level C-no recommendation). While some studies reported additive effects of various combinations of variants in pharmacodynamic genes (**Table S7**), the writing committee found insufficient evidence to make clinical recommendations regarding any of these variant combinations. Thus, another question that requires further study involves the additive effects of multiple variants within the same pharmacodynamic gene (or across multiple genes) on beta-blocker response.

Therapeutic recommendations

The writing committee concluded that sufficient evidence was available to provide recommendations on how to use *CYP2D6* genotype information to guide the prescribing of metoprolol. Insufficient evidence was available to support recommendations for the other beta-blockers reviewed (CPIC level C-no recommendation; **Tables S8–S10**). Importantly, none of the recommendations provided in this guideline should be interpreted in a way that would prevent or impede the up-titration of beta-blocker doses to maximally tolerated or guideline-recommended levels, such as in heart failure with reduced ejection fraction and in the post-myocardial infarction setting. Moreover, specific recommendations for dose reductions were not made in this guideline.

Metoprolol. The evidence supporting the association of *CYP2D6* genotype with metoprolol exposure and response included participants with a variety of health statuses (e.g., healthy, hypertension, heart failure, etc.). Therefore, it may be reasonable to assume that the pharmacokinetic effects of *CYP2D6* variation would affect clinical metoprolol response similarly across a variety of indications, and the dosing recommendations provided could be utilized for most cardiovascular indications (**Table 2**). Recommendations primarily focus on minimizing the risk of adverse effects in CYP2D6 poor metabolizers related to the greater observed reductions in heart rate and blood pressure stemming from increased metoprolol systemic exposure. In addition, the maximally tolerated metoprolol dose may be lower in poor metabolizers compared with normal metabolizers due to these pharmacokinetic differences. Thus, these recommendations are expected to help clinicians predict patients more likely to experience such adverse effects. We found insufficient evidence to support recommendations related to *CYP2D6* genotype and other clinical outcomes.

While the evidence suggests metoprolol plasma concentrations are also increased in CYP2D6 intermediate metabolizers compared with normal metabolizers, these effects appear smaller in magnitude than those observed with poor metabolizers, and there was insufficient evidence to clarify whether these smaller pharmacokinetic differences significantly affect clinical response. Moreover, there was insufficient evidence to determine whether CYP2D6 ultrarapid metabolizers experience clinically significant differences in metoprolol exposure or response. Most of the data available regarding associations between *CYP2D6* genotype and metoprolol response are related to oral formulations; limited evidence exists regarding pharmacogenetic effects with intravenous formulations.

Carvedilol. While there is considerable evidence that CYP2D6 intermediate and poor metabolizers experience increased carvedilol exposure, there are far fewer reports in the literature, compared with metoprolol, assessing whether this translates to clinical differences in heart rate or blood pressure response. This may, in part, be due to the fact that carvedilol is predominantly used in heart failure and is therefore slowly up-titrated, preventing many poor metabolizers from ever receiving a dose that could cause significant bradycardia. In addition, CYP2D6 metabolizes carvedilol to both pharmacologically inactive and active metabolites, which may explain why significant differences in carvedilol exposure by CYP2D6 phenotype do not seem to consistently translate into significant differences in clinical response.[30] The committee acknowledged the assessment from the US Food and Drug Administration that CYP2D6 poor metabolizers may be at a higher risk of dizziness when given carvedilol,[47] which may be based upon unpublished data. However, considering only published results, the writing committee felt there was insufficient evidence to support carvedilol dosing recommendations based on predicted CYP2D6 phenotype (CPIC level C—no recommendation; **Table S8**).

Pediatrics. Beta-blockers are used to treat a variety of indications in children, such as heart failure, hemangiomas, migraine, aggression, and anxiety. However, only two pediatric pharmacogenetic studies of beta-blockers were identified.[48,49] Therefore, more evidence is needed before clinical recommendations can be specifically made for pediatric patients. It may be appropriate, with caution, to extrapolate the recommendations for CYP2D6 and metoprolol to most children because *CYP2D6* genotype appears to correlate with CYP2D6 activity as early as 2 weeks of age.[50]

Biogeographical groups. These recommendations are derived from studies that primarily included individuals of European ancestry as defined elsewhere.[51] Although studies including individuals from other ancestry groups are needed, the effects of functional *CYP2D6* genetic variants on beta-blocker exposure or treatment outcomes are expected to be similar across biogeographic groups. However, selecting *CYP2D6* genetic tests that include variants present in the patient population being cared for is critical to ensure that phenotypes are accurately predicted (see the "Caveats" section below).

Table 2 Dosing recommendations for metoprolol based on CYP2D6 phenotype

Phenotype	Activity score	Implications[a]	Recommendations	Classification of recommendations[b]
CYP2D6 ultrarapid metabolizer	>2.25	Increased metabolism of metoprolol leading to decreased drug concentrations; however, it is unclear whether this results in clinically significant changes in heart rate, blood pressure, or clinical outcomes.	No recommendation for metoprolol therapy due to insufficient evidence regarding diminished metoprolol effectiveness clinically.	No recommendation
CYP2D6 normal metabolizer	1.25≤x≤2.25	Normal metabolism of metoprolol	Initiate standard dosing.	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	Decreased metabolism of metoprolol leading to increased drug concentrations; however, this does not appear to translate into clinically significant changes in heart rate, blood pressure, or clinical outcomes.	Initiate standard dosing.	Moderate
CYP2D6 poor metabolizer	0	Decreased metabolism of metoprolol leading to markedly increased drug concentrations; this leads to greater heart rate and blood pressure reductions. The effect on clinical outcomes is unclear.	Initiate therapy with lowest recommended starting dose. Carefully titrate dose upward to clinical effect or guideline-recommended dose; monitor more closely for bradycardia. Alternatively, consider selecting another beta-blocker.	Moderate
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.
[a]Metoprolol has no known active metabolites via CYP2D6. [b]Rating scheme described in Supplemental Materials

Recommendations for incidental findings

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

Other considerations

Patients already receiving metoprolol. The therapeutic recommendations described above predominately apply to patients with genotypes predicting CYP2D6 poor metabolism who will be newly prescribed (or receiving a revised prescription for) metoprolol. However, because millions of patients are already prescribed metoprolol, it is expected that many patients already receiving metoprolol may later become aware of their predicted CYP2D6 phenotype. With daily dosing of metoprolol succinate (an extended-release formulation), plasma concentrations are expected to achieve steady-state in as soon as 5 days within the general population.[52] Moreover, the most common adverse effects of metoprolol (e.g., bradycardia and hypotension) are dose-dependent and generally expected to occur after the first few doses. Therefore, if a CYP2D6 poor metabolizer has already been tolerating stable metoprolol therapy, additional CYP2D6-associated adverse effects become less likely—assuming no changes in metoprolol dose or other health, medication, or lifestyle changes occur. Thus, modifying metoprolol therapy in CYP2D6 poor metabolizers on a well-tolerated regimen solely based on *CYP2D6* genotype is probably unnecessary. This recommendation is primarily based on expert opinion and the clinical differences observed in CYP2D6 poor metabolizers after acute administration of metoprolol in studies with a very small sample size.[28]

Drug–drug interactions and phenoconversion. Genetic test results do not consider other clinical characteristics that may also significantly affect CYP2D6 enzyme activity, including a phenomenon known as "phenoconversion." Drug–drug interactions are a common cause of phenoconversion.[53] For example, a *CYP2D6* genetic test result may predict that the patient is a CYP2D6 normal metabolizer. However, if the patient concomitantly takes another drug or a phytochemical

that strongly inhibits CYP2D6, the predicted phenotype may convert to poor CYP2D6 metabolizer. As many as 30% of patients may be taking a concomitant CYP2D6 inhibitor leading to phenoconversion.[53] CYP2D6 inhibitors are classified as strong, moderate, or weak.[54] It is recommended to assume a CYP2D6 activity score of zero (i.e., poor metabolizer) in patients taking adequate doses of a concomitant strong CYP2D6 inhibitor and to reduce the predicted activity score by half in patients taking a moderate inhibitor. No activity score adjustment is suggested for weak inhibitors,[55] and there are no known drugs that significantly induce CYP2D6 enzyme activity.

Implementation of this guideline. The guideline supplement and CPIC website[3] contain resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* in the **Supplemental Material**).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of using *CYP2D6* genotype data to guide metoprolol therapy is the avoidance of supratherapeutic plasma concentrations and the associated exaggerated hemodynamic responses in CYP2D6 poor metabolizers. It would also potentially prevent patients from experiencing symptoms and adverse clinical effects related to these responses.

As with any laboratory test, a possible risk to patients is an error in genotyping or phenotype prediction. Such an error could lead to lower initial beta-blocker dosing. However, this risk is mitigated by recommendations (supported by this guideline) to up-titrate beta-blocker doses to either the dose maximally tolerated by the patient or to guideline-directed doses, when clinically appropriate.

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

As with any diagnostic test, *CYP2D6* genotype is just one factor that clinicians should consider when prescribing metoprolol. There can be important limitations to *CYP2D6* genetic testing. Targeted genotyping tests focus on interrogating previously described star (*) alleles and therefore are not designed to detect novel variants. Furthermore, rare allelic *CYP2D6* variants may not be included in the targeted genotype test used, and patients with these rare variants may be assigned a metabolizer status that does not reflect their true enzymatic phenotype. As such, alleles assigned by "default," especially *CYP2D6*1*, could potentially harbor an undetected genetic variant that results in altered metabolism and drug exposure. Many rare variants are predominantly found in non-European populations, increasing the likelihood of inaccurate phenotype assignments for non-European ancestry patients in the absence of testing. The Association for Molecular Pathology in collaboration with other professional organizations has published recommendations for a minimum set of variants that should be included in clinical genotyping assays for *CYP2D6*.[56] As described in more detail above, phenoconversion of the genetically predicted CYP2D6 metabolizer status, due to non-genetic factors such as drug–drug interactions, is common and must also be considered with the genetic test results. In addition, many other clinical factors (e.g., liver function, concurrent cardiac conditions, and diabetes) may affect patient response to metoprolol and other beta-blockers.

SUPPORTING INFORMATION

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

ACKNOWLEDGMENTS

We acknowledge the critical input of Dr. Mary V. Relling and members of the Clinical Pharmacogenetics Implementation Consortium (CPIC), funded by the National Institutes of Health. CPIC members are listed here: https://cpicpgx.org/members/.

FUNDING

This work was funded by the National Institutes of Health (NIH) for CPIC (R24GM115264 and U24HG010135) and PharmGKB (U24HG010615). Additional grant funding includes R01HG011800 (J.D.D.), K08HL146990 (J.A.L.), the Robert Bosch Stiftung Stuttgart, Germany (M.S.), R35 GM131770 (C.M.S), P50MD017351 (D.E.L.), and R01HL132154 (D.E.L.).

CONFLICT OF INTEREST

A.G. is the director of PharmVar and a consultant for Delix Pharmapeutics. D.E.L. is a consultant for Janssen, Ortho Diagnostics, Cytokinetics, AstraZeneca, Otsuka, Abbott Laboratories, Illumina, has participated in research from Amgen, Lilly, AstraZeneca, Pfizer, Bayer, Illumina, and Janssen, and has a patent (held by Henry Ford Health) for a beta blocker response polygenic score. J.A.L. is a consultant for Ariel Precision Medicine. All other authors declare no competing interests for this work.

DISCLAIMER

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

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