Supplement to:

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

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TABLE OF CONTENTS

LITERATURE REVIEW

The PubMed® database (1966 to April 2023) was searched for the following keywords: (((Acebutolol) OR (Atenolol) OR (beta blocker) OR (Bisoprolol) OR (Carvedilol) OR (Esmolol) OR (Labetalol) OR (Metoprolol) OR (Nadolol) OR (Nebivolol) OR (Pindolol) OR (Propranolol) OR (Sotalol) OR (betaxolol) OR (celiprolol) OR (betablocker) OR (β-blocker) AND ((CYP2D6) OR (ADRB1) OR (ADRB2) OR (ADRA2C) OR (GRK4) OR (GRK5)) AND ((genotype) OR (varia*) OR (allele))). The search was limited to studies conducted in humans or relevant experimental models and written in the English language. Review articles and studies only published as abstracts were excluded. Studies on polygenic scores were excluded. Using these search terms, 349 publications were identified. Study inclusion criteria included publications that incorporated analyses for the association between *CYP2D6, ADRB1, ADRB2, ADRA2C, GRK4,* or *GRK5* genotype and beta-blocker pharmacokinetic parameters or beta-blocker-related clinical outcomes in patients. Following the application of these criteria, 243 publications were reviewed and included in the evidence tables (**Tables S2-S7**).

GENE: *CYP2D6*

Genetic Test Interpretation

CYP2D6 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* haplotypes are described using star (*) allele nomenclature to allow for the standardization of genetic variation annotation (1). A complete list of *CYP2D6* star alleles along with the genetic

variants that define each star allele is available at https://www.pharmvar.org/gene/CYP2D6, and the ***CYP2D6* Allele Definition Table** may be found at https://cpicpgx.org/guidelines/cpic-guideline-for-beta-blockers/. Knowing which SNPs or other genetic variants a particular pharmacogenomic test interrogates is important because the inclusion or exclusion of certain variants in the test could affect the reported star allele result.

Clinical laboratories typically report a diplotype (often referred to as a genotype), which is the summary of inherited maternal and paternal star alleles (e.g., *CYP2D6*1/*4*, where an individual inherited a **1* allele and a **4* allele). Commonly reported *CYP2D6* star alleles are categorized into function groups (e.g., increased function, normal function, decreased function, or no function) based on the predicted activity of the encoded enzyme (***CYP2D6* Allele Functionality Table**) (2, 3). The predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype.

Calculating CYP2D6 Activity Score. Gaedigk *et al.* developed a scoring system to provide a uniform approach for assigning a predicted CYP2D6 phenotype (4). For this guideline, an updated method to translate *CYP2D6* genotype into phenotype is utilized (5). The activity values assigned to each allele are added together to calculate the CYP2D6 activity score for the reported diplotype. For example, to calculate the activity score of a *CYP2D6*1/*17* diplotype, the activity values of **1* (activity value = 1) and **17* (activity value = 0.5) are totaled to provide the CYP2D6 activity score of 1.5. Note that an activity value of 0.5 indicates decreased activity and not that the activity conveyed by the allele is half of that encoded by a normal function allele with an activity value of 1. CYP2D6 activity scores translate genotype into phenotype as follows: activity score of 0 = poor metabolizer (PM), activity scores of $0 < x < 1.25$ =

intermediate metabolizer (IM), activity scores of $1.25 \leq x \leq 2.25$ = normal metabolizer (NM), and activity scores greater than 2.25 = ultrarapid metabolizer (UM). Therefore, a pharmacogenomic test result of *CYP2D6*1/*17* would result in a CYP2D6 activity score of 1.5 and a predicted phenotype of NM.

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

A copy number greater than two indicates the presence of a *CYP2D6* gene duplication or multiplication. When a *CYP2D6* gene duplication is present, the diplotype may be reported as *CYP2D6 (*1/*2)3N*, where "*3N*" represents gene copy number. A clinical laboratory may not report an exact copy number or which allele has the duplication, but rather indicate that an additional copy or copies of the *CYP2D6* gene are present (e.g., *CYP2D6*1/*2* duplication or *CYP2D6 (*1/*2)xN*). In instances where a duplication or multiplication is present, and the exact

copy number is not reported, most patients will likely have a *CYP2D6* gene copy number of 3. However, individuals carrying as many as 13 *CYP2D6* gene copies have been reported (6). Some clinical laboratories may not determine which allele is duplicated; therefore, when calculating CYP2D6 activity score the duplication must be considered for each allele reported in the diplotype (7). 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 normal function *CYP2D6*1* allele and one copy of the nonfunctional *CYP2D6*4* allele (*CYP2D6*1x2/*4*), or one copy of the *CYP2D6*1* allele and two copies of the *CYP2D6*4* allele (*CYP2D6*1/*4x2*). If the normal function *CYP2D6*1* allele carries the duplication, the CYP2D6 activity score of this diplotype will be 2 (NM), whereas if the nonfunctional *CYP2D6*4* allele carries the duplication, the activity score will be 1 (IM). Likewise, if the number of gene copies is not determined and it remains unknown which allele carries the duplication or multiplication, a *CYP2D6 (*1/*10)xN* genotype, for example, can be consistent with a normal metabolizer phenotype (*CYP2D6*1/*10x2*, activity score of 1.5 or *CYP2D6*1x2/*10,* activity score of 2.25) or UM phenotype (*CYP2D6*1x2/*10x2*, activity score of 2.5 or *CYP2D6*1x3/*10*, activity score of 3.25). As these examples illustrate, phenotype prediction will be more accurate if testing determines which allele carries the duplication or multiplication and the number of gene copies present. Consequences of *CYP2D6* copy number variation on pharmacotherapy have been reviewed by Jarvis *et al*. 2019 (8).

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 gene duplication on one allele and a gene deletion on the other for a total number of two gene copies. This diplotype may also be reported as *CYP2D6*2/*2*.

Other structural variants include gene copies that consist of *CYP2D6* and *CYP2D7*-derived sequences (9-11). An overview of these variants can also be found in the "Structural Variation" document at https://www.pharmvar.org/gene/CYP2D6. The no function *CYP2D7:CYP2D6* hybrid genes, collectively assigned as *CYP2D6*13* (12), may not be detected by a particular genotype test or gene copy number testing. In such cases the test may detect only the allele present on the second chromosome and report the diplotype as homozygous for that allele. For example, a test that does not detect *CYP2D6*13* will report a *CYP2D6*1/*13* diplotype as *CYP2D6*1/*1*. Hybrid genes can also occur in duplication configurations and cause positive gene duplication test results that may lead to an overestimation of activity and false-positive prediction of ultrarapid metabolism (10, 13). For example, a *CYP2D6*1/*13+*2* diplotype (activity score = 2, predicting normal metabolism) may be assigned as *CYP2D6*1/*2xN* (activity score ≥ 3, predicting ultrarapid metabolism).

Additional information can be found in the PharmVar Tutorial on *CYP2D6* Structural Variation Testing and Recommendations on Reporting (14).

Limitations of the Star (*) Nomenclature and Allele Assignments. PharmVar star (*) allele nomenclature provides suballele definitions (e.g., *CYP2D6*2.001, CYP2D6*4.002*), but these are typically not distinguished by current testing. This is of no consequence for *CYP2D6*4*, as all **4* suballeles share the 1847G>A variant causing aberrant splicing and absence of functional protein. However, for *CYP2D6*2* it is unknown whether any of the sequence variations defining the suballeles convey a functional consequence. Also, there is no, or little, information regarding their frequencies because most laboratories do not discriminate between the suballeles. In addition, there are likely numerous known variants and suballeles that have not been designated

by PharmVar at this time (investigators and clinical laboratories are encouraged to submit novel information to PharmVar).

The accuracy of a pharmacogenomic 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 interrogated, the allele assignment may vary. For example, if 2851C>T is present, but 1022C>T is not, the assignment is *CYP2D6*2*. In contrast, if 1022C>T is also present, the allele would be assigned as *CYP2D6*17*. Additional examples are provided in the PharmVar *CYP2D6* GeneFocus paper (11). Also see 'CYP2D6 Other Considerations' below.

Note that the variant positions provided above and below are according to the NG_008376.4 reference sequence (RefSeq). The M33388 "legacy" RefSeq contains errors causing certain SNP positions to shift by 1-base when mapped to the NG_008376.4 RefSeq. PharmVar uses NG_008376.4 for allele definitions and strongly encourages the use and reporting of positions in respect to NG_008376.4 RefSeq. To facilitate variant mapping, PharmVar cross-references positions between NG_008376.4 and M33388 (https://www.pharmvar.org/gene/CYP2D6). Of note, NG_008376.4 corresponds to the sequence present in the GRCh38 genome build.

Recent findings indicate that a variant (rs5758550) in a distal enhancer region impacts allele activity on the transcriptional level (15, 16). Specifically, it was reported that *CYP2D6*2* alleles lacking the "enhancer" SNP have decreased function. However, one subsequent study found that the enhancer SNP did not lead to improved prediction of endoxifen concentrations in breast cancer patients using tamoxifen (17). Another was inconclusive as to whether the small observed effects were indeed caused by the enhancer SNP or were due to its incomplete linkage

with other variants within the gene. Furthermore, it was also reported (18) that this SNP can occur on many other star alleles besides *CYP2D6*2,* and that the portion of an allele with and without rs5758550 may considerably vary among biogeographical groups. Thus, it remains uncertain whether the effect of this SNP on CYP2D6 activity *in vivo* is of clinical significance. rs5758550 is currently not included in common *CYP2D6* genotyping panels, nor is it included in star allele definitions.

Available Genetic Test Options

Commercially available genetic testing options change over time. The Genetic Testing Registry provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr. Desirable characteristics of pharmacogenomic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (19) as well as the American College of Medical Genetics and Genomics (ACMG) (20). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables adhere to these allele nomenclature standards. Moreover, these tables (**Allele Definition Tables**, **Allele Functionality Tables**, and **Allele Frequency Tables**) may be used to assemble lists of known functional and actionable genetic variants and their population frequencies, which may inform decisions as to whether pharmacogenomic tests are adequately comprehensive with the interrogated alleles (2, 3). Furthermore, the Association for Molecular Pathology (AMP) has published a recommendation for the key attributes of alleles recommended for clinical testing and a minimum set of variants that should be included in clinical genotyping assays for *CYP2D6* (21) and other pharmacogenes.

Other Considerations

There are several factors that cause potential uncertainty in *CYP2D6* genotyping results and phenotype predictions as follows: **1)** Given that it is currently impractical to test for every variation in the *CYP2D6* gene, genotyping assays may not detect rare 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* (i.e., correspond to the reference) 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)** Suballeles of *CYP2D6*4* and other star alleles have been identified that harbor additional variants which have no added functional consequence (e.g., *CYP2D6*4.001*, **4.002*, **4.003*, and **4.004*). Therefore, only analyzing for the defining variant, or core SNP of *CYP2D6*4* (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 (22). 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 the 1846G>A 'core' SNP, but also 100C>T. If a patient is heterozygous for these two SNPs, a *CYP2D6*1/*4* is typically assigned. However, the rare *CYP2D6*4.012* subvariant does not carry 100C>T, which in isolation defines the *CYP2D6*10* decreased function allele. Therefore, a *CYP2D6*4.012/*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 ancestral backgrounds (biogeographical groups). 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 groups such as Europeans. Moreover, *CYP2D6*114 (formerly *14A)* is present in Asian populations and the core variant defining this allele (1758G>A) is typically incorporated into Asian genotyping panels (23). Thus, the alleles that should be tested for a given population may vary considerably. **7)** Certain alleles carry genes in duplication arrangements. One such example is *CYP2D6*36+*10* (one copy of the no function *CYP2D6*36* allele and one copy of the decreased function *CYP2D6*10* allele). This duplication is frequently found in East Asians and their descendants and is typically defaulted as *CYP2D6*10* due to limitations of many test platforms identifying this structural variant. The complexity of the *CYP2D6* locus is detailed in the PharmVar CYP2D6 GeneFocus review (11) and PharmVar tutorial on CYP2D6 structural variation testing and recommendations for reporting(14). Additional information regarding gene analysis, interpretation, and phenotype assignment is summarized by Hicks *et al*., Gaedigk, and Jarvis *et al.* (8, 10, 24) and the complexity of testing is commented on by Nofziger & Paulmichl (25). **8)** Genetic test results do not take into account other clinical characteristics of the patient that may also significantly affect CYP2D6 enzyme activity; a phenomenon referred to as “phenoconversion.” Drug-drug interactions are a common cause of phenoconversion (26). For example, a patient’s *CYP2D6*

genetic test result may indicate that they are a CYP2D6 normal metabolizer, but if they are taking a concomitant strong CYP2D6 inhibitor, then their clinical phenotype is that of a CYP2D6 poor metabolizer. As many as 30% of patients may be taking a concomitant medication (i.e., CYP2D6 moderate or strong inhibitor) that inhibits CYP2D6 causing phenoconversion (26). Other clinical characteristics, such as inflammation and pregnancy, have also been associated with CYP2D6 enzyme activity (27). Thus, clinicians must also consider non-genetic factors that may influence CYP2D6 activity along with the genetic test results.

DRUGS: BETA-BLOCKERS

Therapeutic Recommendations

Pediatrics. Only two pharmacogenetic studies of beta-blockers in pediatric patients were identified (28, 29). Wang *et al.* analyzed the association of two variants in *CYP2D6* (rs1065852, 100C>T (found in *CYP2D6*4, *10* and others) and rs1135840, 4181G>C found in numerous star alleles including *CYP2D6*2*) with the clinical response to propranolol in 72 Chinese infants with hemangiomas (median [IQR] age 65.5 [48.2-93.8] days) (29). Patients with the rs1135840 G/G genotype had the highest clinical response rate to propranolol ($p = 0.031$), whereas rs1065852 was not significantly associated with clinical response rate ($p = 0.541$). Van Driest *et al.* analyzed the association of *ADRB1* rs1801252 (p.Ser49Gly) and rs1801253 (p. Arg389Gly) and *CYP2C9* rs1799853 (*CYP2C9*2*) and rs1057910 (*CYP2C9*3*) with the response to atenolol (change in maximum aortic root diameter) in pediatric patients with Marfan syndrome (28). They performed a post-hoc analysis of a randomized controlled trial comparing treatment of atenolol versus losartan in 250 white, non-Hispanic participants (mean ± sd age 12.0 ± 6.5) (28). The

ADRB1 p.Arg389/Arg389 genotype resulted in a significantly greater rate of improvement in aortic root diameter with atenolol compared with patients carrying the p.Gly389 allele (time × genotype interaction p = 0.005). The other variants were not significantly associated with atenolol response. Given the small sample sizes and the specific indications in these studies by Wang *et al* and Van Driest *et al*, more evidence is needed before recommendations can be made regarding *CYP2D6* and propranolol or *ADRB1* and atenolol in pediatric populations.

Other Considerations

The evidence available related to pharmacogenetic associations with beta-blockers primarily focused on oral formulations. Thus, it is not clear whether these associations are similar with other routes of administration such as intravenous, transdermal, or ophthalmic. Metoprolol is available in both as immediate and extended-release formulations. Most of the reviewed studies did not specify which formulation was investigated, so whether *CYP2D6* associations apply to specific formulations could not be determined. However, the bioavailability of both immediate and extended release oral formulations are high, and metoprolol systemic exposure is increased to a similar degree with each formulation following administration of the strong CYP2D6 inhibitor paroxetine (30); thus, the observed *CYP2D6* pharmacogenetic associations with metoprolol exposure and effects are expected to likely apply to both formulations.

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Tables S2-S7** is graded 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 the indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of the limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors 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/reference or variant-containing CYP2D6, *in vitro* CYP2D6 enzyme activity from tissues isolated from individuals of known *CYP2D6* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

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

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

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

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

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenomics at the point of care (31-33). See https://cpicpgx.org/guidelines/cpic-guideline-for-beta-blockers/ for resources to support the adoption of CPIC guidelines within an EHR (2, 32). 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* genotype results in an EHR to guide metoprolol therapy.

Effective incorporation of pharmacogenomic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenomic test results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR. To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted drug metabolism

phenotype (**Table 1, main manuscript; *CYP2D6* Diplotype to Phenotype Table** (2, 3)). 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's summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **Metoprolol Pre- and Post-Test Alerts and Flow Chart**, for example, CDS alerts; https://cpicpgx.org/guidelines/cpic-guideline-for-beta-blockers/) (2).

Because pharmacogenomic test results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include complete diplotype to phenotype translation tables, diagram(s) that illustrate how *CYP2D6* pharmacogenomic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see https://cpicpgx.org/guidelines/cpic-guideline-for-beta-blockers/) (2, 34).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (see https://cpicpgx.org/guidelines/cpic-guideline-for-beta-blockers/ (2)).

TABLE S1. PHARMACOLOGIC PROPERTIES OF ORALLY ADMINISTERED BETA-BLOCKERS INCLUDED IN THIS GUIDELINE

Drug	Alpha adrenergic antagonism	Beta-1 adrenergic selectivity	Primary Site of elimination	Metabolic enzymes involved
Acebutolol	No	Yes	Hepatic	CYP2D6
Atenolol	No	Yes	Renal	N/A (excreted unchanged)
Betaxolol	No	Yes	Hepatic	CYP1A2, CYP2D6
Bisoprolol	No	Yes	Renal (~50%) and hepatic	CYP2D6, CYP3A4
Carvedilol	Yes	No	Hepatic	CYP1A1, CYP1A2, CYP2C9, CYP2D6, CYP2E1
Esmolol	No	Yes	Blood	Esterases
Labetalol	Yes	No	Hepatic	UDP-Glucuronosyltransferase
Metoprolol	No	Yes	Hepatic	CYP2D6
Nadolol	No	No	Renal	N/A (excreted unchanged)
Nebivolol	No	Yes	Hepatic	CYP2D6, UDP-Glucuronosyltransferase
Pindolol	No	No	Renal (~40%) and hepatic	UDP-Glucuronosyltransferase, Sulfotransferases
Propranolol	No	No	Hepatic	CYP1A2, CYP2D6
Sotalol	No	No	Renal	N/A (excreted unchanged)

TABLE S2. EVIDENCE LINKING *CYP2D6* GENETIC VARIATION TO BETA-BLOCKER PHENOTYPE

Type of Experiment	Major findings	References	Level of Evidence
Atenolol			
Clinical	*CYP2D6* genetic variants are NOT associated with heart rate in individuals treated with atenolol.	Bijl, *et al.* (2009)(35)	Weak
Betaxolol			
Clinical	The dose of betaxolol in hypertensive patients is NOT significantly affected by genetic variants in *CYP2D6*.	Zateyshchikov, *et al.* (2007)(36)	Weak
Clinical	*CYP2D6* genetic variation associated with heart rate in patients with hypertension treated with betaxolol.	Zateyshchikov, *et al.* (2007)(36)	Weak
Clinical	*CYP2D6* genetic variation associated with blood pressure in patients with hypertension treated with betaxolol.	Zateyshchikov, *et al.* (2007)(36)	Weak
Bisoprolol			
Clinical	Bisoprolol exposure in vivo is significantly affected by genetic variants in *CYP2D6*.	Nozawa, *et al*. (2005)(37) Taguchi, *et al*. (2005)(38) Nakayama, *et al.* (2015)(39) Mohammed Alkreathy, *et al.* (2020)(40) Chan, *et al*. (2021)(41)	Weak
Clinical	The dose of bisoprolol in patients with ischemic heart disease is significantly affected by genetic variants in *CYP2D6*.	Fedorinov, *et al.* (2018)(42)	Weak
Clinical	The dose of bisoprolol in patients treated for a variety of indications is NOT significantly affected by genetic variants in *CYP2D6*.	Nozawa, *et al*. (2005)(37)	Weak
Clinical	The risk of adverse events in patients treated with bisoprolol for a variety of indications is significantly affected by genetic variants in *CYP2D6*.	Nakayama, *et al*. (2015)(39)	Weak

Clinical	*CYP2D6* genetic variation is NOT associated with heart rate in patients treated with bisoprolol.	Nozawa, *et al.* (2005)(37) Chan, *et al*. (2021)(41)	Weak
Clinical	*CYP2D6* genetic variation is associated with blood pressure in patients treated with bisoprolol.	Mohammed Alkreathy, *et al.* (2020)(40) Chan, *et al*. (2021)(41)	Weak
Carvedilol			
In vitro	Carvedilol metabolism in vitro is significantly affected by genetic variants in *CYP2D6*.	Wang, *et al*. (2016)(43)	Moderate
Clinical	Carvedilol exposure in vivo is significantly affected by genetic variants in *CYP2D6*.	Zhou, *et al.* (1995)(44) Giessmann, *et al.* (2004) (45) Honda, *et al*. (2005)(46) Honda, *et al.* (2006)(47) Takekuma*, et al.* (2006)(48) Saito, *et al.* (2010)(49) Sehrt, *et al*. (2011)(50) Nikolic, *et al.* (2013)(51) Jung, *et al.* (2018)(52)	High
Clinical	The risk of adverse events in healthy volunteers (50) and heart failure patients (53) treated with carvedilol are NOT significantly affected by genetic variants in *CYP2D6*.	Sehrt, *et al.* (2011)(50) Shihmanter, *et al.* (2014)(53)	Weak
Clinical	Genetic variants in *CYP2D6* are NOT associated with reduction in heart rate in healthy volunteers (50) and heart failure patients (53) treated with carvedilol.	Sehrt, *et al.* (2011)(50) Shihmanter, *et al.* (2014)(53)	Weak
Clinical	Genetic variants in *CYP2D6* are NOT associated with reduction in blood pressure in healthy volunteers (50) and heart failure patients (53) treated with carvedilol.	Sehrt, *et al.* (2011)(50) Shihmanter, *et al.* (2014)(53)	Weak

Clinical	Genetic variants in *CYP2D6* are NOT associated with other surrogate responses to carvedilol (e.g., tolerability, improvement in heart failure) in heart failure patients.	Baudhuin, *et al.* (2010)(54)	Weak
Clinical	The dose of carvedilol in heart failure patients is significantly affected by genetic variants in *CYP2D6*.	Baudhuin, *et al.* (2010)(54) Shihmanter, *et al.* (2014)(53) Luzum, *et al.* (2017)(55)	Weak
Labetalol			
Clinical	C allele of rs1065852 (100C>T) is associated with lack of blood pressure response to labetalol.	Sun, *et al.* (2018)(56)	Weak
Metoprolol			
In vitro	Metoprolol metabolism in vitro is significantly affected by genetic variants in *CYP2D6*.	Lennard, *et al.* (1982)(57) Marez-Allorge, *et al.* (1999)(58) Allorge, *et al.* (2001)(59) Bapiro, *et al.* (2002)(60) Yang, *et al.* (2019)(61)	Moderate
Clinical	Metoprolol exposure in vivo is significantly affected by genetic variants in *CYP2D6*.	Deroubaix, *et al.* (1996)(62) Masimirembwa, *et al.* (1996)(63) Koytchev, *et al.* (1998)(64) Huang, *et al.* (1999)(65) Hamelin, *et al.* (2000)(66) Tamminga, *et al.* (2001)(67) Wennerholm, *et al.* (2002)(68) Rau, *et al.* (2002)(69) Taguchi, *et al*. (2003)(70) Werner, *et al.* (2003)(71) Kirchheiner, *et al.* (2004)(72) Werner, *et al.* (2004)(73) Zineh, *et al.* (2004)(74) Allorge, *et al.* (2005)(75)	High

		Fux*, et al.* (2005)(76) Nozawa, *et al*. (2005)(37) Sharma, *et al.* (2005)(77) Ismail, *et al.* (2006)(78) Werner, *et al.* (2006)(79) Goryachkina, *et al.* (2008)(80) Jin, *et al.* (2008)(81) Wang, *et al.* (2008)(82) Seeringer, *et al.* (2008)(83) Rau, *et al.* (2009)(84) Sharp*, et al.* (2009)(85) Veiga, *et al.* (2009)(86) Duricova, *et al.* (2013)(87) Bae, *et al.* (2014)(88) Batty, *et al.* (2014)(89) Donzelli, *et al.* (2014)(90) Wojtczak, *et al.* (2014)(91) Matthaei, *et al.* (2015)(92) Derungs, *et al.* (2016)(93) Ryu, *et al.* (2016)(94) Li, *et al*. (2017)(95) Byeon, *et al.* (2018)(96) Cusinato, *et al.* (2019)(97) Anstensrud, *et al.* (2020)(98) Brocker, *et al.* (2020)(99) Schlosser, *et al.* (2020)(100) Thomas, *et al.* (2020)(101) Meloche, *et al*. (2022) (102) Hindi, *et al*. (2023) (103)	

Clinical	*CYP2D6* genetic variants associated with heart rate in healthy volunteers (57, 64, 66, 83), patients with hypertension (101, 104), heart failure patients (54, 85, 89, 105), ischemic heart disease (80, 98, 106), and various indications (107) treated with metoprolol with most consistent effects in poor metabolizers compared to non-poor metabolizers.	Lennard, *et al.* (1982)(57) Koytchev, *et al.* (1998)(64) Hamelin, *et al.* (2000)(66) Nozawa, *et al.* (2005)(37) Sharma, *et al.* (2005)(77) Terra, *et al.* (2005)(105) Goryachkina, *et al.* (2008)(80) Seeringer, *et al.* (2008)(83) Bijl, *et al.* (2009)(35) Rau, *et al.* (2009)(84) Sharp, *et al.* (2009)(85) Baudhuin, *et al*. (54) Batty, *et al.* (2014)(89) Hamadeh, *et al.* (2014)(104) Gao, *et al.* (2017)(106) Li, *et al.* (2017)(95) Anstensrud, *et al.* (2020)(98) Thomas, *et al.* (2020)(101) Collett, *et al*. (2023)(107)	High
Clinical	Genetic variants in *CYP2D6* are NOT associated with other surrogate responses to metoprolol (e.g., tolerability, improvement in heart failure) in heart failure (54, 85, 105) or ischemic heart disease (98) patients.	Terra, *et al.* (2005)(105) Sharp. *et al.* (2009)(85) Baudhuin, *et al.* (2010)(54) Anstensrud, *et al.* (2020)(98)	Weak
Clinical	*CYP2D6* genetic variants associated with blood pressure in healthy volunteers (64, 66), patients with hypertension (74, 76, 104, 108-112), and heart failure patients (54, 85, 89, 105) treated with metoprolol.	Koytchev, *et al.* (1998)(64) Hamelin, *et al.* (2000)(66) Zineh, *et al.* (2004)(74) Fux, *et al.* (2005)(76) Terra, *et al.* (2005)(105) Yuan, *et al.* (2008)(108) Bijl, *et al.* (2009)(35) Rau, *et al.* (2009)(84) Sharp, *et al.* (2009)(85) Baudhuin, *et al*. (54)	Moderate

		Batty, *et al.* (2014)(89) Hamadeh, *et al.* (2014)(104) Ayyappadihas, *et al.* (2015)(110) Wu, *et al.* (2015)(109) Li, *et al.* (2017)(95) Chen, *et al.* (2018)(111) Meloche, *et al.* (2020)(113) Eadon, *et al*. (2022)(112)	
Clinical	Clinical outcomes in heart failure patients treated with metoprolol are NOT significantly affected by genetic variants in *CYP2D6*.	Terra, *et al*. (2005)(105) Batty, *et al.* (2014)(89)	Weak
Clinical	The dose of metoprolol in heart failure patients is significantly affected by genetic variants in *CYP2D6*.	Terra, *et al.* (2005)(105) Sharp, *et al.* (2009)(85) Baudhuin, *et al.* (2010)(54) Batty, *et al.* (2014)(89) Luzum, *et al.* (2017)(55)	Weak
Clinical	The risk of adverse events in patients with a variety of diseases treated with metoprolol are significantly affected by genetic variants in *CYP2D6*.	Wuttke, *et al.* (2002)(114) Zineh, *et al.* (2004)(74) Fux, *et al.* (2005)(76) Fux, *et al.* (2007)(115) Bijl, *et al.* (2009)(35) Rau, *et al.* (2009)(84) Batty, *et al.* (2014)(89) Excler, *et al.* (2014)(116) Rietveld, *et al.* (2015)(117) Poulussen, *et al.* (2019)(118) Anstensrud, *et al.* (2020)(98) Meloche, *et al.* (2020)(113) Chen, *et al*. (2022)(119) Collett, *et al*. (2023)(107)	Moderate

Clinical	The dose of metoprolol in hypertensive patients is NOT significantly affected by genetic variants in *CYP2D6*.	Zineh, *et al.* (2004)(74) Hamadeh, *et al.* (2014)(104)	Moderate
Clinical	The dose of metoprolol in patients with ischemic heart disease is NOT significantly affected by genetic variants in *CYP2D6*.	Gao, *et al.* (2017)(106) Fedorinov, *et al.* (2018)(42) Anstensrud, *et al.* (2020)(98)	Moderate
Clinical	Clinical outcomes in patients with ischemic heart disease treated with metoprolol are NOT significantly affected by genetic variants in *CYP2D6*.	Swadi, *et al.* (2019)(120)	Weak
Clinical	The dose of metoprolol in patients treated for a variety of indications is significantly affected by genetic variants in *CYP2D6*.	Rau, *et al.* (2002)(69) Nozawa, *et al.* (2005)(37) Poulussen, *et al.* (2019)(118) Meloche, *et al.* (2020)(113) Chen, *et al*. (2022)(119)	Weak
Nebivolol			
In vitro	Nebivolol metabolism in vitro is significantly affected by genetic variants in *CYP2D6*	Hu, *et al.* (2016)(121)	Moderate
Clinical	Nebivolol exposure in vivo is affected by genetic variants in *CYP2D6* and is significantly higher in *CYP2D6* poor metabolizers compared to non-poor metabolizers.	Lefebvre, *et al.* (2007)(122) Briciu, *et al.* (2015)(123) Vieira, *et al.* (2018)(124) Guo, *et al.* (2020)(125)	Moderate
Clinical	The risk of adverse events in hypertensive patients treated with nebivolol is NOT significantly affected by genetic variants in *CYP2D6*.	Lefebvre, *et al.* (2007)(122)	Weak
Clinical	*CYP2D6* genetic variation associated with heart rate in patients with hypertension treated with nebivolol.	Lefebvre, *et al.* (2007)(122)	Weak
Clinical	*CYP2D6* genetic variation NOT associated with blood pressure in patients with hypertension treated with nebivolol.	Lefebvre, *et al.* (2007)(122)	Weak

Propranolol			
In vitro	Propranolol metabolism in vitro is significantly affected by genetic variants in *CYP2D6*.	Masubuchi, *et al.* (1994)(126) Rowland, *et al.* (1996)(127) Kong, *et al.* (2012)(128) Liang, *et al.* (2016)(129)	Moderate
Clinical	Propranolol exposure in vivo is significantly affected by genetic variants in *CYP2D6*.	Ward, *et al.* (1989)(130) Lai, *et al.* (1995)(131) Sowinski, *et al.* (1997)(132) Huang, *et al.* (2003)(133)	Weak
Clinical	*CYP2D6* genetic variants NOT associated with heart rate in healthy volunteers treated with propranolol.	Sowinski, *et al.* (1997)(132) Huang, *et al.* (2003)(133)	Weak
Clinical	*CYP2D6* genetic variants NOT associated with blood pressure in healthy volunteers treated with propranolol.	Huang, *et al.* (2003)(133)	Weak
Clinical	*CYP2D6* genotype is not associated with migraine response to propranolol.	Atasayar, *et al.* (2016)(134)	Weak
Clinical	rs1065852 (100C>T) genotype is not associated with response to propranolol (defined by changes in hemangioma lesions).	Wang, *et al.* (2020)(29)	Weak
Clinical	CC genotype of 4181G>C is associated with reduced response to propranolol (defined by changes in hemangioma lesions).	Wang, *et al.* (2020)(29)	Weak
Clinical	rs1065852 (100C>T) genotype is a significant predicting factor of propranolol response (looking at changes in hepatic venous pressure gradient).	Zhang, *et al.* (2016)(135)	Weak
Clinical	4181G>C genotype is not associated with propranolol response (looking at changes in hepatic venous pressure gradient).	Zhang, *et al.* (2016)(135)	Weak

Beta-blockers			
Clinical	The dose of beta-blockers in heart failure patients treated with a combination of different beta-blockers is NOT significantly affected by genetic variants in *CYP2D6*.	Zoghi, *et al.* (2016)(136)	Weak
Clinical	The risk of adverse events in patients treated with beta-blockers for a variety of indications is significantly affected by genetic variants in *CYP2D6*.	Kertai, *et al.* (2014)(137) Mugoša, *et al.* (2016)(138)	Weak
Clinical	The dose of beta-blockers in patients treated for a variety of indications is significantly affected by genetic variants in *CYP2D6*.	Bijl, *et al.* (2009)(35)	Weak
Clinical	*CYP2D6* genetic variants associated with blood pressure in individuals treated with beta-blockers.	Bijl, *et al.* (2009)(35)	Weak

TABLE S3. EVIDENCE LINKING *ADRB1* GENETIC VARIATION TO BETA-BLOCKER PHENOTYPE

Type of Experiment	Major findings	References	Level of Evidence
Atenolol			
Clinical	Clinical outcomes in patients with a variety of conditions and treated with atenolol are NOT significantly affected by rs1801252 (Ser49Gly), rs1801253 (Arg389Gly) haplotype.	Pacanowski, *et al.* (2008)(139)	Weak
Clinical	Heart rate lowering in healthy volunteers treated with atenolol is significantly greater in volunteers with the rs1801252 A, rs1801253 C haplotype (Ser49, Arg389).	Kurnik, *et al.* (2008)(140)	Weak
Clinical	Blood pressure in patients with hypertension and treated with atenolol is NOT significantly affected by the rs1801252, rs1801253 (Ser49Gly, Arg389Gly) haplotype.	Filigheddu, *et al.* (2010)(141)	Weak
Clinical	Atenolol dose in patients with Marfan syndrome is NOT significantly affected by rs1801253 genotype (Arg389Gly).	Van Driest, *et al.* (2020)(142)	Weak
Clinical	Clinical outcomes in patients with Marfan syndrome and treated with atenolol are NOT significantly affected by rs1801253 genotype (Arg389Gly).	Van Driest, *et al.* (2020)(142)	Weak
Clinical	Surrogate measures of atenolol efficacy in patients with Marfan syndrome are significantly better in patients with the rs1801253 CC genotype (Arg/Arg389).	Van Driest, *et al.* (2020)(142)	Weak
Clinical	Surrogate measures of atenolol efficacy in patients with Marfan syndrome are NOT significantly affected by rs1801252 genotype (Ser49Gly).	Van Driest, *et al.* (2020)(142)	Weak

Clinical	Surrogate measures of atenolol efficacy in patients with Marfan syndrome are significantly better in patients with the rs1801252 AA, rs1801253 CC diplotype (Ser/Ser49, Arg/Arg389).	Van Driest, *et al.* (2020)(142)	Weak
Bucindolol			
Clinical	Compared with metoprolol, bucindolol reduced AF burden, improved maintenance of sinus rhythm, and lowered the need for additional rhythm control interventions in patients with heart failure and the ADRB1 Arg389Arg genotype.	Piccini, *et al*. (2021)(143)	Weak
Clinical	In patients with heart failure, ADRB1 Arg389 homozygotes, but not Gly389 carriers, had a lower risk of mortality when treated with bucindolol compared to placebo.	Liggett, *et al*. (2006)(144)	Moderate
Carvedilol			
Clinical	Blood pressure lowering in patients with hypertension and treated with carvedilol is significantly greater in patients with the rs1801252 AG, rs1801253 CC diplotype compared to the rs1801252 AA, rs1801253 GG diplotype.	Si, *et al.* (2014)(145)	Weak
Clinical	Changes in echocardiographic measures of carvedilol efficacy in patients with ischemic heart disease are significantly greater in patients with the rs1801252 A rs1801253 C haplotype (Ser49, Arg389) compared to patients with the rs1801252 G rs1801253 C haplotype (Gly49, Arg389).	Chen, *et al.* (2007)(146)	Weak

Metoprolol			
In vitro	The beta blockade activity of metoprolol is significantly greater with ADRB1 receptors with the rs1801252 G allele (Gly49) compared to those with the A allele (Ser49).	Levin, *et al.* (2002)(147) Rathz, *et al.* (2002)(148)	Weak
Clinical	Changes in echocardiographic measures of metoprolol efficacy in patients with heart failure are significantly greater in patients with the rs1801252 AA, rs1801253 CG diplotype (Ser/Ser49, Arg/Gly389).	Terra, *et al.* (2005)(149)	Weak
Clinical	Other surrogate measures of metoprolol efficacy in patients with heart failure are significantly greater in patients with the rs1801252 AG, rs1801253 CC diplotype (Ser/Gly49, Arg/Arg389) compared to the rs1801252 AA, rs1801253 CC diplotype (Ser/Ser49, Arg/Arg389), the rs1801252 GA, rs1801253 CG diplotype (Gly/Ser49, Arg/Gly389) or the rs1801252 AA, rs1801253 CG diplotype (Ser/Ser49, Arg/Gly389).	Luo, *et al.* (2007)(150)	Weak
Clinical	Heart rate of patients with hypertension and treated with metoprolol is NOT significantly affected by the rs1801252 AA, rs1801253 CC diplotype (Ser/Ser49, Arg/Arg389) or rs1801252 AA, rs1801253 CG diplotype (Ser/Ser49, Arg/Gly389) compared the s1801252 AA, rs1801253 GG diplotype (Ser/Ser49, Gly/Gly389) or rs1801252 AG, rs1801253 CG diplotype (Ser/Gly49, Arg/Gly389).	Liu, *et al.* (2006)(151)	Weak
Clinical	Blood pressure lowering in patients with hypertension and treated with metoprolol is significantly greater in volunteers with the rs1801252 AA, rs1801253 CC diplotype (Ser/Ser49, Arg/Arg389) or rs1801252 AA, rs1801253 CG diplotype (Ser/Ser49, Arg/Gly389) compared to volunteers with the s1801252 AA,	Johnson, *et al.* (2003)(152) Liu, *et al.* (2006)(151)	Weak

	rs1801253 GG diplotype (Ser/Ser49, Gly/Gly389) or rs1801252 AG, rs1801253 CG diplotype (Ser/Gly49, Arg/Gly389).		
Clinical	Heart rate lowering in patients with a variety of conditions and treated with metoprolol is significantly greater in patients with the rs1801252, rs1801253 AA, CC and AA, CG diplotypes compared to the rs1801252, rs1801253 AG, CC; AG, CG and GG, GG diplotypes	Cotarlan, *et al.* (2013)(153)	Weak
Beta-blockers			
In vitro	Effect of beta-blockers on ADRB1 receptors in vitro is significantly greater in receptors with the rs1801253 C allele (Arg389) compared to those with the G allele (Gly389).	Molenaar, *et al.* (2002)(154) Mialet Perez, *et al.* (2003)(155) Joseph, *et al.* (2004)(156) Sandilands, *et al.* (2004)(157) Liggett, *et al.* (2004)(144) Rochais, *et al.* (2007)(158)	Weak
Clinical	Clinical outcomes in patients with ischemic heart disease and treated with beta-blockers are significantly worse in patients carrying the rs1801252 G allele (Gly49).	Lanfear, *et al.* (2005)(159) Magvanjav, *et al.* (2017)(160)	Weak
Clinical	Clinical outcomes in patients with heart failure and treated with beta-blockers are significantly better in patients carrying the rs1801252 G allele (Gly49).	Börjesson, *et al.* (2000)(161) Magnusson, *et al.* (2005)(162) Biolo, *et al.* (2008)(163) Sehnert, *et al.* (2008)(164) Fiuzat, *et al.* (2013)(165) Pereira, *et al.* (2013)(166) Guerra, *et al.* (2022)(167)	Weak
Clinical	Clinical outcomes of patients with hypertension and treated with beta-blockers are NOT significantly affected by rs7907426 (used as a marker for rs1801252 (Ser49Gly)) genotype.	Lemaitre, *et al.* (2008)(168)	Weak
Clinical	Clinical outcomes in patients with heart failure and treated with beta-blockers are significantly better in	White, *et al.* (2003)(169) Magnusson, *et al.* (2005)(162)	Weak

	patients carrying the rs1801253 C allele (Arg389) compared to patients with the GG genotype (Gly/Gly389).	Liggett, *et al.* (2006)(144) Biolo, *et al.* (2008)(163) Sehnert, *et al.* (2008)(164) Cresci, *et al.* (2009)(170) Fiuzat, *et al.* (2013)(165) Pereira, *et al.* (2013)(166) Kang, *et al.* (2015)(171) Lee, *et al.* (2016)(172) Huang, *et al.* (2018)(173) Parikh, *et al.* (2018)(174) Piccini, *et al.* (2019)(175) Guerra, *et al.* (2022)(167)	
Clinical	Clinical outcomes in patients with hypertension and treated with beta-blockers are significantly better in patients carrying the rs1801253 C allele (Arg389) compared to patients with the GG genotype (Gly/Gly389).	Lemaitre, *et al.* (2008)(168)	Weak
Clinical	Clinical outcomes in patients with ischemic heart disease and treated with beta-blockers are significantly better in patients carrying the rs1801253 C allele (Arg389) compared to patients with the GG genotype (Gly/Gly389).	Lanfear, *et al.* (2005)(159) Cresci, *et al.* (2012)(176)	Weak
Clinical	Clinical outcomes in patients with ischemic heart disease and treated with beta-blockers are NOT significantly affected by rs1801252 (Ser49Gly), rs1801253 (Arg389Gly) haplotype.	Sehnert, *et al.* (2008)(164)	Weak
Clinical	Clinical outcomes of patients with hypertension and treated with beta-blockers are NOT significantly affected by rs4917675 genotype located upstream of *ADRB1*.	Lemaitre, *et al.* (2008)(168)	Weak

Clinical	Clinical outcomes of patients with hypertension and treated with beta-blockers are NOT significantly affected by rs17875474 genotype located upstream of *ADRB1*.	Lemaitre, *et al.* (2008)(168)	Weak
Clinical	Clinical outcomes of patients with hypertension and treated with beta-blockers are NOT significantly affected by rs3813720 genotype located downstream of *ADRB1*.	Lemaitre, *et al.* (2008)(168)	Weak
Clinical	Clinical outcomes of patients with hypertension and treated with beta-blockers are significantly worse in patients carrying the rs2429511 G allele located upstream of *ADRB1*.	Lemaitre, *et al.* (2008)(168)	Weak
Clinical	Clinical outcomes of patients with hypertension and treated with beta-blockers are significantly worse in patients carrying the rs17875422 G allele located upstream of *ADRB1*.	Lemaitre, *et al.* (2008)(168)	Weak
Clinical	Risk of adverse events in patients treated with beta-blockers is NOT significantly affected by rs1801252 genotype (Ser49Gly).	Terra, *et al.* (2005)(105) Sehrt, *et al.* (2011)(50) Vardeny, *et al.* (2012)(177) Jeff, *et al.* (2014)(178)	Weak
Clinical	Risk of adverse events in patients treated with beta-blockers is NOT significantly affected by rs1801253 genotype (Arg389Gly).	Terra, *et al.* (2005)(105) Sehrt, *et al.* (2011)(50) Vardeny, *et al.* (2012)(177) Jeff, *et al.* (2014)(178)	Weak
Clinical	Heart rate lowering response in patients treated with beta-blockers is significantly greater in patients with the rs1801252 AA genotype (Ser/Ser49) compared to patients carrying the G allele (Gly49).	Karlsson, *et al.* (2004)(179) de Groote, *et al.* (2005)(180) Beitelshees, *et al.* (2006)(181) Liu, *et al.* (2006)(151) Kurnik, *et al.* (2008)(140) Mahesh Kumar, *et al.* (2008)(182) Rau, *et al.* (2009)(84) Kindermann, *et al.* (2011)(183)	Weak

		Sasaguri, *et al.* (2011)(184) Sehrt, *et al.* (2011)(50) Parvez, *et al.* (2012)(185) Rau, *et al.* (2012)(186) Cotarlan, *et al.* (2013)(153) Zeng, *et al*. (2022)(187)	
Clinical	Blood pressure lowering response in patients treated with beta-blockers is significantly greater in patients with the rs1801252 AA genotype (Ser/Ser49) compared to patients carrying the rs1801252 G allele (Gly49).	Renouf, *et al.* (1958)(188) Johnson, *et al.* (2003)(152) Liljedahl, *et al.* (2003)(189) Karlsson, *et al.* (2004)(179) de Groote, *et al.* (2005) (180) Liu, *et al.* (2006)(151) Mahesh Kumar, *et al.* (2008)(182) Rau, *et al.* (2009)(84) Suonsyrjä, *et al.* (2010)(190) Kindermann, *et al.* (2011)(183) Lee, *et al.* (2011)(191) Sagaguri, *et al.* (2011)(184) Sehrt, *et al.* (2011)(50) Si, *et al.* (2014)(145) Magvanjav, *et al.* (2017)(160) Zeng, *et al*. (2022)(187)	Weak
Clinical	Heart rate lowering response in patients treated with beta-blockers is significantly greater in patients with the rs1801253 CC genotype (Arg/Arg389) compared to those carrying the G allele (Gly389)	O'Shaughnessy, *et al.* (2000)(192) Liu, *et al.* (2003)(193) White, *et al.* (2003)(169) Sofowora, *et al.* (2003)(194) Karlsson, *et al.* (2004)(179) Bruck, *et al.* (2005)(195) de Groote, *et al.* (2005) (180) Terra, *et al.* (2005)(149) Beitelshees, *et al.* (2006)(181)	Weak

		Liggett, *et al.* (2006)(144) Liu, *et al.* (2006)(151) Zateyshchikov, *et al.* (2007)(36) Lobmeyer, *et al.* (2007)(196) Kurnik, *et al.* (2008)(140) Mahesh Kumar, *et al* (2008)(182) Rau, *et al.* (2009)(84) Huntgeburth, *et al.* (2011)(197) Kindermann, *et al.* (2011)(183) Sasaguri, *et al.* (2011) (184) Parvez, *et al.* (2012)(185) Peterson, *et al.* (2012)(198) Rau, *et al.* (2012)(186) Cotarlan, *et al.* (2013)(153) Muszkat, *et al.* (2013)(199) Lee, *et al.* (2016)(172) Zeng, *et al*. (2022)(187)	
Clinical	Blood pressure lowering response in patients treated with beta-blockers is significantly greater in patients with the rs1801253 CC genotype (Arg/Arg389) compared to those carrying the G allele (Gly389).	O'Shaughnessy, *et al.* (2000)(192) Johnson, *et al.* (2003)(152) Liljedahl, *et al.* (2003)(189) Liu, *et al.* (2003)(193) Sofowora, *et al.* (2003)(194) Karlsson, *et al.* (2004)(179) de Groote, *et al.* (2005)(180) Terra, *et al.* (2005)(149) Liu, *et al.* (2006)(151) Luo, *et al.* (2007)(150) Zateyshchikov, *et al.* (2007)(36) Mahesh Kumar, *et al.* (2008)(182) Rau, *et al.* (2009)(84)	Weak

		Filigheddu, *et al.* (2010)(141) Suonsyrjä, *et al.* (2010)(190) Kindermann, *et al.* (2011)(183) Lee, *et al.* (2011)(191) Sasaguri, *et al.* (2011)(184) Si, *et al.* (2014)(145) Wu, *et al.* (2015)(109) Lee, *et al.* (2016)(172) Magvanjav, *et al.* (2017)(160) Chen, *et al.* (2018)(111) Zeng, *et al*. (2022)(187)	
Clinical	Heart rate lowering in patients with hypertension and treated with beta-blockers is significantly worse in patients with the rs1801252 AA, rs1801253 CC diplotype (Ser/Ser49, Arg/Arg389).	Fehr, *et al.* (2004)(200)	Weak
Clinical	No difference in effect of *ADRB1* rs1801253 on the development of postoperative atrial fibrillation after coronary artery bypass grafting in patients receiving beta-blockers as compared to non-carriers.	El Gindy, *et al*. (2022)(201)	Weak
Clinical	Beta-blocker exposure is NOT significantly affected by rs1801252 genotype (Ser49Gly).	Johnson, *et al.* (2003)(152) Mahesh Kumar, *et al.* (2008)(182) Sasaguri, *et al.* (2011)(184)	Moderate
Clinical	Beta-blocker exposure is NOT significantly affected by rs1801253 genotype (Arg389Gly).	Johnson, *et al.* (2003)(152) Liu, *et al.* (2003)(193) Sofowora, *et al.* (2003)(194) Bruck, *et al.* (2005)(195) Terra, *et al.* (2005)(149) Mahesh Kumar, *et al.* (2008)(182) Sasaguri, *et al.* (2011)(184)	Strong

Clinical	Beta-blocker dose is significantly lower in patients carrying the rs1801252 G allele (Gly49) compared to patients with the AA genotype (Ser/Ser49).	Johnson, *et al.* (2003)(152) De Groote, *et al.* (2005)(180) Magnusson, *et al.* (2005)(162) Terra, *et al.* (2011)(149)	Weak
Clinical	Beta-blocker dose is higher in those with the rs1801253 CC genotype (Arg/Arg389) compared to the CG and GG genotypes (Arg/Gly389 and Gly/Gly389)	Johnson, *et al.* (2003)(152) Mialet Perez, *et al.* (2003)(155) White, *et al.* (2003)(169) De Groote, *et al.* (2005)(180) Terra, *et al.* (2005)(149) Baudhuin, *et al.* (2010)(54) Lee, *et al.* (2010)(172) Gao, *et al.* (2017)(106)	Weak
Clinical	Beta-blocker dose in patients with ischemic heart disease is higher in those with the rs1801252 AA, rs1801253 CC diplotype (Ser/Ser49, Arg/Arg389) than in patients with the rs1801252 AA, rs1801253 CG diplotype (Ser/Ser49, Arg/Gly389).	Parvez, *et al.* (2012)(185)	Weak
Clinical	Changes in echocardiographic measures of beta-blocker efficacy are significantly greater in patients with the rs1801252 AA genotype (Ser/Ser49) compared to patients carrying the G allele (Gly49).	Liljedahl, *et al.* (2004)(202) de Groote, *et al.* (2005) (180) Terra, *et al.* (2005)(149) Hu, *et al.* (2007)(203) Muthumala, *et al.* (2008)(204) Nonen, *et al.* (2008)(205) Kindermann, *et al.* (2011)(183) Luzum, *et al.* (2019)(206)	Weak
Clinical	Changes in echocardiographic measures of beta-blocker efficacy (i.e., left ventricular ejection fraction) are significantly greater in patients with the rs1801253 CC genotype (Arg/Arg389) compared to those compared to those carrying the G allele (Gly389).	Mialet Perez, *et al.* (2003)(155) Liljedahl, *et al.* (2004)(202) de Groote, *et al.* (2005)(180) Terra, *et al.* (2005)(149) Liggett, *et al.* (2006)(144) Chen, *et al.* (2007)(146) Hu, *et al.* (2007)(203) Lobmeyer, *et al.* (2007)(196)	Weak

		Luo, *et al.* (2007)(150) Nonen, *et al.* (2008)(205) Metra, *et al.* (2010)(207) Huntgeburth, *et al.* (2011)(197) Kindermann, *et al.* (2011)(183) Luzum, *et al.* (2019)(205, 206)	
Clinical	Other measures of beta-blocker efficacy are NOT significantly affected by the rs1801253 variant (Arg/Gly389).	Luo, *et al.* (2007)(150) Zateyshchikov, *et al.* (2007)(36) Baudhuin, *et al.* (2010)(54)	Weak
Clinical	In patients with Duchenne Muscular Dystrophy treated with beta-blockers, ADRB1 rs1801253 (Gly389 and Arg389) genotype are not associated with changes in echocardiographic measures.	Kelley, *et al.* (2022)(208)	Weak
Clinical	In patients with acute coronary syndrome, there is no association between *ADRB1* variants (rs1801253 Arg389Gly and rs1801252 Ser49Gly) and mortality among those taking a beta-blocker or not taking a beta-blocker.	Lanfear, *et al*. (2005)(159)	Weak
Clinical	In patients with hypertension, carriers of the ADRB1 Ser49-Arg389 haplotype (rs1801252 and rs1801253) had a higher risk adverse clinical outcomes when treated with a non-beta-blocker anti-hypertensive medication compared to a beta-blocker.	Pacanowski, *et al*. (2008)(209) Lemaitre, *et al*. (2008)(168)	Weak
Clinical	In patients with hypertension and a history of stroke, beta-blocker-treated ADRB1 Gly49 carriers (rs1801252) had increased MACE versus non-beta-blocker-treated individuals and noncarriers.	Magvanjav, *et al*. (2017)(210)	Weak
Clinical	In patients with heart failure, carriers of ADRB1 rs1801253 Arg389 had a higher risk of mortality than Gly389 carriers when treated with a low-dose or no beta-blocker therapy, but no difference in risk with high-dose beta-blocker therapy.	White, *et al*. (2003)(211) Magnusson, *et al*. (2005)(162) Liggett, *et al*. (2006)(144) Biolo, *et al*. (2008)(163) Cresci, *et al*. (2009)(170) Fiuzat, *et al*. (2013)(165)	Weak

		Huang, *et al*. (2018)(212) Parikh, *et al*. (2018)(213) Guerra, *et al*. (2002)(214)	
Clinical	In patients with heart failure receiving a low-dose beta-blocker, ADRB1 rs1801252 Ser49 carriers had a higher mortality rate than Gly49 carriers, but no difference in risk with high-dose beta-blockers.	Borjesson, *et al*. (2000)(161) Magnusson, *et al*. (2005)(162) Biolo, *et al*.(2008)(163) Fiuzat, *et al*. (2013)(165) Lanfear, *et al*. (2020)(215) Guerrra, *et al*. (2022)(214) Lanfear, *et al*. (2023)(216)	Weak

TABLE S4. EVIDENCE LINKING *ADRB2* GENETIC VARIAION TO BETA-BLOCKER PHENOTYPE

Type of Experiment	Major Findings	References	Level of Evidence
Atenolol			
Clinical	Surrogate measures of atenolol efficacy in patients with hypertension are NOT significantly affected by rs1042711 genotype located in the 5'UTR.	Filigheddu, *et al.* (2010)(141)	Weak
Clinical	Surrogate measures of atenolol efficacy in patients with hypertension are NOT significantly affected by haplotypes of rs1042713, rs1042714 and rs1042711, (Gly16Arg, Glu27Gln, 5'UTR variant).	Filigheddu, *et al.* (2010)(141)	Weak
Clinical	Surrogate measures of atenolol efficacy in patients treated for a variety of indications are NOT significantly affected by rs1042711 genotype.	Liljedahl, *et al.* (2004)(202)	Weak
Clinical	Surrogate measures of atenolol efficacy in patients treated for a variety of indications are NOT significantly affected by rs1801704 genotype.	Liljedahl, *et al.* (2004)(202)	Weak
Carvedilol			
Clinical	Clinical outcomes of patients with heart failure and treated with carvedilol are NOT significantly affected by rs1042713 genotype (Gly16Arg).	Pereira, *et al.* (2013)(166)	Weak
Clinical	Clinical outcomes of patients with heart failure and treated with carvedilol are NOT significantly affected by rs1042714 genotype (Glu27Gln).	Peterson, *et al.* (2011)(217) Pereira, *et al.* (2013)(166)	Weak
Clinical	Risk of adverse events in healthy volunteers treated with carvedilol are NOT significantly affected by rs1042713 genotype (Gly16Arg).	Sehrt, *et al.* (2011)(50)	Weak

Clinical	The risk of adverse events in patients treated with carvedilol is decreased in patients carrying the rs1042714 C allele (Gln27) compared to patients with the GG genotype (Glu/Glu27).	Vardeny, *et al.* (2008)(218) Sehrt, *et al.* (2011)(50)	Weak
Clinical	Surrogate measures of carvedilol efficacy in patients with heart failure are better in patients with the rs1042713 GG, rs1042714 GG diplotype (Gly/Gly16, Glu/Glu27) compared to surrogate measures of metoprolol efficacy in patients with the same diplotype.	Truijen, *et al.* (2011)(219)	Weak
Pindolol			
In vitro	The binding affinity of pindolol to ADRB2 receptors is NOT affected by rs1800888 genotype (Thr164Ile).	Green, *et al.* (1993)(220)	Weak
Propranolol			
In vitro	Propranolol has a significantly lower binding affinity to ADRB2 receptors containing the rs1800888 T allele (Ile164).	Green, *et al.* (1993)(220)	Weak
Clinical	Propranolol dose in patients with cirrhosis is NOT significantly affected by combined rs1042713 and rs1042714 genotype.	Kong, *et al.* (2015)(221)	Weak
Clinical	Surrogate measures of propranolol efficacy in patients with asthma are worse in patients carrying the rs1042713 A allele (Arg16).	Anderson, *et al.* (2014)(222)	Weak
Clinical	Blood pressure in patients with cirrhosis and treated with propranolol are NOT significantly affected by rs1042714 genotype (Glu27Gln) and rs1042713GG GG, rs1042714 CG diplotype (Gly/Gly16, Gln/Glu27).	Turnes, *et al.* (2006)(223) Zhang, *et al.* (2016)(135)	Weak

Clinical	Echocardiographic measures of propranolol efficacy in patients with cirrhosis are significantly better in patients with the rs1042713 GG, rs1042714 CG diplotype (Gly/Gly16, Gln/Glu27).	Turnes, *et al.* (2006)(223)	Weak
Clinical	Other measures of propranolol efficacy in patients with cirrhosis are significantly better in patients with the rs1042713 GG, rs1042714 CG diplotype (Gly/Gly16, Gln/Glu27).	Turnes, *et al.* (2006)(223)	Weak
Non-B1 selective beta-blockers			
Clinical	Heart rate of patients treated with non-B1 selective beta blockers is NOT significantly affected by rs1042713 AG genotype (Gly16Arg).	de Groote, *et al.* (2005) (180) Sehrt, *et al.* (2011)(50)	Weak
Clinical	Blood pressure of patients treated with non-B1 selective beta blockers are NOT significantly affected by rs1042713 AG genotype (Gly16Arg).	de Groote, *et al.* (2005) (180) Metra, *et al.* (2010)(207) Sehrt, *et al.* (2011)(50) Si, *et al.* (2014)(145) Zhang, *et al.* (2016)(135)	Moderate
Clinical	Echocardiographic measures of efficacy in patients treated with non-B1 selective beta blockers are NOT significantly affected by rs1042713 AG genotype (Gly16Arg).	Kaye, *et al.* (2003)(224) de Groote, *et al.* (2005) (180) Chen, *et al.* (2007)(146) Metra, *et al.* (2010)(207) Pereira, *et al.* (2013)(166)	Moderate
Clinical	Heart rate REDUCTION of patients treated with non-B1 selective beta-blockers is greater in patients carrying the rs1042714 G allele (Glu27) compared to patients with the CC genotype (Gln/Gln27).	de Groote, *et al.* (2005) (180) Troncoso, *et al.* (2009)(225) Sehrt, *et al.* (2011)(50)	Weak
Clinical	Blood pressure REDUCTION of patients treated with non-B1 selective beta-blockers is better GREATER in patients carrying the rs1042714 G allele (Glu27) compared to patients with the CC genotype (Gln/Gln27).	de Groote, *et al.* (2005) (180) Metra, *et al.* (2010)(207) Sehrt, *et al.* (2011)(50) Si, *et al.* (2014)(145)	Weak

Clinical	Echocardiographic measures of efficacy in patients treated with non-B1 selective beta-blockers are better in patients carrying the rs1042714 G allele (Glu27) compared to patients with the CC genotype (Gln/Gln27).	Kaye, *et al.* (2003)(224) de Groote, *et al.* (2005)(180) Chen, *et al.* (2007)(146) Troncoso, *et al.* (2009)(225) Metra, *et al.* (2010)(207) Pereira, *et al.* (2013)(166)	Weak
Clinical	Other measures of efficacy in patients treated with non-B1 selective beta-blockers are not affected by rs1042714 genotype (Glu27Gln).	Troncoso, *et al.* (2009)(225)	Weak
Clinical	Heart rate of patients treated with non-B1 selective beta-blockers is NOT significantly affected by rs1800888 genotype (Thr164Ile).	de Groote, *et al.* (2005)(180)	Weak
Clinical	Blood pressure of patients treated with non-B1 selective beta-blockers is NOT significantly affected by rs1800888 genotype (Thr164Ile).	de Groote, *et al.* (2005)(180)	Weak
Clinical	Echocardiographic measures of efficacy in patients treated with non-B1 selective beta-blockers is NOT significantly affected by rs1800888 genotype (Thr164Ile).	de Groote, *et al.* (2005)(180) Chen, *et al.* (2007)(146)	Weak
Clinical	Heart rate in healthy volunteers treated with non-B1 selective beta-blockers shows a greater reduction in patients with the rs1042713 G, rs1042714 CC haplotype (Gly16,Gln/Gln27).	Sehrt, *et al.* (2011)(50)	Weak
Clinical	Blood pressure in healthy volunteers treated with non-B1 selective beta-blockers shows a greater reduction in patients with the rs1042713 G, rs1042714 CC haplotype (Gly16,Gln/Gln27).	Sehrt, *et al.* (2011)(50)	Moderate
Clinical	Blood pressure REDUCTION of patients treated with non-B1 selective beta-blockers is significantly better GREATER in patients with the rs1042713 GG, rs1042714 GG diplotype (Gly/Gly16, Glu/Glu27).	Metra, *et al.* (2010)(207) Truijen, *et al.* (2011)(219)	Weak
Clinical	Echocardiographic measures of efficacy in patients treated with non-B1 selective beta-blockers are	Metra, *et al.* (2010)(207)	Weak

	significantly better in patients with the rs1042713 GG, rs1042714 GG diplotype (Gly/Gly16, Glu/Glu27).		
Clinical	Heart rate of patients with cirrhosis treated with non-B1 selective beta-blockers is significantly better in patients with the rs1042713 GG, rs1042714 CG diplotype (Gly/Gly16, Gln/Glu27).	Turnes, *et al.* (2006)(223)	Weak
B1-selective beta-blockers			
Clinical	Clinical outcomes of patients treated with B1-selective beta blockers are NOT significantly affected by rs1042718 genotype (synonymous variant).	Lemaitre, *et al.* (2008)(168) Pacanowski, *et al.* (2008)(139)	Weak
Clinical	Clinical outcomes of patients treated with B1-selective beta-blockers are significantly better in patients carrying the rs1042713 G allele (Gly16) compared to patients with the AA genotype (Arg/Arg16).	Hindorff, *et al.* (2005)(226) Lanfear, *et al.* (2005)(159) Lemaitre, *et al.* (2008)(168) Pacanowski, *et al.* (2008)(139) Sehnert, *et al.* (2008)(164) Pereira, *et al.* (2013)(166) Huang, *et al.* (2018)(173) Guerra, *et al.* (2022)(167)	Weak
Clinical	Clinical outcomes of patients with heart failure and treated with B1-selective beta-blockers are significantly better in patients with the rs1042714 GG genotype (Glu/Glu27) compared to those carrying the C allele (Gln27).	Hindorff, *et al.* (2005)(226) Lanfear, *et al.* (2005)(159) Lemaitre, *et al.* (2008)(168) Pacanowski, *et al.* (2008)(139) Sehnert, *et al.* (2008)(164) Guerra, *et al.* (2022)(167)	Weak
Clinical	The risk of adverse events in patients treated with B1-selective beta-blockers is increased in patients with the rs1042713 GG genotype (Gly/Gly16) compared to patients with the AG genotype (Arg/Gly16).	Iaccarino, *et al.* (2005)(227) Isaza, *et al.* (2007)(228) Vardeny, *et al.* (2008)(218) Vardeny, *et al.* (2012)(177)	Weak
Clinical	The risk of adverse events in patients treated with B1-selective beta-blockers is increased in patients carrying the rs1042714 G allele (Glu27).	Iaccarino, *et al.* (2005)(227) Isaza, *et al.* (2007)(228) Vardeny, *et al.* (2008)(218) Vardeny, *et al.* (2012)(177)	Weak

Clinical	Heart rate in patients treated with B1-selective beta-blockers is NOT significantly affected by rs1042713 GA genotype (Gly16Arg).	de Groote, *et al.* (2005)(180) Cotarlan, *et al.* (2013)(153)	Weak
Clinical	Blood pressure in patients treated with B1-selective beta-blockers is NOT significantly worse in patients with the rs1042713 AA genotype (Arg/Arg16).	Liljedahl, *et al.* (2003)(189) de Groote, *et al.* (2005)(180) Filigheddu, *et al.* (2010)(141) Suonsyrjä, *et al.* (2010)(190)	Moderate
Clinical	Echocardiographic measures of B1-selective beta-blocker efficacy in patients treated for a variety of indications are NOT significantly affected by rs1042713 GA genotype (Gly16Arg).	Liljedahl, *et al.* (2004)(202) de Groote, *et al.* (2005)(180)	Weak
Clinical	Heart rate of patients treated with B1-selective beta-blockers is NOT significantly affected by rs1042714 genotype (Glu27Gln).	de Groote, *et al.* (2005)(180) Cotarlan, *et al*, (2013)(153)	Weak
Clinical	Blood pressure of patients treated with B1-selective beta-blockers is significantly better in patients with the rs1042714 CC genotype (Gln/Gln27).	Liljedahl, *et al.* (2003)(189) de Groote, *et al.* (2005)(180) Filigheddu, *et al.* (2010)(141) Suonsyrjä, *et al.* (2010)(190)	Weak
Clinical	Echocardiographic measures of efficacy in patients treated with B1-selective beta-blockers are NOT significantly affected by the rs1042714 genotype (Glu27Gln).	Liljedahl, *et al.* (2004)(202) de Groote, *et al.* (2005) (180) Iaccarino, *et al.* (2006)(229)	Weak
Clinical	Heart rate of patients treated with B1-selective beta-blockers is NOT significantly affected by rs1800888 genotype (Thr164Ile).	de Groote, *et al.* (2005)(180) Cotarlan, *et al.* (2013)(153)	Weak
Clinical	Blood pressure of patients treated with B1-selective beta-blockers is NOT significantly affected by rs1800888 genotype (Thr164Ile).	de Groote, *et al.* (2005)(180)	Weak
Clinical	Echocardiographic measures of B1-selective beta-blockers efficacy are NOT significantly affected by rs1800888 genotype (Thr164Ile).	Liljedahl, *et al.* (2004)(202) de Groote, *et al.* (2005)(180)	Weak

Beta-blockers			
Clinical	Clinical outcomes of patients with hypertension and treated with beta-blockers are NOT significantly affected by rs1042719 genotype (synonymous variant).	Lemaitre, *et al.* (2008)(168)	Weak
Clinical	Clinical outcomes of patients with hypertension and treated with beta-blockers are NOT significantly affected by rs1042720 genotype (synonymous variant).	Lemaitre, *et al.* (2008)(168)	Weak
Clinical	Clinical outcomes of patients with heart failure and treated with beta-blockers are significantly better in patients with the rs1800888 CC genotype (Thr/Thr164) compared to the TT or TC genotypes (Ile/Ile164 or Ile/Thr164).	Littlejohn, *et al.* (2008)(230)	Weak
Clinical	Clinical outcomes of patients with ischemic heart disease treated with beta-blockers are significantly worse in patients with the rs1042713 AA, rs1042714 CC diplotype (Arg/Arg16, Gln/Gln27).	Lanfear, *et al.* (2005)(159) Sehnert, *et al.* (2008)(164)	Weak
Clinical	The risk of adverse events in patients with hypertension and treated with beta-blockers is NOT significantly affected by rs1800888 genotype (Thr164Ile).	Iaccarino, *et al.* (2005)(227)	Weak
Clinical	Patients with hypertension and/or coronary artery disease and the ADRB2 rs1042713 Arg16 allele have significantly greater improvement in clinical outcomes with beta-blocker vs. no/low dose beta-blocker than patients with the Gly16 allele.	Lanfear, *et al*. (2005)(159) Hindorff, *et al*. (2005)(226) Pacanowski, *et a.l* (2008)(209) Lemaitre, *et al.* (2008)(168) Cresci, *et al.* (2012)(176)	Weak
Clinical	Patients with hypertension and/or coronary artery disease and the ADRB2 rs1042714 Glu27 allele have significantly greater improvement in clinical outcomes with beta-blocker vs. no/low dose beta-blocker than patients with the Gln27 allele.	Lanfear, *et al*. (2005)(159) Hindorff, *et al*. (2005)(226) Pacanowski, *et a.l* (2008)(209) Lemaitre, *et al.* (2008)(168) Cresci, *et al.* (2012)(176)	Weak
Clinical	Patients with heart failure and homozygous for ADRB2 rs1800888 Thr164 have significantly greater improvement in clinical outcomes with beta-blocker vs.	Littlejohn, *et al*. (2008)(230) Nonen, *et al*. (2008)(205) de Groote, *et al*. (2005)(180)	Weak

	no/low dose beta-blocker than patients carrying ADRB2 Ile164		
Clinical	Patients with heart failure and the ADRB2 rs1042713 Arg16 allele have significantly greater improvement in clinical outcomes with beta-blocker vs. no/low dose beta-blocker than patients with the Gly16 allele	de Groote, *et al*. (2005)(180) Huang, *et al*. (2018)(212) Guerra, *et al*. (2022)(214)	Weak
Clinical	Patients with heart failure and the ADRB2 rs1042714 Glu27 allele have significantly greater improvement in clinical outcomes with beta-blocker vs. no/low dose beta-blocker than patients with the Gln27 allele	de Groote, *et al*. (2005)(180) Peterson, *et al*. (2011)(217]) Huang, *et al*. (2018)(212) Guerra, *et al*. (2022)(214)	Weak

TABLE S5. EVIDENCE LINKING *ADRA2C* GENETIC VARIAION TO BETA-BLOCKER PHENOTYPE

Type of Experiment	Major findings	References	Level of Evidence
In vitro	The deletion of 4 amino acids in ADRA2C (rs61767072; p.Gly324_Ala327del and also commonly referred to as $Del_{322-325}$) results in significantly decreased ADRA2C receptor function compared to the insertion allele.	Small, *et al*. (2000)(231)	Moderate
Bucindolol			
Clinical	Patients with heart failure with reduced ejection fraction and ADRA2C rs61767072 deletion carriers have significantly greater reduction in plasma norepinephrine levels with bucindolol than patients without the ADRA2C deletion.	Bristow, *et al*. (2010)(232)	Moderate
Clinical	Patients with heart failure with reduced ejection fraction and ADRA2C rs61767072 deletion carriers have significantly greater reduction in the risk for adverse clinical outcomes with bucindolol than patients without the ADRA2C deletion.	Bristow, *et al*. (2010)(232) Parikh, *et al*. (2018)(213)	Weak
Clinical	Patients with heart failure with reduced ejection fraction and the combination of the ADRA2C rs61767072 deletion allele with other increased adrenergic function alleles (e.g., ADRB1 rs1801253 Arg389) have significantly greater improvement in clinical outcomes with bucindolol than patients with the reference ADRA2C allele and other reduced adrenergic function alleles (e.g., ADRB1 rs1801253 Gly389).	O'Connor, *et al*. (2022)(233) Aleong, *et al*. (2013)(234) Parikh, *et al*. (2018)(213)	Weak
Beta-blockers			

Clinical	The deletion of 4 amino acids (rs61767072; p.Gly324_Ala327del and also commonly referred to as $Del_{322-325}$) in ADRA2C results in significantly increased release of norepinephrine compared to the reference allele.	Neumeister, *et al*. (2005)(235)	Moderate
Clinical	ADRA2C rs61767072 deletion carriers had greater survival compared to patients without a deletion.	Cresci, *et al*. (2012)(176)	Weak
Clinical	Patients with hypertension and the ADRA2C rs61767072 deletion allele have significantly greater reduction in blood pressure with beta-blocker than patients without the ADRA2C deletion allele.	Rau, *et al*. (2009)(84)	Weak
Clinical	Patients with hypertension and the ADRA2C rs61767072 deletion allele have significantly greater reduction in heart rate with beta-blocker than patients without the ADRA2C deletion allele.	Rau, *et al*. (2009)(84)	Weak
Clinical	Healthy individuals with the ADRA2C rs61767072 deletion allele have significantly greater reduction in heart rate with beta-blocker than healthy individuals without the ADRA2C deletion.	Kurnik, *et al*. (2008)(140)	Weak
Clinical	Patients with heart failure with reduced ejection fraction and ADRA2C rs61767072 deletion carriers have significantly greater improvement in heart function with beta-blocker than patients without the ADRA2C deletion allele.	Lobmeyer, *et al*. (2007)(196) Nonen, *et al*. (2008)(205)	Weak
Clinical	Patients with heart failure with reduced ejection fraction and ADRA2C rs61767072 deletion carriers have significantly greater reduction in heart rate with beta-blocker than patients without the ADRA2C deletion allele.	Lobmeyer, *et al*. (2007)(196) Nonen, *et al*. (2008)(205)	Weak
Clinical	Patients with heart failure with reduced ejection fraction and ADRA2C rs61767072 deletion carriers have significantly greater reduction in the risk for adverse clinical outcomes with beta-blockers than patients without the ADRA2C deletion allele.	Parikh, *et al*. (2018)(213)	Weak

Clinical	Patients with heart failure with reduced ejection fraction and the combination of the ADRA2C rs61767072 deletion allele with other increased adrenergic function alleles (e.g., ADRB1 Arg389) have significantly greater improvement in heart function with beta-blockers than patients without the ADRA2C deletion allele and other reduced adrenergic function alleles (e.g., ADRB1 Gly389).	Lobmeyer, *et al*. (2007)(196) Reddy, *et al*. (2015)(236)	Weak
Clinical	Patients with heart failure with reduced ejection fraction and the combination of the ADRA2C rs61767072 deletion allele with other increased adrenergic function alleles (e.g., ADRB1 Arg389) have significantly greater improvement in hemodynamics with beta-blockers than patients without the ADRA2C deletion allele and other reduced adrenergic function alleles (e.g., ADRB1 Gly389).	Reddy, *et al*. (2015)(236)	Weak
Clinical	Patients with heart failure with reduced ejection fraction and the combination of the ADRA2C rs61767072 deletion allele with other increased adrenergic function alleles (e.g., ADRB1 Arg389) have significantly greater improvement in clinical outcomes with beta-blockers than patients with the reference ADRA2C allele and other reduced adrenergic function alleles (e.g., ADRB1 Gly389).	Parikh, *et al*. (2018)(213)	Weak

TABLE S6. EVIDENCE LINKING *GRK4/5* GENETIC VARIATION TO BETA-BLOCKER PHENOTYPE

Type of Experiment	Major Findings	References	Level of Evidence
GRK5			
Atenolol			
Clinical	Heart rate in patients treated with atenolol is NOT affected by rs2230345 (Gln41Leu) genotype.	Kurnik, *et al.* (2009)(237) Lobmeyer, *et al.* (2011)(238)	Weak
Clinical	Blood pressure in patients treated with atenolol is NOT affected by rs2230345 (Gln41Leu) genotype.	Lobmeyer, *et al.* (2011)(238)	Weak
Carvedilol			
Clinical	Carvedilol dose is significantly lower in patients carrying the rs2230345 T (Leu41) allele compared to patients with the AA (Gln/Gln41) genotype.	Ramalingam, *et al.* (2021)(239)	Weak
Beta-blockers			
Clinical	Clinical outcomes in patients treated with beta-blockers are better in patients carrying the rs2230345 T (Leu41) allele.	Liggett, *et al.* (2008)(240) Cresci, *et al.* (2009)(170) Cresci, *et al.* (2012)(176) Kang, *et al.* (2015)(171) Huang, *et al.* (2018)(173) Ramalingam, *et al.* (2021)(239) El Gindy, *et al*. (2022)(201)	Weak
Clinical	Clinical outcomes in patients treated with beta-blockers are significant worse in patients with the rs2230349 AA (His/His304) genotype compared to those with the GG (Arg/Arg304) or GA (Arg/His304) genotypes.	Huang, *et al.* (2018)(173)	Weak

Clinical	The risk of post-op atrial fibrillation in patients treated with beta-blockers is significantly increased by the intronic variants rs3740563 A allele, the rs11198893 A allele and the rs10787959 G allele.	Kertai, *et al.* (2014)(137)	Weak
Clinical	Echocardiographic measures of beta-blocker efficacy are significantly better in patients carrying the rs2230345 T (Leu41) allele.	Ramalingam, *et al.* (2021)(239)	Weak
GRK4			
Beta-blockers			
Clinical	Blood pressure in patients treated with beta-blockers is significantly worse in patients carrying haplotypes of the rs2960306 T (Leu65) and rs1024323 C (Ala142) alleles.	Bhatnagar, *et al.* (2009)(241) Vandell, *et al.* (2012)(242)	Weak

TABLE S7. EVIDENCE LINKING *ADRB1*, *ADRB2, ADRA2C,* AND *GRK4/5* GENETIC VARIANT COMBINATIONS TO BETA-BLOCKER PHENOTYPE

Type of Experiment	Major Findings	References	Level of Evidence
Clinical	Patients with heart failure with reduced ejection fraction and a combination of more increased adrenergic function alleles (e.g., ADRB1 Arg389 and Ser49, ADRB2 Arg16 and Glu27, ADRA2C 322-325 Del, GRK5 Gln41, and GRK4 Ala142 and Val486) have significantly greater improvement in clinical outcomes with beta-blockers than patients with a combination of more reduced adrenergic function alleles (e.g., ADRB1 Gly389 and Gly49, ADRB2 Gly16, Gln27, ADRA2C 322-325 Ins, GRK5 Leu41, and GRK4 Val142 and Ala486).	Cresci, *et al*. (2009)(170) Huang, *et al*. (2018(212) Parikh, *et al*. (2018)(213) Lanfear, *et al*. (2020)(215) Guerra, *et al*. (2022)(214) Lanfear, *et al*. (2023)(216)	Weak
Clinical	Patients with hypertension and a combination of more increased adrenergic function alleles (e.g., ADRB1 Arg389 and Ser49, ADRB2 Arg16 and Glu27, ADRA2C 322-325 Del, GRK5 Gln41, and GRK4 Ala142 and Val486) have significantly greater reduction in blood pressure with beta-blockers than patients with a combination of more reduced adrenergic function alleles (e.g., ADRB1 Gly389 and Gly49, ADRB2 Gly16, Gln27, ADRA2C 322-325 Ins, GRK5 Leu41, and GRK4 Val142 and Ala486).	Johnson, *et al*. (2003)(152) Liljedahl, *et al*. (2003)(189) Liu, *et al*. (2006)(151) Filigheddu, *et al*. (2010)(141) Si, *et al*. (2014)(243) Zeng, *et al*. (2022)(187)	Weak

TABLE S8. DOSING RECOMMENDATIONS FOR CARVEDILOL BASED ON CYP2D6 PHENOTYPE

Phenotype	Activity Score	*Implications	Recommendations	Classification of Recommendations
CYP2D6 ultrarapid metabolizer	>2.25	Increased metabolism of carvedilol leading to decreased drug concentrations; it is unclear whether this results in clinically significant changes in heart rate and blood pressure	No recommendation for carvedilol therapy due to insufficient evidence regarding diminished clinical effectiveness	No recommendation
CYP2D6 normal metabolizer	1.25≤x≤2.25	Normal carvedilol metabolism	Initiate standard dosing	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	Decreased metabolism of carvedilol leading to small increases in drug concentrations; it is unclear whether this results in clinically significant changes in heart rate, blood pressure or major clinical outcomes	No recommendation for carvedilol therapy due to insufficient evidence regarding clinical effectiveness	No recommendation
CYP2D6 poor metabolizer	0	Decreased metabolism of carvedilol leading to increased drug concentrations; it is unclear whether this results in clinically significant changes in heart rate, blood pressure or major clinical outcomes	No recommendation for carvedilol therapy due to insufficient evidence regarding clinical effectiveness	No recommendation
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

*CYP2D6 metabolizes carvedilol to both pharmacologically inactive and active metabolites.

TABLE S9. DOSING RECOMMENDATIONS FOR ACEBUTOLOL, BETAXOLOL, BISOPROLOL, AND PROPRANOLOL BASED ON CYP2D6 PHENOTYPE

Phenotype	Activity Score	Implications	Recommendations	Classification of recommendation
CYP2D6 ultrarapid metabolizer	> 2.25	No or insufficient evidence for drug exposure, blood pressure, and heart rate	No recommendation for therapy due to insufficient or no evidence regarding drug exposure and clinical effectiveness	No recommendation
CYP2D6 normal metabolizer	$1.25 \leq x \leq 2.25$	Normal metabolism	Initiate standard dosing	Strong
CYP2D6 intermediate metabolizer	$0 < x < 1.25$	No or insufficient evidence for drug exposure, blood pressure, and heart rate	No recommendation for therapy due to insufficient or no evidence regarding drug exposure and clinical effectiveness	No recommendation
CYP2D6 poor metabolizer	0	No or insufficient evidence for drug exposure, blood pressure, and heart rate	No recommendation for therapy due to insufficient or no evidence regarding drug exposure and clinical effectiveness	No recommendation
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

TABLE S10. DOSING RECOMMENDATIONS FOR NEBIVOLOL BASED ON CYP2D6 PHENOTYPE

Phenotype	Activity Score	Implications	Recommendations	Classification of recommendation
CYP2D6 ultrarapid metabolizer	> 2.25	No or insufficient evidence for drug exposure, blood pressure, and heart rate	No recommendation for therapy due to insufficient or no evidence regarding drug exposure and clinical effectiveness	No recommendation
CYP2D6 normal metabolizer	$1.25 \leq x \leq 2.25$	Normal metabolism	Initiate standard dosing	Strong
CYP2D6 intermediate metabolizer	$0 < x < 1.25$	Decreased metabolism of nebivolol leading to a small increase in drug exposure; it is unclear whether this results in clinically significant changes in heart rate and blood pressure	No recommendation for therapy due to insufficient evidence regarding drug exposure and clinical effectiveness	No recommendation
CYP2D6 poor metabolizer	0	Decreased metabolism of nebivolol leading to increased drug exposure; it is unclear whether this results in clinically significant changes in heart rate and blood pressure	No recommendation for therapy due to insufficient or no evidence regarding drug exposure and clinical effectiveness	No recommendation

CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

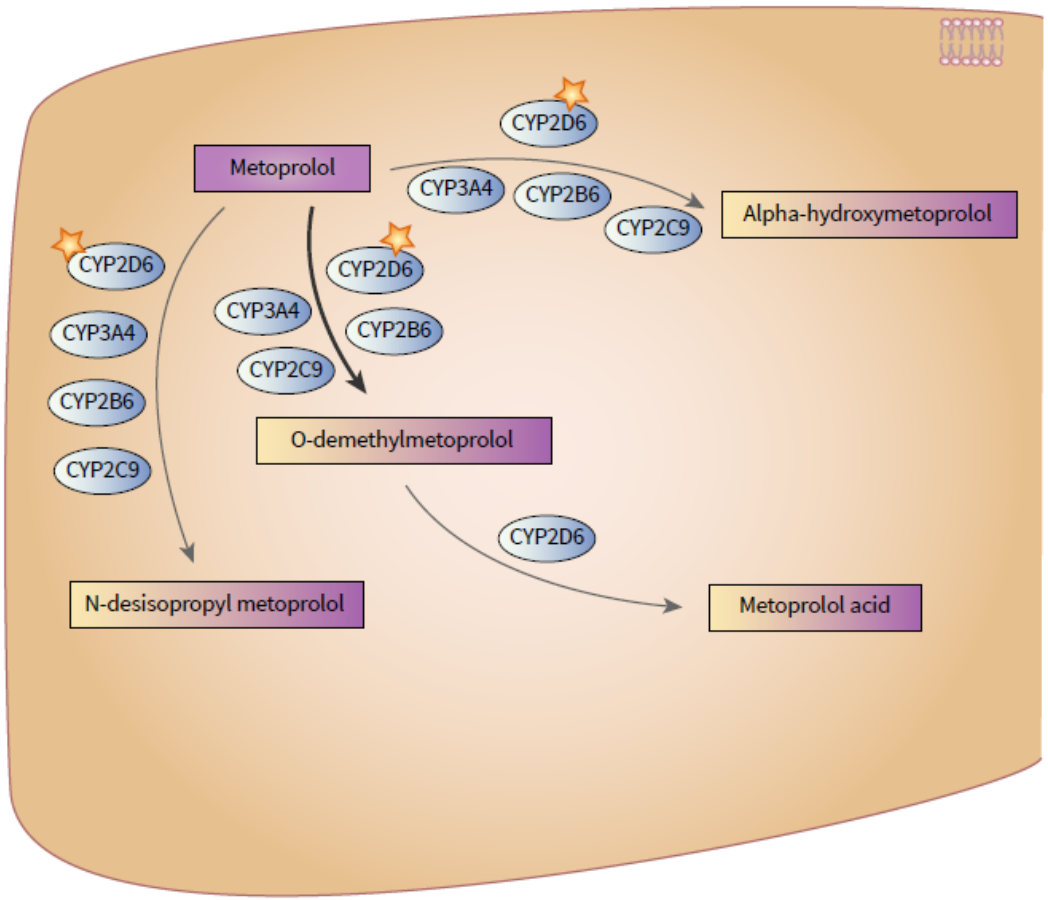

FIGURE S1. METOPROLOL PATHWAY, PHARMACOKINETICS

For a detailed and updated description, please see: https://www.pharmgkb.org/pathway/PA166179273. Image is available under a Creative Commons BY-SA 4.0 license (244).

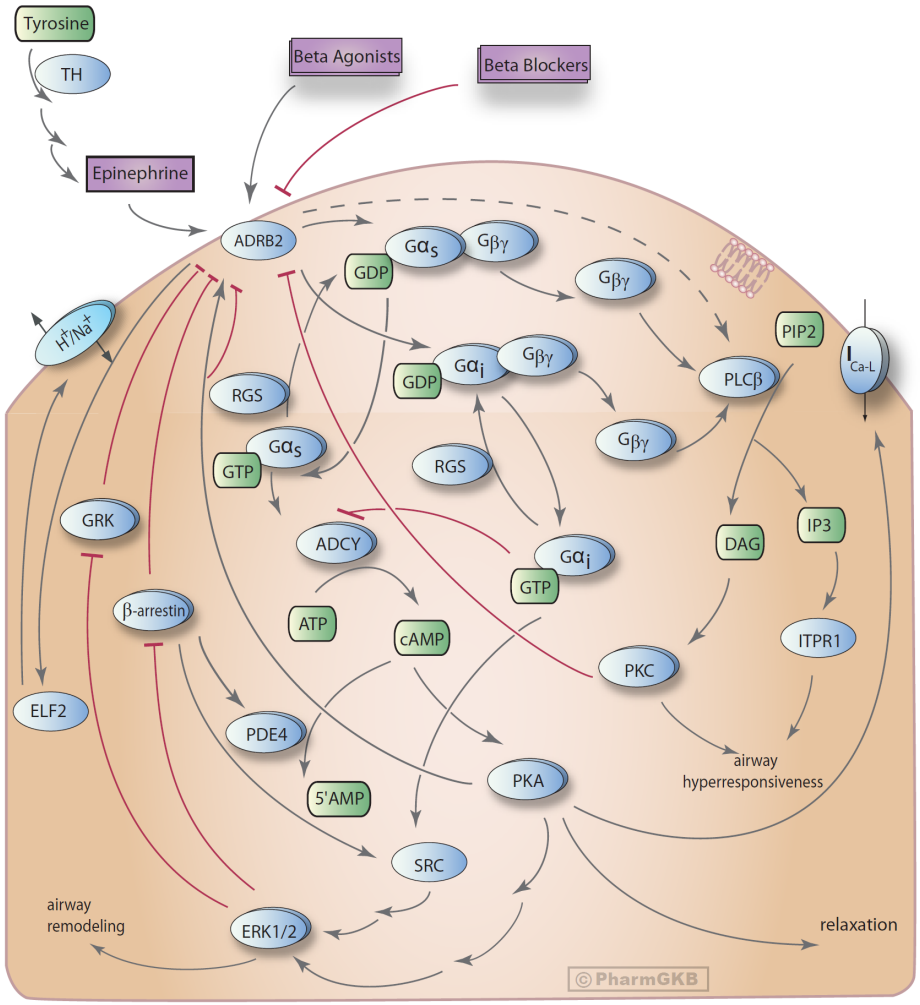

FIGURE S2. BETA-AGONIST/BETA-BLOCKER PATHWAY, PHARMACODYNAMICS
For a detailed and updated description, please see: https://www.pharmgkb.org/pathway/PA2024. Image is available under a Creative Commons BY-SA 4.0 license (245).

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