

**Supplement to:  
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19  
and Voriconazole Therapy**

Authors

Brad Moriyama<sup>1</sup>, Aniwaa Owusu Obeng<sup>2,3,4</sup>, Julia Barbarino<sup>5</sup>, Scott R. Penzak<sup>6</sup>,  
Stacey A. Henning<sup>1</sup>, Stuart A. Scott<sup>2,7</sup>, José A. G. Agúndez<sup>8</sup>, John R. Wingard<sup>9</sup>,  
Howard L McLeod<sup>10</sup>, Teri E. Klein<sup>5</sup>, Shane Cross<sup>11, 12</sup>, Kelly E. Caudle<sup>11</sup>, and  
Thomas J. Walsh<sup>13</sup>

<sup>1</sup>NIH Clinical Center Pharmacy Department, Bethesda, MD

<sup>2</sup>Icahn School of Medicine at Mount Sinai, The Charles Bronfman Institute for Personalized Medicine, New York, NY, USA

<sup>3</sup>The Mount Sinai Hospital, Department of Pharmacy, New York, NY, USA

<sup>4</sup>Icahn School of Medicine at Mount Sinai, Department of Medicine, Division of General Internal Medicine, New York, NY, USA

<sup>5</sup>Department of Genetics, Stanford University, Stanford, CA

<sup>6</sup>Department of Pharmacotherapy, University of North Texas, System College of Pharmacy, Fort Worth Texas, USA

<sup>7</sup>Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY

<sup>8</sup>Dept. Pharmacology, University of Extremadura. Avda de la Universidad s/n 10071, Cáceres, Spain.

<sup>9</sup>University of Florida College of Medicine, Gainesville, FL

<sup>10</sup>Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA;

<sup>11</sup>Department of Clinical Pharmacy, University of Tennessee College of Pharmacy, Memphis, TN, USA

<sup>12</sup>Transplantation-Oncology Infectious Diseases Program, Department of Medicine, Pediatrics, and Microbiology and Infectious Diseases, Weill Cornell Medical Center of Cornell University, New York, NY

**Corresponding Author:**

Thomas J. Walsh, MD, PhD (hon), FCCP, FAAM, FIDSA  
Professor of Medicine, Pediatrics, and Microbiology & Immunology  
Weill Cornell Medicine of Cornell University and New York Presbyterian Hospital  
1300 York Ave., Rm A-421  
New York, NY 10065  
thw2003@med.cornell.edu

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## GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2C19* genotypes and the dosing of voriconazole is published in full on <http://www.pharmgkb.org> and <https://cpicpgx.org/guidelines/>. Relevant information will be reviewed periodically and updated guidelines published online.

## LITERATURE REVIEW

We searched the PubMed® database (1966 to May 2016) for the following keywords: (cytochrome P450 2C19 or CYP2C19) AND (voriconazole). Using these search terms, 134 publications were identified. In addition, studies annotated in PharmGKB (<http://www.pharmgkb.org>) were identified. Study inclusion criteria included publications that included analyses for the association between *CYP2C19* genotypes and metabolism of voriconazole or voriconazole-related adverse drug events or clinical outcomes. Non-English manuscripts were excluded. Following application of these inclusion criteria, 35 publications were reviewed and included in the evidence table (**Supplemental Table S1**).

The *CYP2C19* frequency table (1) include updates of those previously published in CPIC guidelines (2-5). Updates to the *CYP2C19* frequency tables were made by searching the PubMed® database (1995 to 2015). The following criteria were used for *CYP2C19*: (CYP2C19 or 2C19 or cytochrome P4502C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve “full-text” and “English” literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2C19* frequency table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses). Diplotype and phenotype frequencies were estimated using the equation describing Hardy Weinberg equilibrium based on reported allele frequencies.

## GENES: *CYP2C19*

### Genetic Test Interpretation

*CYP2C19* genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis. *CYP2C19* haplotypes are assigned a star-allele (\*) nomenclature to allow for the standardization of genetic polymorphism annotation (6). A complete list of *CYP2C19* star-allele nomenclature along with the genetic variants that define each star-allele is available at <http://www.cypalleles.ki.se/cyp2c19.htm>, respectively. Information regarding *CYP2C19* haplotypes (star-alleles) is also available at PharmGKB ([www.pharmgkb.org](http://www.pharmgkb.org)). Knowing which SNPs or other genetic variants a particular test interrogates is important as the inclusion or exclusion of certain genetic variants in a pharmacogenetic test could affect the reported star-allele result.

Reference laboratories usually report a diplotype, which is the summary of inherited maternal and paternal star-alleles (e.g. *CYP2C19*\*1/\*2, where an individual inherited a \*1 allele and a \*2 allele). Commonly reported *CYP2C19* star-alleles are categorized into functional groups (e.g., normal function, decreased function, or no function) based on the predicted activity of the encoded enzyme (*CYP2C19* allele definition table;(1)) the predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype. *CYP2C19* phenotype-predicting tools, such as the *CYP2C19* voriconazole implementation tables, are being developed by CPIC and can be accessed at <https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/>.

***CYP2C19 predicted phenotype.*** The predicted phenotype for a patient carrying the *CYP2C19*\*17 increased function allele in combination with a no function allele (e.g., *CYP2C19*\*2) is less clear. Limited data suggest that *CYP2C19*\*17 may not compensate for a no function allele such as *CYP2C19*\*2 allele (7, 8). Herein, we classified carriers of the *CYP2C19*\*17 allele in combination with a no function allele as intermediate metabolizers, which is consistent with the CPIC guidelines for *CYP2C19* and clopidogrel (4).

Limited data are available to assess the predicted phenotypes for rare *CYP2C19* diplotype combinations that include *CYP2C19* alleles with decreased function and that have low

frequencies in the general population (e.g., \*9, \*10). Therefore, for the purpose of this guideline the following assignments have been proposed: patients with two decreased function alleles OR patients with one normal/increased function allele AND one decreased function allele are categorized as “likely intermediate metabolizers” (e.g., *CYP2C19*\*1/\*9, \*9/\*9, \*9/\*17) and patients with one decreased function allele and one no function allele are categorized as “likely poor metabolizers” (*CYP2C19*\*2/\*9). For many rare alleles, no information regarding enzyme activity is currently available, and those with functional data have only been determined by in vitro studies. Consequently, the proposed “likely intermediate” and “likely poor” metabolizer assignments were developed for diplotypes that contain one allele with an established effect on enzyme activity and a second allele with limited or no available activity data. The diplotypes in these new categories may be revised as new data become available, which will be updated on [cpicpgx.org](http://cpicpgx.org) and [www.pharmgkb.org](http://www.pharmgkb.org) as needed.

### **Available Genetic Test Options**

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at <http://www.pharmgkb.org> or the Genetic Testing Registry (<http://www.ncbi.nlm.nih.gov/gtr/>) (9).

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

## **CYP2C19 Other Consideration**

There are several factors to consider when genotyping *CYP2C19*. Some of these factors may cause potential uncertainty in *CYP2C19* genotyping results and phenotype predictions and are listed as follows: **1)** *CYP2C19*\*2 is the most common no function allele. Subvariants of *CYP2C19*\*2 have been identified that harbor additional SNPs with limited or no added functional consequence (e.g., *CYP2C19*\*2A, \*2B, \*2C, and \*2D). Therefore, only analyzing for the defining *CYP2C19*\*2 SNP (c.681G>A) is considered sufficient to determine a *CYP2C19* phenotype. **2)** Because it is currently impractical to test for every variant in the *CYP2C19* gene, genotyping assays do not typically interrogate rare variants. Depending on the sequence variants (or alleles present) in a given patient, the default genotype may be *CYP2C19*\*1/\*1 (or wild-type) or another diplotype. If the rare or novel variant adversely affects *CYP2C19* enzyme function, then the patient's actual phenotype may differ from the predicted phenotype. **3)** *CYP2C19* allele frequencies vary considerably among individuals of different ethnic backgrounds. For example, *CYP2C19*\*3 has a low prevalence among most ethnic groups, but has an allele frequency of approximately 15% in some Asian populations (2). Thus, the alleles that should be tested for a given population may vary. For Asian populations, *CYP2C19*\*3 should be included in *CYP2C19* genotyping panels. **4)** The SNP defining the no function *CYP2C19*\*4 allele (c.1A>G; rs28399504) has been found in linkage with the SNP defining the *CYP2C19*\*17 allele (c.-806C>T; rs12248560). This haplotype is designated *CYP2C19*\*4B and may occur more frequently in certain ethnic groups, in particular the Ashkenazi Jewish population (2, 10, 11). *CYP2C19*\*17 is a gain-of-function allele, while *CYP2C19*\*4B is a no function allele. Testing for *CYP2C19*\*4 in addition to *CYP2C19*\*17 may improve *CYP2C19* phenotype prediction accuracy. It is noted that discrimination between *CYP2C19*\*4A/\*17 and \*1/\*4B requires additional testing to determine the phase of the variants (i.e., in *cis* or *trans*) in addition to genotyping for both c.-806C>T and 1A>G (12). **5)** A recent study identified a novel allelic variant that carries the *CYP2C19*\*17-defining increased activity -806C>T SNP, but also a nonsynonymous SNP, c.463G>T, that introduces a premature stop codon (p.E155X) (11). While this SNP appears to be rare, it may lead to considerable overestimation of activity in *CYP2C19*\*17 carriers if not interrogated. **6)** Certain genotyping platforms (e.g., Affymetrix DMET) analyze over 15 *CYP2C19* star-alleles, some of which are rare and not well characterized. Therefore, uncertainty exists when translating a genotype result into a predicted

CYP2C19 phenotype in instances where a patient is found to carry a poorly characterized allele. Bioinformatics tools such as Polyphen-2 and Sorting Tolerant From Intolerant (SIFT) algorithms computationally predict the effect of sequence variations found in rare and poorly characterized alleles on CYP2C19 enzymatic function (13) and may assist in diplotype interpretation in instances where a poorly characterized allele is reported. However, these *in silico* methods are not a substitute for *in vitro* and *in vivo* analyses.

## **LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE**

The evidence summarized in **Supplemental Tables S1** is graded (14) on a scale of high, moderate, and weak, based upon the level of evidence:

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

**Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.

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

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

## **STRENGTH OF RECOMMENDATIONS**

CPIC's therapeutic recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type or variant-containing CYP2C19, *in vitro* CYP2C19 enzyme activity from tissues isolated from individuals of known CYP2C19 genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies. The gene-based dosing recommendations in this guideline take into

consideration the affects CYP2C19 genetic variants may have on both clinical outcomes and voriconazole pharmacokinetics.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (15): ‘strong’, where “the evidence is high quality and the desirable effects clearly outweigh the undesirable effects”; ‘moderate’, in which “there is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and ‘optional’, in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

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

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (16-20). See <https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/> for resources to support the adoption of CPIC guidelines within an EHR. 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 the use of *CYP2D6* and/or *CYP2C19* genotype results to guide TCA dosing in an EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (21, 22). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the “person level” rather than at the date-centric



“encounter level”. Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (16, 23).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how *CYP2D6* and/or *CYP2C19* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems for genes relevant to the CPIC guideline (see <https://www.pharmgkb.org/page/cyp2c19RefMaterials>) (24).

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 drugs relevant to the CPIC guideline (see <https://cpicpgx.org/guidelines/guideline-for-voriconazole-and-cyp2c19/>).

**SUPPLEMENTAL TABLE S1. EVIDENCE LINKING *CYP2C19* GENOTYPE TO VORICONAZOLE PHENOTYPE**

Type of experimental model (in vitro, in vivo, preclinical or clinical)	Major findings	References	Level of evidence <sup>a</sup>
Clinical: Pharmacokinetics in healthy volunteers	In healthy volunteers, rapid metabolizers (*1/*17) as (determined by <i>CYP2C19</i> genotyping) have increased metabolism <sup>b</sup> of voriconazole (clearance, area under the plasma-concentration time curve (AUC), and/or dose-adjusted trough concentrations) as compared to normal metabolizers.	Wang, <i>et al.</i> (2009) (25)	Moderate
	In healthy volunteers, intermediate metabolizers (as determined by <i>CYP2C19</i> genotyping) have decreased metabolism <sup>b</sup> of voriconazole (clearance, trough concentration (C <sub>0</sub> ), area under the plasma concentration-time curve (AUC), median residence time (MRT), or terminal elimination half-life (t <sub>1/2</sub> )) as compared to normal metabolizers.	<p><b>Supports Statement:</b>                      Chung, <i>et al.</i> (2015) (26)<sup>c</sup>                      Lee, <i>et al.</i> (2012) (27)                      Scholz, <i>et al.</i> (2009) (28)<sup>d</sup>                      Rengelshausen, <i>et al.</i> (2005)(29)<sup>c</sup></p> <p><b>No significant difference reported:</b>                      Shi, <i>et al.</i> (2010) (30)</p>	Moderate
	In healthy volunteers, intermediate metabolizers (as determined by <i>CYP2C19</i> genotyping) have increased metabolism <sup>b</sup> of voriconazole (based on clearance, area under the plasma concentration-time curve (AUC), or terminal elimination half-life (t <sub>1/2</sub> )) as compared to poor metabolizers.	Shi, <i>et al.</i> (2010) (30)	Moderate

	In healthy volunteers, poor metabolizers (as determined by <i>CYP2C19</i> genotyping) have decreased metabolism <sup>b</sup> of voriconazole (based on clearance, trough concentration (C <sub>0</sub> ), area under the plasma concentration-time curve (AUC), terminal elimination half-life (t <sub>1/2</sub> ), or mean residence time (MRT)) as compared to normal metabolizers.	<p>Chung, <i>et al.</i> (2015) (26)<sup>c</sup>  Lee, <i>et al.</i> (2012) (27)  Shi, <i>et al.</i> (2010) (30)  Scholz, <i>et al.</i> (2009) (28)<sup>d</sup>  Lei, <i>et al.</i> (2009)(31)  Wang, <i>et al.</i> (2009) (25)  Weiss, <i>et al.</i> (2009) (32)<sup>e</sup>  Mikus, <i>et al.</i> (2006) (33)  Rengelshausen, <i>et al.</i> (2005)(29)<sup>c</sup>  Ikeda, <i>et al.</i> (2004) (34)<sup>c</sup></p>	High
Clinical (including case reports): Pharmacokinetics in patients	In adult patients, ultrarapid metabolizers (*17/*17) or and rapid metabolizers (*1/*17) (as determined by <i>CYP2C19</i> genotyping) have decreased trough concentrations of voriconazole as compared to normal metabolizers.	<p>Lamoureux, <i>et al.</i> (2015) (35)  Weigel, <i>et al.</i> (2015) (36)<sup>c</sup>  Abidi, <i>et al.</i> (2015) (37)<sup>c</sup>  Trubiano, <i>et al.</i> (2015) (38)<sup>c</sup>  Wang, <i>et al.</i> (2014) (39)<sup>c</sup>  Bouatou, <i>et al.</i> (2014) (40)<sup>c</sup>  Autmizguine, <i>et al.</i> (2012) (41)<sup>c</sup>  Malingre, <i>et al.</i> (2012) (42)<sup>c</sup></p>	Moderate
	In adult patients, intermediate metabolizers (as determined by <i>CYP2C19</i> genotyping) have increased trough concentrations of voriconazole as compared to normal metabolizers.	<p>Trubiano, <i>et al.</i> (2015) (38)<sup>c</sup>  Calcagno, <i>et al.</i> (2014) (43)<sup>c</sup>  Suan, <i>et al.</i> (2011) (44)<sup>c</sup>  Berge, <i>et al.</i> (2011) (45)</p> <p><b>No difference reported:</b>  Wang, <i>et al</i> (2014) (39)  Chuwongwattan, <i>et al.</i> (2016) (46)  Lamoureux <i>et al.</i> (2015) (35)  Kim, <i>et al.</i> (2011) (47)</p>	Weak

	In adult patients, poor metabolizers (as determined by <i>CYP2C19</i> genotyping) have increased concentrations of voriconazole as compared to normal metabolizers.	Chawla, <i>et al.</i> (2015) (48) Wang, <i>et al.</i> (2014) (39) Zonios, <i>et al.</i> (2014) (49) Moriyama, <i>et al.</i> (2013) (50) <sup>c</sup> Moriyama, <i>et al.</i> (2011) (51) <sup>c</sup> Chuwongwattan, <i>et al.</i> (2016) (46)  Does not support statement: Kim, <i>et al.</i> (2011) (47)	Moderate
Clinical (including case reports) Pediatrics	In pediatric patients, ultrarapid metabolizers (*17/*17) (as determined by <i>CYP2C19</i> genotyping) have decreased concentrations of voriconazole as compared to normal metabolizers.	Cendejas-Bueno <i>et al.</i> (2016) (52) <sup>c</sup> Hicks, <i>et al.</i> (2015) (53)	Moderate
	In pediatric patients, rapid metabolizers (*1/*17) (as determined by <i>CYP2C19</i> genotyping) do <b>not</b> have significantly different concentrations of voriconazole as compared to normal metabolizers.	Hicks, <i>et al.</i> (2015) (53)  <b>Does not support statement :</b> Hicks <i>et al.</i> (2016) (54) <sup>c</sup>	Moderate
	In pediatric patients, intermediate metabolizers (as determined by <i>CYP2C19</i> genotyping) have increased trough concentrations of voriconazole as compared to normal metabolizers.	Hicks, <i>et al.</i> (2015) (53) Narita, <i>et al.</i> (2013) (55)	Moderate
	In pediatric patients, poor metabolizers (as determined by <i>CYP2C19</i> genotyping) have increased concentrations of voriconazole as compared to normal metabolizers.	Hicks, <i>et al.</i> (2015) (53) Mori, <i>et al.</i> (2015) (56) <sup>c</sup> Narita, <i>et al.</i> (2013) (55)	Moderate
Clinical (including case reports) Adverse Reactions/ discontinuation	Ultrarapid metabolizers (as determined by <i>CYP2C19</i> genotyping) are at risk for discontinuation of voriconazole treatment due to undetectable levels of the drug or a lack of response.	Bennis, <i>et al.</i> (2015) (57) <sup>c</sup> Abidi, <i>et al.</i> (2015) (37) <sup>c</sup> Malingre, <i>et al.</i> (2012) (42) <sup>c</sup>	Moderate

	Intermediate metabolizers (as determined by <i>CYP2C19</i> genotyping) are at risk for adverse drug effects when receiving voriconazole, such as hepatotoxicity or hallucinations.	Suan, <i>et al.</i> (2011) (44) <sup>c</sup>	Weak
	Poor metabolizers (as determined by <i>CYP2C19</i> genotyping) are at risk for adverse drug effects when receiving voriconazole, such as QTc prolongation.	Moriyama, <i>et al.</i> (2013) (50) <sup>c</sup>	Weak
	Poor metabolizers (as determined by <i>CYP2C19</i> genotyping) are at risk for discontinuation of voriconazole treatment due to elevated, potentially toxic, levels of the drug.	Moriyama, <i>et al.</i> (2013) (50) <sup>c</sup> Moriyama, <i>et al.</i> (2011) (51) <sup>c</sup>	Moderate
	No significant association was found between <i>CYP2C19</i> metabolizer status (as determined by <i>CYP2C19</i> genotyping) and voriconazole-induced adverse drug effects.	Kim, <i>et al.</i> (2013) (58) Berge, <i>et al.</i> (2011) (45) Matsumoto, <i>et al.</i> (2009) (59) Levin, <i>et al.</i> (2007) (60)	Moderate
Clinical (case reports) Dose requirement	Ultrarapid and rapid metabolizers (as determined by <i>CYP2C19</i> genotyping) require an increase in dose of voriconazole to achieve target levels of the drug.	Lamoureux <i>et al.</i> (2015) (35) Bouatou, <i>et al.</i> (2014) (40) <sup>c</sup> Autmizguine, <i>et al.</i> (2012) (41) <sup>c</sup>	Weak
	Intermediate metabolizers (as determined by <i>CYP2C19</i> genotyping) may require a decrease in dose of voriconazole to achieve target levels of the drug.	Calcagno, <i>et al.</i> (2014) (43) <sup>c</sup>	Weak

<sup>a</sup>Rating scheme described in the Supplemental Material

<sup>b</sup>“Increased metabolism” or “decreased metabolism” defined as changes in pharmacokinetic variables.

<sup>c</sup>Case report or no statistics performed

<sup>d</sup>“Normal Metabolizers” included \*1/\*17 individuals.

<sup>e</sup>This study pooled data from Mikus (2006) and Rengelshausen (2005).

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