

Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing

Kelly A. Birdwell^{1,2}, Brian Decker³, Julia M. Barbarino⁴, Josh F. Peterson^{2,5}, C. Michael Stein^{2,6}, Wolfgang Sadée⁷, Danxin Wang⁸, Alexander A. Vinks⁹, Yijing He¹⁰, Jesse J. Swen¹¹, J. Steven Leeder¹², RHN van Schaik¹³, Kenneth E. Thummel¹⁴, Teri E. Klein⁴, Kelly E. Caudle¹⁵, Iain A.M. MacPhee¹⁶

¹Division of Nephrology Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

²Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

³Division of Nephrology and Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN, USA

⁴Department of Genetics, Stanford University, Stanford, CA

⁵Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, USA

⁶Department of Pharmacology, Vanderbilt University, Nashville, Tennessee, USA

⁷Department of Pharmacology, Program in Pharmacogenomics, College of Medicine, Departments of Pharmacy, Psychiatry, Internal Medicine, and Environmental Health Sciences, The Ohio State University, Columbus, OH, USA

⁸Center for Pharmacogenomics, School of Medicine, The Ohio State University, Columbus, OH, USA

⁹Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio, USA

¹⁰Institute of Clinical Pharmacology, Central South University, Changsha, Hunan, P.R.China

¹¹Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands

¹²Division of Clinical Pharmacology and Therapeutic Innovation, Department of Pediatrics

Children's Mercy Hospitals and Clinics, Kansas City, MO

¹³Department of Clinical Chemistry, Erasmus MC Rotterdam, The Netherlands

¹⁴Departments of Pharmaceutics, University of Washington, Seattle, WA

¹⁵Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA

¹⁶Institute of Medical and Biomedical Education: Renal Medicine, St. George's, University of London, London, UK

Table of Contents

Literature Review.....	3
Genetic Test Interpretation	4
Available Genetic Test Options	4
Levels of Evidence.....	4
Strength of Recommendations	5
Resources to Incorporate Pharmacogenetics into an EHR with CDS.....	5
Supplemental Table S1. Genotypes that constitute the * alleles for <i>CYP3A5</i>	7
Supplemental Table S2. Association between allelic variants and <i>CYP3A5</i> function.....	8
Supplemental Table S3. Frequencies of <i>CYP3A5</i> alleles ¹ in major race/ethnic groups ²	9
Supplemental Table S4. Evidence linking <i>CYP3A5</i> *1, *3, *6 and *7 (rs776746, rs10264272 and rs41303343) genotype with phenotype	10
Supplemental Table S5. Drug(s) that pertain to this guideline.	25
Supplemental Table S6. Gene(s) that pertain to this guideline.....	25
Supplemental Figure S1. <i>CYP3A5</i> Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR	26
Supplemental Figure S2. <i>CYP3A5</i> Genotype and Tacrolimus: Point of Care Clinical Decision Support.....	27
Supplemental Table S7. Example Implementation of this Guideline: Pharmacogenetic Diplotype/Phenotype Summary Entries.....	28
Supplemental Table S8. Example Implementation of this Guideline: Point of Care Clinical Decision Support.....	31
References.....	33

Literature Review

We searched the PubMed database (1966 to January 2015) and Ovid MEDLINE (1950 to January 2015) using several keyword strategies: tacrolimus AND CYP3A5 OR tacrolimus AND CYP3A4. Literature evidence for this guideline was annotated, organized, and assessed using PharmGKB web tools (<http://www.pharmgkb.org>). All papers used as literature evidence for this guideline can be found on the PharmGKB website.

Using the specified search criteria, 201 publications were identified after excluding non-English manuscripts or review articles. Inclusion criteria included publications discussing *in vivo* clinical outcome (e.g. nephrotoxicity, transplant rejection) for tacrolimus in individuals who vary by *CYP3A5* rs776746 genotype/phenotype and *in vivo* or *in vitro* pharmacokinetic data (e.g. dose-adjusted trough concentrations, clearance) for tacrolimus in individuals who vary by *CYP3A5* rs776746 genotype/phenotype. Following application of the inclusion criteria, 187 publications were reviewed and included in the evidence table.

To construct a *CYP3A5**1, *3, *6 and *7 allele frequency table based on ethnicity, the PubMed database (1966 to July 2014) was searched using the criteria *CYP3A5* allele frequency AND *CYP3A5* polymorphism frequency with filter limits set to retrieve “English” literature. Studies from the literature review were also used to construct the frequency table. Studies were considered for inclusion if (1) the ethnicity of the population was clearly indicated; (2) only one ethnicity was analyzed, or in cases where multiple ethnicities were studied, allele frequencies were given for each ethnicity separately; (3) either allele frequencies or alleles for *CYP3A5**1, *3, *6, or *7 genotypes were reported; (4) the method by which *CYP3A5* was genotyped was reliable; (5) the sample size was at least 15 subjects; and (6) the study represented publication of novel data (no reviews or meta-analyses). The combined analysis included 5,285 Africans, 8,226 Asians, 5,954 Caucasians, 2,144 Latin Americans, 1,401 Middle Easterners and 1,411 Southwest Asians.

Genetic Test Interpretation

The haplotype, or star (*) allele name, is determined by a specific SNP or a combination of SNPs that are interrogated in the genotyping analysis. The genotypes that constitute the haplotype, or star (*) alleles for *CYP3A5*, and the rs# for each of the specific genomic nucleotide alterations that define the alleles, are described in **Supplemental Table S1**.

The genotype results are generally reported as a diplotype, which includes one maternal and one paternal star allele (e.g., *1/*3). The *CYP3A5* function associated with each of the common * alleles is summarized in **Supplemental Table S2**.

Available Genetic Test Options

Commercially available genetic testing options change over time. Additional updated information can be found at:

http://www.pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp

Furthermore, the Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at <http://www.ncbi.nlm.nih.gov/gtr/>. At the time of writing, there are two *CYP3A5* genetic tests listed in the GTR (<http://www.ncbi.nlm.nih.gov/gtr/tests/511143/> and <http://www.ncbi.nlm.nih.gov/gtr/tests/508842/>). Note that reference laboratories may not test for all the variants discussed in this guideline.

Levels of Evidence

The evidence summarized in **Supplemental Table S5** is graded using a scaled modified slightly from Valdes et al. [1]

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

Strength of Recommendations

CPIC's dosing recommendations are based weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines [2]. Some of the factors that are taken into account include *in vivo* clinical outcome data for tacrolimus, *in vivo* pharmacokinetic data for tacrolimus, and *in vitro* pharmacokinetic data for tacrolimus.

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. We chose to use 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 (<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>): 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.

Strong recommendation for the statement

Moderate recommendation for the statement

Optional recommendation for the statement

Resources to Incorporate Pharmacogenetics into an EHR with CDS

Use of clinical decision support (CDS) tools within electronic health records (EHRs) can assist clinicians to use genetic information to optimize drug therapy [3-7].

Supplementary material provides resources from CPIC to support the adoption of CPIC guidelines within an EHR [8]. Based on the capabilities of various EHRs and local preferences, we recognize approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for

incorporating the use of *CYP3A5* genotype results to guide tacrolimus dosing in any EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. First, pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR [9]. 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.” Second, results should be entered as standardized and discrete terms to facilitate using them to provide point of care CDS [10, 11]. Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. Point-of-care CDS should be designed to effectively remind clinicians of prescribing implications at any time after the test result is entered into the EHR. Guidance to achieve these objectives is provided in diagrams that illustrate how *CYP3A5* pharmacogenetic test results could be entered into an EHR (**Supplemental Figure S1**) and be used for point-of-care CDS (**Supplemental Figure S2**). **Supplemental Tables S5** and **S6** provide a cross-reference to widely used nomenclature systems for the drug and the gene, respectively.

To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). **Supplemental Table S7** further translates results into a coded diplotype/phenotype summary, priority result notification, and sample interpretative result text. The result tables provide summary genotype/phenotype terms, example text for documentation in the EHR and point-of-care alerts. Finally, sample point-of-care alert text that corresponds to the workflow described in **Supplemental Figure S2** is provided in **Supplemental Table S8**.

Supplemental Table S1. Genotypes that constitute the * alleles for *CYP3A5*

Allele ^a	Nucleotide variation ^b	dbSNP number ^c	Effect on CYP3A5 protein
*1			
*2	27289G>T	rs28365083	T398N
*3	6986T>C	rs776746	Splicing defect
*4	14665T>C	rs56411402	Q200R
*5	12952A>G		Splicing defect
*6	14690C>T	rs10264272	Splicing defect
*7	27131_27132insA	rs41303343	346Frameshift
*8	3699G>A	rs55817950	R28C
*9	19386C>T 6986T>C ^d	rs28383479 rs776746 ^d	A337T Splicing defect ^d

^aSee Human Cytochrome P450 Allele Nomenclature Committee website (<http://www.cypalleles.ki.se>) for comprehensive haplotype definitions of CYP3A5 variant alleles and updated allele information.

^bNucleotide changes Based on NCBI Reference Sequence NG_000004.3 as detailed at <http://www.cypalleles.ki.se/cyp3a5.htm>; all variants have been complemented from the reference sequence to the **positive** chromosomal strand.

^crsID provided as it is catalogued in dbSNP (<http://www.ncbi.nlm.nih.gov/snp/>).

^dCannot exclude the existence of this polymorphism on the same allele.

Supplemental Table S2. Association between allelic variants and CYP3A5 function

Functional Status	Alleles
Normal function ¹	*1
No function	*3, *6, *7
Unknown/limited data	*2, *4, *5, *8, *9
<i>1: an important caveat for all genotyping tests is that the decision to assign an allele a “wild-type” status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. In human DNA, it is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as “wild-type”</i>	

Supplemental Table S3. Frequencies of *CYP3A5* alleles¹ in major race/ethnic groups²

Ethnicity	Alleles							
	*1		*3		*6		*7	
	N	Freq	N	Freq	N	Freq	N	Freq
African	5285	0.558	5285	0.298	3321	0.172	2488	0.077
African American	480	0.605	480	0.316	277	0.111	61	0.120
East African	1244	0.431	1244	0.386	950	0.208	684	0.043
North African	557	0.214	557	0.722	413	0.079	413	0.007
South East African	1531	0.744	1531	0.157	448	0.194	448	0.142
West African	564	0.577	564	0.186	564	0.172	360	0.098
West Central African	909	0.594	909	0.217	669	0.189	522	0.087
Asian	8226	0.258	8226	0.742	1178	0.001	480	0.000
Caucasian	5954	0.078	5954	0.921	1661	0.001	942	0.000
Latin American	2144	0.202	2144	0.765	1148	0.037	1090	0.025
Middle Eastern	1401	0.105	1401	0.881	884	0.019	884	0.002
Southwest Asian	1411	0.342	1411	0.659	1066	0.000	NA	NA

¹ Average allele frequencies are based on the actual number of subjects with each allele reported in multiple studies and then grouped according to ² major race/ethnic groups for studies as defined in http://www.pharmgkb.org/download.action?filename=CYP3A5_Literature_Table.xlsx (details and references).

³ African geographical designations from Bains *et al.* [12].

Supplemental Table S4. Evidence linking *CYP3A51, *3, *6 and *7 (rs776746, rs10264272 and rs41303343) genotype with phenotype**

Type of experimental model (<i>in vitro</i> , <i>in vivo</i> , preclinical or clinical)	Major findings	References	Level of evidence ¹
Clinical	In kidney, heart or lung transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased dose-adjusted trough concentrations (C0/D) of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Rojas et al. (2015) [13] Iwamoto et al. (2015) [14] Xing et al. (2015) [15] Niioka et al. (2014) [16] Lapeyraque et al. (2014) [17] Lesche et al. (2014) [18] Bruckmueller et al. (2014) [19] Hamzah et al. (2014) [20] Cusinato et al. (2014) [21] Hattori et al. (2014) [22] Kurzawski et al. (2014) [23] Lalan et al. (2014) [24] Li et al. (2014) [25] Lunde et al. (2014) [26] Wu et al. (2014) [27] Sy et al. (2013) [28] Ogasawara et al. (2013) [29] Chitnis et al. (2013) [30] Li et al. (2013) [31] Tavira et al. (2013) [32] Spierings et al. (2013) [33] Yoon et al. (2013) [34] Hirano et al. (2012) [35] Niioka et al. (2012) [36] Diaz-Molina et al. (2012) [37] Kim IW, Noh H et al. (2012) [38] Terrazzino et al. (2012) [39] Kim IW, Moon YJ et al. (2012) [40] Gervasini et al. (2012) [41] Birdwell et al. (2012) [42] Cho et al. (2012) [43] de Wildt et al. (2011) [44] Provenzano et al. (2011) [45] Gijzen et al. (2011) [46] Elens et al. (2011) [47] Glowacki et al. (2011) [48] Ferraris et al. (2011) [49] Miura et al. (2011) [50] Tavira et al. (2011) [51] Jacobson et al. (2011) [52] Wu et al. (2011) [53] Zhang et al. (2010) [54] López-Montenegro et al. (2010) [55] Ashavaid et al. (2010) [56]	High

		<p>Capron et al. (2010) [57] Katsakiori et al. (2010) [58] Turolo et al. (2010) [59] Singh et al. (2009) [60] Chen et al. (2009) [61] Jun et al. (2009) [62] Quteineh et al. (2008) [63] Sato et al. (2008) [64] Loh et al. (2008) [65] Tirelli et al. (2008) [66] Hesselink et al. (2008) [67] Op den Buijsch et al. (2007) [68] Renders et al. (2007) [69] Roy et al. (2006) [70] Mourad et al. (2006) [71] Zhang et al. (2005) [72] Mourad et al. (2005) [73] Macphee et al. (2005) [74] Zhao et al. (2005) [75] Tsuchiya et al. (2004) [76] Haufroid et al. (2004) [77] Zheng et al. (2004) [78] Thervet et al. (2003) [79] Hesselink et al. (2003) [80] Zheng et al. (2003) [81]</p>	
Clinical	In kidney or heart transplant patients, no association was found between the CYP3A5 rs776746 genotype and dose-adjusted trough concentrations of tacrolimus.	<p>Shilbayeh et al. (2013) [82] Boso et al. (2013) [83] Jordán de Luna et al. (2011) [84]</p>	
Clinical	In ulcerative colitis patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased dose-adjusted trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Hirai et al. (2014) [85]	Moderate
Clinical	In liver transplant patients, those with the recipient CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased dose-adjusted trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	<p>Chen et al. (2014) [86] Wang et al. (2014) [87] Guy-Viterbo et al. (2014) [88] Uesugi et al. (2014) [89] Xue et al. (2014) [90] Jalil et al. (2014) [91] Buendia et al. (2013) [92] Gómez-Bravo et al. (2013) [93] Shi et al. (2013) [94] Chen et al. (2013) [95] Chen et al. (2013) [96] Ji et al. (2012) [97] Muraki et al. (2011) [98] Uesugi et al. (2006) [99]</p>	Moderate

Clinical	In liver transplant patients, no association was found between recipient CYP3A5 rs776746 genotype and dose-adjusted trough concentrations of tacrolimus.	Rahsaz et al. (2012) [100] de Wildt et al. (2011) [44] Zhang et al. (2011) [101] Jun et al. (2009) [62] Provenzani et al. (2009) [102] Li et al. (2007) [103] Wei-lin et al. (2006) [104] Yu et al. (2006) [105]	
Clinical	In liver transplant patients, those with the donor CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased dose-adjusted trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Chen et al. (2014) [86] Wang et al. (2014) [87] Guy-Viterbo et al. (2014) [88] Uesugi et al. (2014) [89] Xue et al. (2014) [90] Gómez-Bravo et al. (2013) [93] Buendia et al. (2013) [92] Rojas et al. (2013) [106] Durand et al. (2013) [107] Chen et al. (2013) [96] Chen et al. (2013) [95] Ji et al. (2012) [97] Provenzani et al. (2011) [45] Zhang et al. (2011) [101] Muraki et al. (2011) [98] Jun et al. (2009) [62] Provenzani et al. (2009) [102] Li et al. (2007) [103] Wei-lin et al. (2006) [104] Yu et al. (2006) [105]	High
Clinical	In liver transplant patients, no association was found between donor CYP3A5 rs776746 genotype and dose-adjusted trough concentrations of tacrolimus.	Goto et al. (2004) [108]	
Clinical	In kidney or heart transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") require increased doses of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Niioka et al. (2014) [16] Lesche et al. (2014) [18] Kuypers et al. (2014) [109] Bruckmueller et al. (2014) [19] Bergmann et al. (2014) [110] Cusinato et al. (2014) [21] Hattori et al. (2014) [22] Kurzawski et al. (2014) [23] Wu et al. (2014) [27] Vannaprasaht et al. (2013) [111] de Jonge et al. (2013) [112] Tavira et al. (2013) [32] Spierings et al. (2013) [33] Ro et al. (2012) [113] Niioka et al. (2012) [36] Diaz-Molina et al. (2012) [37] Torio et al. (2012) [114] Kim et al. (2012) [38] de Jonge et al. (2012) [115] Elmachad et al. (2012) [116] Garcia-Roca et al. (2012) [117] Stratta et al. (2012) [118] Gervasini et al. (2012) [41]	High

		<p>Cho et al. (2012) [43] Passey et al. (2011) [119] de Wildt et al. (2011) [44] Provenzani et al. (2011) [45] Gijzen et al. (2011) [46] Tang et al. (2011) [120] Glowacki et al. (2011) [48] de Jonge et al. (2011) [121] Li et al. (2011) [122] Ferraris et al. (2011) [49] Glowacki et al. (2011) [123] Pashae et al. (2011) [124] Tavira et al. (2011) [51] Wehland et al. (2011) [125] Ferraresso et al. (2011) [126] Kniepeiss et al. (2011) [127] Wang et al. (2010) [128] Capron et al. (2010) [57] Turolo et al. (2010) [59] Singh et al. (2009) [60] Chen et al. (2009) [61] Satoh et al. (2009) [129] Press et al. (2009) [130] Quteineh et al. (2008) [63] Hesselink et al. (2008) [67] Op den Buijsch et al. (2007) [68] Ferraresso et al. (2007) [131] Renders et al. (2007) [69] Cheung et al. (2006) [132] Zhang et al. (2005) [72] Mourad et al. (2005) [73] Tada et al. (2005) [133] Zhao et al. (2005) [75]</p>	
Clinical	In kidney or hematopoietic stem cell transplant patients, no association was found between CYP3A5 rs776746 genotype and dosage of tacrolimus.	<p>Shilbayeh et al. (2013) [82] Yanagisawa et al. (2011) [134]</p>	
Clinical	In ulcerative colitis patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") require increased doses of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Hirai et al. (2014) [85]	Moderate
Clinical	In liver transplant patients, those with the recipient CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") require increased doses of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	<p>Chen et al. (2014) [86] Xue et al. (2014) [90] Shi et al. (2013) [94] Buendia et al. (2013) [92] Tang et al. (2011) [120]</p>	Weak

Clinical	In liver transplant patients, no association was found between recipient CYP3A5 rs776746 genotype and dosage of tacrolimus.	Rahsaz et al. (2012) [100] de Wildt et al. (2011) [44] Provenzani et al. (2009) [102] Wei-lin et al. (2006) [104]	
Clinical	In liver transplant patients, those with the donor CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") require increased doses of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Tang et al. (2011) [120] Xue et al. (2014) [90] Durand et al. (2013) [107] Buendia et al. (2013) [92] Provenzani et al. (2011) [45] Provenzani et al. (2009) [102] Wei-lin et al. (2006) [104]	High
Clinical, Case Report	In kidney, heart or hematopoietic stem cell transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Cusinato et al. (2014) [21] Kurzawski et al. (2014) [23] Wu et al. (2014) [27] Spierings et al. (2013) [33] Manvizhi et al. (2013) [135] Niioka et al. (2012) [36] Passey et al. (2011) [119] de Wildt et al. (2011) [44] Gijsen et al. (2011) [46] Glowacki et al. (2011) [48] Onizuka et al. (2011) [136] Min et al. (2010) [137] Zhang et al. (2010) [54] Chen et al. (2009) [61] Satoh et al. (2009) [129] Quteineh et al. (2008) [63] Tirelli et al. (2008) [66] Hesselink et al. (2008) [67] Ferraresso et al. (2007) [131] Haufroid et al. (2006) [138] Zhang et al. (2005) [72]	Moderate
Case Report	A patient with Alport Syndrome who received a kidney transplant was found to have unexpectedly high tacrolimus trough blood concentrations. Whole exome sequencing revealed he was homozygous for the CYP3A5 rs776746 C allele (*3/*3; "nonexpresser"). He also had undetectable levels of the CYP3A4 protein due to a SNP resulting in a premature stop signal in the <i>CYP3A4</i> gene.	Werk et al. (2014) [139]	
Clinical	In kidney, heart and hematopoietic stem cell transplant patients, no association was found between CYP3A5 rs776746 genotype and trough concentrations of tacrolimus.	Lesche et al. (2014) [18] Bruckmueller et al. (2014) [19] Shilbayeh et al. (2013) [82] Ro et al. (2012) [113] Diaz-Molina et al. (2012) [37] Glowacki et al. (2011) [123] Yanagisawa et al. (2011) [134] Rong et al. (2010) [140] Capron et al. (2010) [57] Turolo et al. (2010) [59] Renders et al. (2007) [69] Mourad et al. (2005) [73] Mai et al. (2004) [141]	

Clinical	In ulcerative colitis patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Hirai et al. (2014) [85]	Moderate
Clinical	In patients with connective tissue disorders, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Tanaka et al. (2014) [142]	Moderate
Clinical	In liver transplant patients, those with the recipient CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Xue et al. (2014) [90] Gómez-Bravo et al. (2013) [93] Buendia et al. (2013) [92]	Weak
Clinical	In liver transplant patients, no association was found between recipient CYP3A5 rs776746 genotype and trough concentrations of tacrolimus.	Carcas-Sansuán et al. (2013) [143] Rahsaz et al. (2012) [100] de Wildt et al. (2011) [44] Muraki et al. (2011) [98] Provenzani et al. (2009) [102]	
Clinical	In liver transplant patients, those with the donor CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased trough concentrations of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Buendia et al. (2013) [92]	
Clinical	In liver transplant patients, no association was found between donor CYP3A5 rs776746 genotype and trough concentrations of tacrolimus.	Xue et al. (2014) [90] Muraki et al. (2011) [98] Provenzani et al. (2009) [102]	Weak
Clinical	In kidney or lung transplant patients, or in healthy individuals, those with the CT or TT genotype (*1/*3 or *1/*1; "expressers") have increased clearance of tacrolimus as compared to those with the CC genotype (*3/*3; CYP3A5 "nonexpressers").	Storset et al. (2014) [144] Bergmann et al. (2014) [110] Moes et al. (2014) [145] Han et al. (2013) [146] Ogasawara et al. (2013) [29] de Jonge et al. (2013) [112] Zuo et al. (2013) [147] Zhao et al. (2013) [148] Han et al. (2013) [146] Zuo et al. (2013) [149] de Jonge et al. (2012) [115] Monchaud et al. (2012) [150] Passey et al. (2011) [119] Xue et al. (2011) [151] Shi et al. (2011) [152] Rong et al. (2010) [140]	

		Benkali et al. (2010) [153] Zhao et al. (2009) [154] Satoh et al. (2008) [64] Suzuki et al. (2008) [155] Renders et al. (2007) [69] Tada et al. (2005) [133] Tsuchiya et al. (2004) [76]	
Clinical	In kidney or hematopoietic stem cell transplant patients, no association was found between CYP3A5 rs776746 genotype and clearance of tacrolimus.	Asberg et al. (2013) [156] Glowacki et al. (2011) [48] Yanagisawa et al. (2011) [134]	
In vitro	In human liver microsomes, clearance of tacrolimus was higher in those with the CYP3A5 rs776746 CT genotype (*1/*3; "expressers") as compared to those with the CC genotype (*3/*3; "nonexpressers").	Dai et al. (2006) [157]	Moderate
Clinical	In liver transplant patients, those with the recipient CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have increased clearance of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Jalil et al. (2014) [91] Fukudo et al. (2008) [158]	Moderate
Clinical	In liver transplant patients, those with the donor CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have increased clearance of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Gérard et al. (2014) [159] Li et al. (2007) [160] Fukudo et al. (2006) [161]	High
Clinical	In kidney transplant patients, or in healthy individuals, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased area under the concentration-time curve (AUC), both dose-adjusted and non-dose-adjusted, as compared to those with the CC genotype (*3/*3; "nonexpressers").	Yoon et al. (2013) [34] Zuo et al. (2013) [149] Niioka et al. (2012) [36] de Jonge et al. (2012) [115] Glowacki et al. (2011) [123] Miura et al. (2011) [50] Miura et al. (2011) [162] Rong et al. (2010) [140] Satoh et al. (2008) [64] Suzuki et al. (2008) [155] Choi et al. (2007) [163] Op den Buijsch et al. (2007) [68] Renders et al. (2007) [69] Haufroid et al. (2006) [138] Cheung et al. (2006) [132] Tada et al. (2005) [133] Tsuchiya et al. (2004) [76]	High
Clinical	In kidney transplant patients, no association was found between CYP3A5 rs776746 genotype and area under the concentration-time curve (AUC) of tacrolimus.	Lapeyraque et al. (2014) [17] Glowacki et al. (2011) [123] Satoh et al. (2009) [129] Satoh et al. (2008) [64]	
Clinical	In liver transplant patients, no association was found between recipient CYP3A5 rs776746 genotype and area under the concentration-time curve (AUC) of tacrolimus.	Carcas-Sansuán et al. (2013) [143]	Weak
Clinical	In kidney transplant patients, or in healthy individuals, those with the CYP3A5 rs776746 CT	Zuo et al. (2013) [149] Miura et al. (2011) [162]	Weak

	or TT genotype (*1/*3 or *1/*1; "expressers") have decreased maximum plasma concentrations (C _{max}) of tacrolimus, both dose-adjusted and non-dose-adjusted, as compared to those with the CC genotype (*3/*3; "nonexpressers").	Satoh et al. (2008) [64] Choi et al. (2007) [163] Op den Buijsch et al. (2007) [68]	
Clinical	In kidney transplant patients, no association was found between CYP3A5 rs776746 genotype and maximum plasma concentration (C _{max}) of tacrolimus.	Lapeyraque et al. (2014) [17] Zuo et al. (2013) [149] Rong et al. (2010) [140] Satoh et al. (2009) [129] Tada et al. (2005) [133]	
Clinical	In liver transplant patients, no association was found between recipient CYP3A5 rs776746 genotype and maximum plasma concentration (C _{max}) of tacrolimus.	Carcas-Sansuán et al. (2013) [143]	Weak
Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have increased volume of distribution (V _d) of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Tirelli et al. (2008) [66] Haufroid et al. (2006) [138] Tsuchiya et al. (2004) [76]	High
Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased dose-adjusted 2-hour post-dose concentrations (C _{2/D}) of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Ogasawara et al. (2013) [29] Chitnis et al. (2013) [30]	High
Clinical	In kidney or liver transplant patients, no association was found between CYP3A5 rs776746 genotype (recipient genotype for liver transplant patients) and time to maximum plasma concentration (T _{max}) of tacrolimus.	Carcas-Sansuán et al. (2013) [143] Rong et al. (2010) [140] Tada et al. (2005) [133]	Weak
Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased half-life (T _{1/2}) of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Niioka et al. (2012) [36]	Weak
Clinical	In kidney transplant patients, no association was found between CYP3A5 rs776746 genotype half-life (T _{1/2}) of tacrolimus.	Miura et al. (2011) [162] Rong et al. (2010) [140] Tada et al. (2005) [133]	
Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased bioavailability of tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers").	Storset et al. (2014) [144] Asberg et al. (2013) [156] Niioka et al. (2013) [164]	Moderate
Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased dose-adjusted trough concentrations of 15-O-desmethyl tacrolimus (M-III) and 13-O-desmethyl tacrolimus (M-I) as compared to those with the CC genotype (*3/*3; "nonexpressers").	Chitnis et al. (2013) [30] Yoon et al. (2013) [34] Hirano et al. (2012) [35] Dai et al. (2006) [157]	Weak

Clinical	In kidney transplant patients, no association was found between CYP3A5 rs776746 genotype and dose-adjusted trough concentrations of 13-O-desmethyl tacrolimus.		
Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT genotype (*1/*3; "expressers") have an increased ratio of 13-O-desmethyl tacrolimus to tacrolimus (M-I/tacrolimus) as compared to those with the CC genotype (*3/*3; "nonexpressers").		
In vitro	In human liver and kidney microsomes, those with the CYP3A5 rs776746 CT genotype (*1/*3; "expressers") had increased formation rates of 13-O-desmethyl tacrolimus as compared to those with the CC genotype (*3/*3; "nonexpressers"). In liver microsomes only, those with the CT genotype also had increased formation rates of 31-O-desmethyl tacrolimus and 12-hydroxy tacrolimus. No significant results were seen for 15-O-desmethyl tacrolimus.		
Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased peripheral blood mononuclear cell (PBMC) dose-adjusted trough concentrations (C0/D) of tacrolimus, as compared to those with the CC genotype (*3/*3; "nonexpressers"). No significant association was seen when considering PBMC trough concentrations.	Capron et al. (2010) [57]	Moderate
Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have a decreased chance of achieving target tacrolimus concentrations as compared to those with the CC genotype (*3/*3; "nonexpressers").	Shilbayeh (2014) [165] Tavira et al. (2011) [51] Zhang et al. (2010) [54] Wang et al. (2010) [128] Thervet et al. (2010) [166]	High
Clinical	In kidney transplant patients, no association was found between the CYP3A5 rs776746 genotype and chance of achieving target tacrolimus concentrations.	Li et al. (2014) [25]	
Clinical	In ulcerative colitis patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have a decreased chance of achieving target tacrolimus concentrations as compared to those with the CC genotype (*3/*3; "nonexpressers").	Hirai et al. (2014) [85]	Moderate
Case Report	A liver transplant patient was reported to have great difficulty in reaching desired tacrolimus trough levels. They were homozygous for the CYP3A5 rs776746 C allele (*3/*3; "nonexpressers") and their donor liver was homozygous for the rs776746 T allele (*1/*1; "expresser")	Provenzani et al. (2012) [167]	Weak

Clinical	In kidney transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") took more time to achieve target tacrolimus concentrations as compared to those with the CC genotype (*3/*3; "nonexpressers").	Roy et al. (2006) [70] Macphee et al. (2005) [74]	High
Clinical	In liver transplant patients, those with the donor CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") took more time to achieve target tacrolimus concentrations as compared to those with the CC genotype (*3/*3; "nonexpressers").	Durand et al. (2013) [107]	Moderate
Clinical	In kidney or liver transplant patients, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") had a larger number of dose changes to achieve stable tacrolimus concentrations as compared to those with the CC genotype (*3/*3; "nonexpressers"; donor genotype in liver transplant patients).	Durand et al. (2013) [107] de Wildt et al. (2011) [44]	Moderate
Clinical	In heart transplant patients, those with the CYP3A4 rs35599367 AG genotype (*1/*22) and the CYP3A5 rs776746 CC genotype (*3/*3; "nonexpressers") were grouped as "poor metabolizers" (PMs). These PMs required decreased doses of tacrolimus as compared to those with the CYP3A4 GG (*1/*1) and CYP3A5 CC (*3/*3) genotype ("intermediate metabolizers") and those with the CYP3A4 GG (*1/*1) and CYP3A5 CT and TT (*1/*3 and *1/*1) genotype ("extensive metabolizers")	Gijzen et al. (2013) [168]	Moderate
Clinical	In kidney transplant patients, or in healthy individuals, those who carry two copies of CYP3A5 loss-of-function alleles (rs776746 C/*3, rs10264272 T/*6 and rs41303343 A/*7) have increased dose-adjusted trough concentrations (C0/D) and decreased clearance of tacrolimus as compared to those who carry one loss-of-function allele, or those who carry no loss-of-function alleles.	Santoro et al. (2013) [169] Zheng et al. (2012) [170] Santoro et al. (2011) [171]	High
Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have an increased risk of rejection as compared to those with the CC genotype (*3/*3; "nonexpressers").	Rojas et al. (2015) [13] Tang et al. (2011) [120] Min et al. (2010) [137] Singh et al. (2009) [60] Chen et al. (2009) [61] Quteineh et al. (2008) [63] Tirelli et al. (2008) [66] Ferraresso et al. (2007) [131]	Moderate
Clinical	In kidney transplant patients receiving tacrolimus, no association was found between CYP3A5 rs776746 genotype and risk for rejection.	Terrazzino et al. (2012) [39] Lesche et al. (2014) [18] Hattori et al. (2014) [22] Shilbayeh (2014) [165] Ro et al. (2012) [113] Gervasini et al. (2012) [41] Cho et al. (2012) [43] Glowacki et al. (2011) [48]	

		Satoh et al. (2009) [129] Hesselink et al. (2008) [67] Roy et al. (2006) [70]	
Clinical	In liver transplant patients receiving tacrolimus, no association was found between recipient CYP3A5 rs776746 genotype and risk for rejection.	Xue et al. (2014) [90] Gómez-Bravo et al. (2013) [93]	Weak
Clinical	In liver transplant patients receiving tacrolimus, those with the donor CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have an increased risk of rejection as compared to those with the CC genotype (*3/*3; "nonexpressers").	Uesugi et al. (2014) [89]	Weak
Clinical	In liver transplant patients receiving tacrolimus, no association was found between donor CYP3A5 rs776746 genotype and risk for rejection.	Xue et al. (2014) [90] Gómez-Bravo et al. (2013) [93] Durand et al. (2013) [107]	
Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have an increased risk of nephrotoxicity as compared to those with the CC genotype (*3/*3; "nonexpressers").	Rojas et al. (2015) [13] Glowacki et al. (2011) [48] Kuypers et al. (2010) [172]	Weak
Clinical, Case Report	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have a decreased risk of nephrotoxicity as compared to those with the CC genotype (*3/*3; "nonexpressers").	Quaglia et al. (2013) [173] Chen et al. (2009) [61] Satoh et al. (2009) [129]	
Clinical	In kidney, heart or hematopoietic stem cell transplant patients receiving tacrolimus, no association was found between CYP3A5 rs776746 genotype and risk for nephrotoxicity.	Shilbayeh (2014) [165] Gervasini et al. (2012) [41] Metalidis et al. (2011) [174] Grenda et al. (2009) [175] Quteineh et al. (2008) [63] Woodahl et al. (2008) [176] Klauke et al. (2008) [177]	
Clinical	In liver transplant patients receiving tacrolimus, those with the recipient CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have a decreased risk of renal dysfunction as compared to those with the CC genotype (*3/*3; "nonexpressers").	Fukudo et al. (2008) [158]	Weak
Clinical	In hematopoietic stem cell transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT genotype (*1/*3; "expressers") have an increased risk of neurotoxicity as compared to those with the CC genotype (*3/*3; "nonexpressers").	Yanagimachi et al. (2010) [178]	Weak
Clinical	In kidney transplant patients receiving tacrolimus, no association was found between CYP3A5 rs776746 genotype and risk for neurotoxicity.	Gervasini et al. (2012) [41]	
Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers")	Ferraresso et al. (2011) [126]	Weak

	have increased systolic and diastolic blood pressure as compared to those with the CC genotype (*3/*3; "nonexpressers").		
Clinical	In kidney transplant patients receiving tacrolimus, no association was found between CYP3A5 rs776746 genotype and blood pressure.	Shilbayeh et al. (2014) [165] Torio et al. (2012) [114] Glowacki et al. (2011) [48]	
Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have a decreased risk for hyperlipidemia as compared to those with the CC genotype (*3/*3; "nonexpressers").	Wang et al. (2010) [128]	Weak
Clinical	In liver transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have an increased risk for infectious complications as compared to those with the CC genotype (*3/*3; "nonexpressers").	Xue et al. (2014) [90] Muraki et al. (2011) [98]	Weak
Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 the CT genotype (*1/*3; "expresser") have an increased risk for viral infections as compared to those with the CC genotype (*3/*3; "nonexpressers").	Hattori et al. (2014) [22]	Weak
Clinical	In kidney transplant patients receiving tacrolimus, no association was found between CYP3A5 rs776746 genotype and risk for viral, fungal or bacterial infections.	Shilbayeh (2014) [165]	
Clinical	In ulcerative colitis patients receiving tacrolimus, those with the CYP3A5 rs776746 CT genotype (*1/*3; "expressers") have a decreased chance of achieving remission from ulcerative colitis as compared to those with the CC genotype (*3/*3; "nonexpressers").	Hirai et al. (2014) [85]	Weak
Clinical	In liver transplant patients receiving tacrolimus, those with the recipient CYP3A5 rs776746 TT genotype (*1/*1) have decreased urine transferrin levels compared to those with the CC or CT genotype (*3/*3 or *1/*3).	Shi et al. (2013) [94]	Moderate
Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have decreased estimated glomerular filtration rates as compared to those with the CC genotype (*3/*3; "nonexpressers").	Min et al. (2010) [137]	Weak
In vitro	The rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") is associated with increased expression of CYP3A5 mRNA as compared to the CC genotype (*3/*3; "nonexpressers").	Uesugi et al. (2014) [89] Goto et al. (2004) [108]	High
Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CC genotype (*3/*3; "nonexpressers") have an increased risk for late, severe, noninfectious diarrhea.	Zhao et al. (2013) [179]	Moderate

Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have a decreased risk for experiencing an adverse event (e.g. hypokalemia, nephrotoxicity, chest pain, dehydration) as compared to those with the CC genotype (*3/*3; "nonexpressers").	Sy et al. (2013) [28]	Weak
Clinical	In hematopoietic stem cell or kidney transplant patients receiving tacrolimus, no association was found between CYP3A5 rs776746 genotype and risk for various adverse events (e.g. hyperuricemia, hypertension, nephrotoxicity, hyperkalemia).	Shilbayeh (2014) [165] Yanagisawa et al. (2011) [134]	
Clinical	In kidney transplant patients receiving tacrolimus, those with the CYP3A5 rs776746 TT genotype (*1/*1; "expresser") have increased creatinine clearance as compared to those with the CC genotype (*3/*3; "nonexpressers").	Shilbayeh (2014) [165]	Weak
Clinical	In kidney transplant patients receiving tacrolimus, no association was found between CYP3A5 rs776746 genotype and creatinine clearance.	Elens et al. (2013) [180]	
Clinical	In liver transplant patients receiving tacrolimus, those with the recipient CYP3A5 rs776746 CT or TT genotype (*1/*3 or *1/*1; "expressers") have an increased risk for calcineurin inhibitor-induced hepatic toxicity as compared to those with the CC genotype (*3/*3; "nonexpressers").	Xue et al. (2014) [90]	Weak
Clinical	In kidney and heart transplant patients receiving tacrolimus, low systemic exposure to tacrolimus correlates with acute rejection	Undre et al. (2002) [181] Vincenti et al. (1996) [182] Undre et al. (1999) [183]	High
Clinical	In kidney transplant patients receiving tacrolimus, adequate tacrolimus concentrations (5-15ng/ml) are related to the desired immunosuppressive effects of preventing organ rejection and toxicity.	Laskow et al. (1996) [184] Vincenti et al. (1996) [182]	Moderate

¹High: 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.

Detailed annotations of the references in this table can be found by following the links below.

You will need a PharmGKB account to access (registration is free and easy

<https://www.pharmgkb.org/home/registration/step1.action>).

Studies regarding pharmacokinetic parameters of tacrolimus in kidney, heart, lung or hematopoietic stem cell transplant patients or ulcerative colitis patients can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=9812037>

Studies regarding pharmacokinetic parameters of tacrolimus in liver transplant patients where donor genotype is considered can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=982046323>

Studies regarding pharmacokinetic parameters of tacrolimus in liver transplant patients where recipient genotype is considered can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=1184999911>

Studies regarding the risk of transplant rejection in kidney transplant patients taking tacrolimus can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=981203808>

Studies regarding the risk of transplant rejection in liver transplant patients taking tacrolimus where donor genotype is considered can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=1184999957>

Studies regarding the risk of nephrotoxicity in kidney transplant patients taking tacrolimus can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=981203790>

Studies regarding the risk of hyperlipidemia in kidney transplant patients taking tacrolimus can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=981203854>

Studies regarding the risk for renal dysfunction in liver transplant patients taking tacrolimus where recipient genotype is considered can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=1185000052>

Studies regarding the risk of neurotoxicity in kidney and hematopoietic stem cell transplant patients taking tacrolimus can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=1185000205>

Studies regarding the change in blood pressure in kidney transplant patients taking tacrolimus can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=1185000213>

Studies regarding the risk for infection in kidney and liver transplant patients taking tacrolimus can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=1185000225>

Studies regarding the chance of remission in ulcerative colitis patients taking tacrolimus can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=1185000238>

Studies regarding the risk for hepatic toxicity in liver transplant patients taking tacrolimus can be found here:

<https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=1185000260>

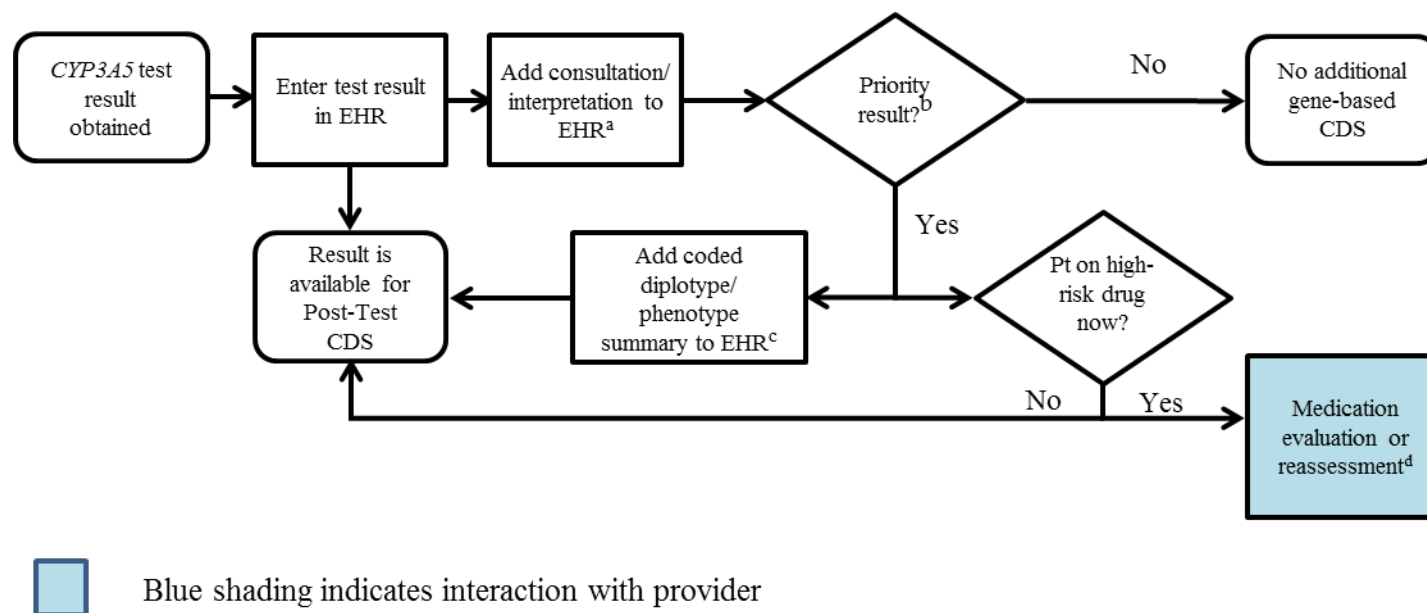
Supplemental Table S5. Drug(s) that pertain to this guideline.

Drug or Ingredient	Source	Code Type	Code
Tacrolimus	RxNorm	RxCUI	42316
Tacrolimus	DrugBank	Accession Number	DB00864
Tacrolimus	ATC	ATC Code	L04AD02
Tacrolimus	PharmGKB	PharmGKB ID	PA451578

Supplemental Table S6. Gene(s) that pertain to this guideline.

Gene Symbol	Source	Code Type	Code
CYP3A5	HGNC	Symbol	CYP3A5
CYP3A5	HGNC	HGNC ID	HGNC:2638
CYP3A5	NCBI	Gene ID	1577
CYP3A5	Ensembl	Ensembl ID	ENSG00000106258
CYP3A5	PharmGKB	PharmGKB ID	PA131

Supplemental Figure S1. *CYP3A5* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR



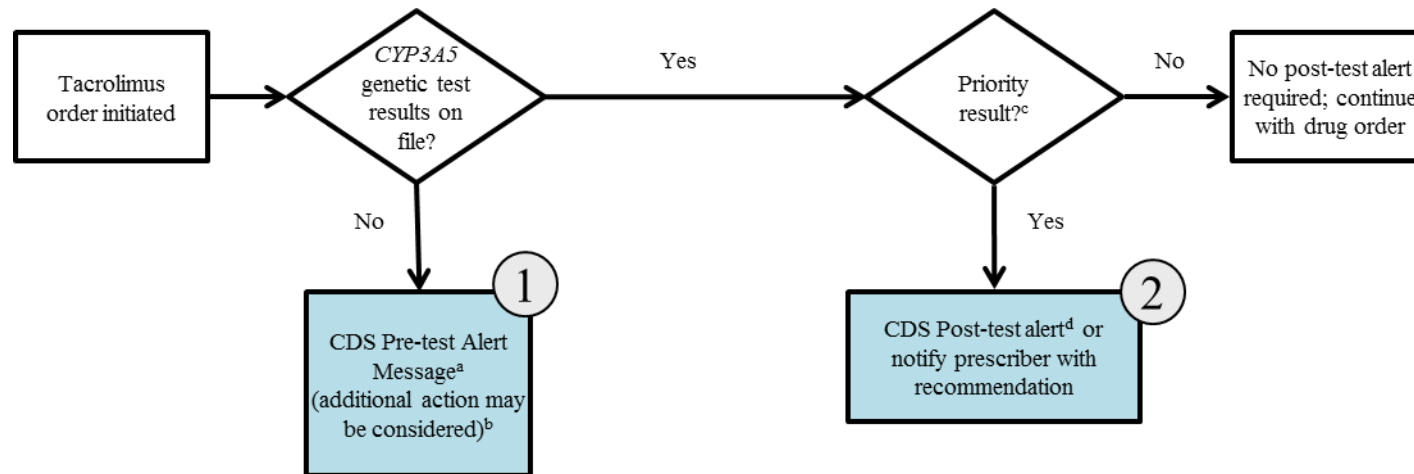
^a See **Supplementary Table S8** for diplotype/phenotype specific example

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

^c Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently inform prescribing decisions. See **Supplementary Table S8** for genotype/phenotype-specific summaries.

^d Given the availability of therapeutic drug monitoring, *CYP3A5* genetic testing is most helpful prior to initiation of the drug in order to rapidly achieve therapeutic drug concentrations, or in patients in whom achieving therapeutic levels has been difficult. If patient's tacrolimus level is already in therapeutic range, no action may be required.

Supplemental Figure S2. *CYP3A5* Genotype and Tacrolimus: Point of Care Clinical Decision Support



^a See **Supplementary Table S9** for diplotype/phenotype specific pre-test alert example.

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

^c Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

^d Post-test CDS targeting initial prescription of tacrolimus may be indication-specific or give general dosing advice. See

Supplementary Table S9 for diplotype/phenotype specific post-test alert example.

Supplemental Table S7. Example Implementation of this Guideline: Pharmacogenetic Diplotype/Phenotype Summary Entries^a

Diplotype Test Result for <i>CYP3A5</i>	Coded Diplotype/Phenotype Summary^b	EHR Priority Result Notation^c	Consultation (Interpretation) Text Provided with Test Result^d
<i>*1/*1</i>	CYP3A5 Extensive metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has two copies of a normal function allele (<i>*1</i>). Patients with this genotype are expected to require higher starting tacrolimus dosing (1.5 times to 2 times the standard dose-maximum starting dose not to exceed 0.3mg/kg/day). Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors (e.g., medication interactions, or hepatic function). Please consult a clinical pharmacist for more specific dosing information.
<i>*1/*3</i>	CYP3A5 Intermediate metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has one copy of a normal function allele (<i>*1</i>) and one copy of a no function allele (<i>*3</i>). Patients with this genotype are expected to require higher starting tacrolimus dosing (1.5 times to 2 times the standard dose-maximum starting dose not to exceed 0.3mg/kg/day). Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors (e.g., medication interactions, or hepatic function). Please consult a clinical pharmacist for more specific dosing information.
<i>*1/*6</i>	CYP3A5 Intermediate metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has one copy of a normal function allele (<i>*1</i>) and one copy of a no function allele (<i>*6</i>). Patients with this genotype are expected to require higher starting tacrolimus dosing (1.5 times to 2 times the standard dose-maximum starting dose not to exceed 0.3mg/kg/day). Further dose adjustments or selection of alternative therapy may be necessary due

			to other clinical factors (e.g., medication interactions, or hepatic function). Please consult a clinical pharmacist for more specific dosing information.
*1/*7	CYP3A5 Intermediate metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has one copy of a normal function allele (*1) and one copy of a no function allele (*7). Patients with this genotype are expected to require higher starting tacrolimus dosing (1.5 times to 2 times the standard dose-maximum starting dose not to exceed 0.3mg/kg/day). Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors (e.g., medication interactions, or hepatic function). Please consult a clinical pharmacist for more specific dosing information.
*3/*3	CYP3A5 Poor metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a no function allele (*3). Patients with this genotype are expected to require standard tacrolimus dosing . Please consult a clinical pharmacist for more specific dosing information.
*6/*6	CYP3A5 Poor metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a non-functional allele (*6). Patients with this genotype are expected to require standard tacrolimus dosing . Please consult a clinical pharmacist for more specific dosing information.
*7/*7	CYP3A5 Poor metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a no function allele (*7). Patients with this genotype are expected to require standard tacrolimus dosing . Please consult a clinical pharmacist for more specific dosing information.
*3/*6	CYP3A5 Poor metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a no function allele (*3 and *6). Patients with this genotype are expected to

			require standard tacrolimus dosing . Please consult a clinical pharmacist for more specific dosing information.
*3/*7	CYP3A5 Poor metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a no function allele (*3 and *7). Patients with this genotype are expected to require standard tacrolimus dosing . Please consult a clinical pharmacist for more specific dosing information.
*6/*7	CYP3A5 Poor metabolizer	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a no function allele (*6 and *7). Patients with this genotype are expected to require standard tacrolimus dosing . Please consult a clinical pharmacist for more specific dosing information.

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

^aA more comprehensive table of genotype/phenotype EHR entries for possible diplotype combinations of all variants listed in **Supplemental Table S2** is available at <https://www.pharmgkb.org/drug/PA451578>.

^bThe coded diplotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites.

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

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

Supplemental Table S8. Example Implementation of this Guideline: Point of Care Clinical Decision Support

Flow Chart Reference Point (See Supplemental Figure S2)	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text ^a
1	Pre-Test	No <i>CYP3A5</i> result on file	<i>CYP3A5</i> results may be important for tacrolimus dosing. A <i>CYP3A5</i> genotype does not appear to have been ordered for this patient. Use of an alternative dose may be recommended. Please consult a clinical pharmacist ^b for more information.
2	Post-Test	<i>CYP3A5</i> Extensive metabolizer	Based on the genotype result, this patient is predicted to have lower tacrolimus serum drug levels if initiated on a standard tacrolimus starting dose. Consider increasing the starting dose to 1.5 times to 2 times the standard dose. Total starting dose should not exceed 0.3mg/kg/day. Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors (e.g., medication interactions, or hepatic function). Use therapeutic drug monitoring to guide dose adjustments. Please consult a clinical pharmacist ^b for more information.
2	Post-Test	<i>CYP3A5</i> Intermediate metabolizer	Based on the genotype result, this patient is predicted to have lower tacrolimus serum drug levels if initiated on a standard tacrolimus starting dose. Consider increasing the starting dose to 1.5 times to 2 times the standard dose. Total starting dose should not exceed 0.3mg/kg/day. Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors (e.g., medication interactions, or hepatic function). Use therapeutic drug

			monitoring to guide dose adjustments. Please consult a clinical pharmacist ^b for more information.
--	--	--	---

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

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

References:

1. Valdes, R., Payne, D.A. & Linder, M.W. *Laboratory analysis and application of pharmacogenetics to clinical practice*. The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines, 2010.
2. Relling, M.V. and T.E. Klein, *CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network*. Clin Pharmacol Ther, 2011. **89**(3): p. 464-7.
3. Shuldiner, A.R., et al., *The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation*. Clin Pharmacol Ther, 2013. **94**(2): p. 207-10.
4. Wilke, R.A., et al., *The emerging role of electronic medical records in pharmacogenomics*. Clin Pharmacol Ther, 2011. **89**(3): p. 379-86.
5. Peterson, J.F., et al., *Electronic health record design and implementation for pharmacogenomics: a local perspective*. Genet Med, 2013. **15**(10): p. 833-41.
6. Gottesman, O., et al., *The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future*. Genet Med, 2013. **15**(10): p. 761-71.
7. Kullo, I.J., et al., *Leveraging the electronic health record to implement genomic medicine*. Genet Med, 2013. **15**(4): p. 270-1.
8. Martin, M.A., et al., *Clinical pharmacogenetics implementation consortium guidelines for hla-B genotype and abacavir dosing: 2014 update*. Clin Pharmacol Ther, 2014. **95**(5): p. 499-500.
9. Hicks, J.K., et al., *A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record*. Clin Pharmacol Ther, 2012. **92**(5): p. 563-6.
10. Bell, G.C., et al., *Development and use of active clinical decision support for preemptive pharmacogenomics*. J Am Med Inform Assoc, 2013.
11. Pulley, J.M., et al., *Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project*. Clin Pharmacol Ther, 2012. **92**(1): p. 87-95.
12. Bains, R.K., et al., *Molecular diversity and population structure at the Cytochrome P450 3A5 gene in Africa*. BMC Genet, 2013. **14**: p. 34.
13. Rojas, L., et al., *Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies*. Pharmacogenomics J, 2015. **15**(1): p. 38-48.
14. Iwamoto, T., et al., *Effect of genetic polymorphism of CYP3A5 and CYP2C19, and concomitant use of voriconazole on blood tacrolimus concentration in patients receiving hematopoietic stem cell transplantation*. Ther Drug Monit, 2015.
15. Xing, J., et al., *Association between interleukin-18 promoter variants and tacrolimus pharmacokinetics in Chinese renal transplant patients*. Eur J Clin Pharmacol, 2015. **71**(2): p. 191-8.
16. Niioka, T., et al., *Capability of Utilizing CYP3A5 Polymorphisms to Predict Therapeutic Dosage of Tacrolimus at Early Stage Post-Renal Transplantation*. Int J Mol Sci, 2014. **16**(1): p. 1840-54.

17. Lapeyraque, A.L., et al., *Conversion from twice- to once-daily tacrolimus in pediatric kidney recipients: a pharmacokinetic and bioequivalence study*. *Pediatr Nephrol*, 2014. **29**(6): p. 1081-8.
18. Lesche, D., et al., *CYP3A5*3 and POR*28 genetic variants influence the required dose of tacrolimus in heart transplant recipients*. *Ther Drug Monit*, 2014. **36**(6): p. 710-5.
19. Bruckmueller, H., et al., *Which genetic determinants should be considered for tacrolimus dose optimization in kidney transplantation? A combined analysis of genes affecting the CYP3A locus*. *Ther Drug Monit*, 2014.
20. Hamzah, S., et al., *Pharmacogenotyping of CYP3A5 in predicting dose-adjusted trough levels of tacrolimus among Malaysian kidney-transplant patients*. *Can J Physiol Pharmacol*, 2014. **92**(1): p. 50-7.
21. Cusinato, D.A., et al., *Relationship of Cyp3a5 Genotype and Abcb1 Diplotype to Tacrolimus Disposition in Brazilian Kidney Transplant Patients*. *Br J Clin Pharmacol*, 2014.
22. Hattori, Y., et al., *Influence of cytochrome P450 3A5 polymorphisms on viral infection incidence in kidney transplant patients treated with tacrolimus*. *Transplant Proc*, 2014. **46**(2): p. 570-3.
23. Kurzawski, M., et al., *CYP3A5 and CYP3A4, but not ABCB1 polymorphisms affect tacrolimus dose-adjusted trough concentrations in kidney transplant recipients*. *Pharmacogenomics*, 2014. **15**(2): p. 179-88.
24. Lalan, S., et al., *Effect of CYP3A5 genotype, steroids, and azoles on tacrolimus in a pediatric renal transplant population*. *Pediatr Nephrol*, 2014.
25. Li, C.J., et al., *Impact of the CYP3A5, CYP3A4, COMT, IL-10 and POR genetic polymorphisms on tacrolimus metabolism in Chinese renal transplant recipients*. *PLoS One*, 2014. **9**(1): p. e86206.
26. Lunde, I., et al., *The influence of CYP3A, PPARA, and POR genetic variants on the pharmacokinetics of tacrolimus and cyclosporine in renal transplant recipients*. *Eur J Clin Pharmacol*, 2014.
27. Wu, M.J., et al., *Reduced variability of tacrolimus trough level in once-daily tacrolimus-based Taiwanese kidney transplant recipients with high-expressive genotype of cytochrome P450 3A5*. *Transplant Proc*, 2014. **46**(2): p. 403-5.
28. Sy, S.K., et al., *A Markov chain model to evaluate the effect of CYP3A5 and ABCB1 polymorphisms on adverse events associated with tacrolimus in pediatric renal transplantation*. *AAPS J*, 2013. **15**(4): p. 1189-99.
29. Ogasawara, K., et al., *Multidrug resistance-associated protein 2 (MRP2/ABCC2) haplotypes significantly affect the pharmacokinetics of tacrolimus in kidney transplant recipients*. *Clin Pharmacokinet*, 2013. **52**(9): p. 751-62.
30. Chitnis, S.D., et al., *Concentration of tacrolimus and major metabolites in kidney transplant recipients as a function of diabetes mellitus and cytochrome P450 3A gene polymorphism*. *Xenobiotica*, 2013. **43**(7): p. 641-9.
31. Li, D.Y., et al., *CYP3A4/5 polymorphisms affect the blood level of cyclosporine and tacrolimus in Chinese renal transplant recipients*. *Int J Clin Pharmacol Ther*, 2013. **51**(6): p. 466-74.
32. Tavira, B., et al., *A search for new CYP3A4 variants as determinants of tacrolimus dose requirements in renal-transplanted patients*. *Pharmacogenet Genomics*, 2013. **23**(8): p. 445-8.

33. Spierings, N., D.W. Holt, and I.A. MacPhee, *CYP3A5 genotype had no impact on inpatient variability of tacrolimus clearance in renal transplant recipients*. Ther Drug Monit, 2013. **35**(3): p. 328-31.
34. Yoon, S.H., et al., *CYP3A and ABCB1 genetic polymorphisms on the pharmacokinetics and pharmacodynamics of tacrolimus and its metabolites (M-I and M-III)*. Transplantation, 2013. **95**(6): p. 828-34.
35. Hirano, K., et al., *Impact of CYP3A5 genetic polymorphism on cross-reactivity in tacrolimus chemiluminescent immunoassay in kidney transplant recipients*. Clin Chim Acta, 2012. **414**: p. 120-4.
36. Niioka, T., et al., *Comparison of pharmacokinetics and pharmacogenetics of once- and twice-daily tacrolimus in the early stage after renal transplantation*. Transplantation, 2012. **94**(10): p. 1013-9.
37. Diaz-Molina, B., et al., *Effect of CYP3A5, CYP3A4, and ABCB1 genotypes as determinants of tacrolimus dose and clinical outcomes after heart transplantation*. Transplant Proc, 2012. **44**(9): p. 2635-8.
38. Kim, I.W., et al., *Identification of factors affecting tacrolimus level and 5-year clinical outcome in kidney transplant patients*. Basic Clin Pharmacol Toxicol, 2012. **111**(4): p. 217-23.
39. Terrazzino, S., et al., *The effect of CYP3A5 6986A>G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis*. Pharmacogenet Genomics, 2012. **22**(8): p. 642-5.
40. Kim, I.W., et al., *Clinical and genetic factors affecting tacrolimus trough levels and drug-related outcomes in Korean kidney transplant recipients*. Eur J Clin Pharmacol, 2012. **68**(5): p. 657-69.
41. Gervasini, G., et al., *Impact of genetic polymorphisms on tacrolimus pharmacokinetics and the clinical outcome of renal transplantation*. Transpl Int, 2012. **25**(4): p. 471-80.
42. Birdwell, K.A., et al., *The use of a DNA biobank linked to electronic medical records to characterize pharmacogenomic predictors of tacrolimus dose requirement in kidney transplant recipients*. Pharmacogenet Genomics, 2012. **22**(1): p. 32-42.
43. Cho, J.H., et al., *Impact of cytochrome P450 3A and ATP-binding cassette subfamily B member 1 polymorphisms on tacrolimus dose-adjusted trough concentrations among Korean renal transplant recipients*. Transplant Proc, 2012. **44**(1): p. 109-14.
44. de Wildt, S.N., et al., *The interactions of age, genetics, and disease severity on tacrolimus dosing requirements after pediatric kidney and liver transplantation*. Eur J Clin Pharmacol, 2011. **67**(12): p. 1231-41.
45. Provenzano, A., et al., *Influence of CYP3A5 and ABCB1 gene polymorphisms and other factors on tacrolimus dosing in Caucasian liver and kidney transplant patients*. Int J Mol Med, 2011. **28**(6): p. 1093-102.
46. Gijzen, V., et al., *Age and CYP3A5 genotype affect tacrolimus dosing requirements after transplant in pediatric heart recipients*. J Heart Lung Transplant, 2011. **30**(12): p. 1352-9.
47. Elens, L., et al., *A new functional CYP3A4 intron 6 polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients*. Clin Chem, 2011. **57**(11): p. 1574-83.

48. Glowacki, F., et al., *CYP3A5 and ABCB1 polymorphisms in donor and recipient: impact on Tacrolimus dose requirements and clinical outcome after renal transplantation*. Nephrol Dial Transplant, 2011. **26**(9): p. 3046-50.
49. Ferraris, J.R., et al., *Influence of CYP3A5 polymorphism on tacrolimus maintenance doses and serum levels after renal transplantation: age dependency and pharmacological interaction with steroids*. Pediatr Transplant, 2011. **15**(5): p. 525-32.
50. Miura, M., et al., *Impact of the CYP3A4*1G polymorphism and its combination with CYP3A5 genotypes on tacrolimus pharmacokinetics in renal transplant patients*. Pharmacogenomics, 2011. **12**(7): p. 977-84.
51. Tavira, B., et al., *Pharmacogenetics of tacrolimus after renal transplantation: analysis of polymorphisms in genes encoding 16 drug metabolizing enzymes*. Clin Chem Lab Med, 2011. **49**(5): p. 825-33.
52. Jacobson, P.A., et al., *Novel polymorphisms associated with tacrolimus trough concentrations: results from a multicenter kidney transplant consortium*. Transplantation, 2011. **91**(3): p. 300-8.
53. Wu, P., et al., *Polymorphisms in CYP3A5*3 and MDRI, and haplotype modulate response to plasma levels of tacrolimus in Chinese renal transplant patients*. Ann Transplant, 2011. **16**(1): p. 54-60.
54. Zhang, J., et al., *Value of CYP3A5 genotyping on determining initial dosages of tacrolimus for Chinese renal transplant recipients*. Transplant Proc, 2010. **42**(9): p. 3459-64.
55. Lopez-Montenegro Soria, M.A., et al., *Genetic polymorphisms and individualized tacrolimus dosing*. Transplant Proc, 2010. **42**(8): p. 3031-3.
56. Ashavaid, T., et al., *Effect of gene polymorphisms on the levels of calcineurin inhibitors in Indian renal transplant recipients*. Indian J Nephrol, 2010. **20**(3): p. 146-51.
57. Capron, A., et al., *CYP3A5 and ABCB1 polymorphisms influence tacrolimus concentrations in peripheral blood mononuclear cells after renal transplantation*. Pharmacogenomics, 2010. **11**(5): p. 703-14.
58. Katsakiori, P.F., et al., *Factors affecting the long-term response to tacrolimus in renal transplant patients: pharmacokinetic and pharmacogenetic approach*. Int J Med Sci, 2010. **7**(2): p. 94-100.
59. Turolo, S., et al., *Frequencies and roles of CYP3A5, CYP3A4 and ABCB1 single nucleotide polymorphisms in Italian teenagers after kidney transplantation*. Pharmacol Rep, 2010. **62**(6): p. 1159-69.
60. Singh, R., et al., *Impact of CYP3A5 and CYP3A4 gene polymorphisms on dose requirement of calcineurin inhibitors, cyclosporine and tacrolimus, in renal allograft recipients of North India*. Naunyn Schmiedebergs Arch Pharmacol, 2009. **380**(2): p. 169-77.
61. Chen, J.S., et al., *Effect of CYP3A5 genotype on renal allograft recipients treated with tacrolimus*. Transplant Proc, 2009. **41**(5): p. 1557-61.
62. Jun, K.R., et al., *Tacrolimus concentrations in relation to CYP3A and ABCB1 polymorphisms among solid organ transplant recipients in Korea*. Transplantation, 2009. **87**(8): p. 1225-31.
63. Quteineh, L., et al., *Influence of CYP3A5 genetic polymorphism on tacrolimus daily dose requirements and acute rejection in renal graft recipients*. Basic Clin Pharmacol Toxicol, 2008. **103**(6): p. 546-52.

64. Satoh, S., et al., *Lack of tacrolimus circadian pharmacokinetics and CYP3A5 pharmacogenetics in the early and maintenance stages in Japanese renal transplant recipients*. Br J Clin Pharmacol, 2008. **66**(2): p. 207-14.
65. Loh, P.T., et al., *Significant impact of gene polymorphisms on tacrolimus but not cyclosporine dosing in Asian renal transplant recipients*. Transplant Proc, 2008. **40**(5): p. 1690-5.
66. Tirelli, S., et al., *The effect of CYP3A5 polymorphisms on the pharmacokinetics of tacrolimus in adolescent kidney transplant recipients*. Med Sci Monit, 2008. **14**(5): p. CR251-254.
67. Hesselink, D.A., et al., *CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant recipients*. Pharmacogenet Genomics, 2008. **18**(4): p. 339-48.
68. Op den Buijsch, R.A., et al., *Tacrolimus pharmacokinetics and pharmacogenetics: influence of adenosine triphosphate-binding cassette B1 (ABCB1) and cytochrome (CYP) 3A polymorphisms*. Fundam Clin Pharmacol, 2007. **21**(4): p. 427-35.
69. Renders, L., et al., *CYP3A5 genotype markedly influences the pharmacokinetics of tacrolimus and sirolimus in kidney transplant recipients*. Clin Pharmacol Ther, 2007. **81**(2): p. 228-34.
70. Roy, J.N., et al., *Cyp3A4, Cyp3A5, and MDR-1 genetic influences on tacrolimus pharmacokinetics in renal transplant recipients*. Pharmacogenet Genomics, 2006. **16**(9): p. 659-65.
71. Mourad, M., et al., *The influence of genetic polymorphisms of cytochrome P450 3A5 and ABCB1 on starting dose- and weight-standardized tacrolimus trough concentrations after kidney transplantation in relation to renal function*. Clin Chem Lab Med, 2006. **44**(10): p. 1192-8.
72. Zhang, X., et al., *Influence of CYP3A5 and MDR1 polymorphisms on tacrolimus concentration in the early stage after renal transplantation*. Clin Transplant, 2005. **19**(5): p. 638-43.
73. Mourad, M., et al., *Sirolimus and tacrolimus trough concentrations and dose requirements after kidney transplantation in relation to CYP3A5 and MDR1 polymorphisms and steroids*. Transplantation, 2005. **80**(7): p. 977-84.
74. Macphee, I.A., et al., *Tacrolimus pharmacogenetics: the CYP3A5*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians*. Transplantation, 2005. **79**(4): p. 499-502.
75. Zhao, Y., et al., *Genetic polymorphisms of CYP3A5 genes and concentration of the cyclosporine and tacrolimus*. Transplant Proc, 2005. **37**(1): p. 178-81.
76. Tsuchiya, N., et al., *Influence of CYP3A5 and MDR1 (ABCB1) polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients*. Transplantation, 2004. **78**(8): p. 1182-7.
77. Haufroid, V., et al., *The effect of CYP3A5 and MDR1 (ABCB1) polymorphisms on cyclosporine and tacrolimus dose requirements and trough blood levels in stable renal transplant patients*. Pharmacogenetics, 2004. **14**(3): p. 147-54.
78. Zheng, H., et al., *Tacrolimus dosing in adult lung transplant patients is related to cytochrome P4503A5 gene polymorphism*. J Clin Pharmacol, 2004. **44**(2): p. 135-40.

79. Thervet, E., et al., *Impact of cytochrome p450 3A5 genetic polymorphism on tacrolimus doses and concentration-to-dose ratio in renal transplant recipients*. Transplantation, 2003. **76**(8): p. 1233-5.
80. Hesselink, D.A., et al., *Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus*. Clin Pharmacol Ther, 2003. **74**(3): p. 245-54.
81. Zheng, H., et al., *Tacrolimus dosing in pediatric heart transplant patients is related to CYP3A5 and MDR1 gene polymorphisms*. Am J Transplant, 2003. **3**(4): p. 477-83.
82. Shilbayeh, S., R. Zmeili, and R.I. Almardini, *The impact of CYP3A5 and MDR1 polymorphisms on tacrolimus dosage requirements and trough concentrations in pediatric renal transplant recipients*. Saudi J Kidney Dis Transpl, 2013. **24**(6): p. 1125-36.
83. Boso, V., et al., *Increased hospital stay and allograft dysfunction in renal transplant recipients with Cyp2c19 AA variant in SNP rs4244285*. Drug Metab Dispos, 2013. **41**(2): p. 480-7.
84. Jordan de Luna, C., et al., *Pharmacogenetic study of ABCB1 and CYP3A5 genes during the first year following heart transplantation regarding tacrolimus or cyclosporine levels*. Transplant Proc, 2011. **43**(6): p. 2241-3.
85. Hirai, F., et al., *Impact of CYP3A5 genetic polymorphisms on the pharmacokinetics and short-term remission in patients with ulcerative colitis treated with tacrolimus*. J Gastroenterol Hepatol, 2014. **29**(1): p. 60-6.
86. Chen, Y.K., et al., *Personalized tacrolimus dose requirement by CYP3A5 but not ABCB1 or ACE genotyping in both recipient and donor after pediatric liver transplantation*. PLoS One, 2014. **9**(10): p. e109464.
87. Wang, Z., et al., *Influence of TLR4 rs1927907 locus polymorphisms on tacrolimus pharmacokinetics in the early stage after liver transplantation*. Eur J Clin Pharmacol, 2014. **70**(8): p. 925-31.
88. Guy-Viterbo, V., et al., *Influence of donor-recipient CYP3A4/5 genotypes, age and fluconazole on tacrolimus pharmacokinetics in pediatric liver transplantation: a population approach*. Pharmacogenomics, 2014. **15**(9): p. 1207-21.
89. Uesugi, M., et al., *Impact of cytochrome P450 3A5 polymorphism in graft livers on the frequency of acute cellular rejection in living-donor liver transplantation*. Pharmacogenet Genomics, 2014. **24**(7): p. 356-66.
90. Xue, F., et al., *CYP3A5 genotypes affect tacrolimus pharmacokinetics and infectious complications in Chinese pediatric liver transplant patients*. Pediatr Transplant, 2014. **18**(2): p. 166-76.
91. Jalil, M.H., et al., *Population pharmacokinetic and pharmacogenetic analysis of tacrolimus in paediatric liver transplant patients*. Br J Clin Pharmacol, 2014. **77**(1): p. 130-40.
92. Buendia, J.A., G. Bramuglia, and C.E. Staatz, *Effects of Combinational CYP3A5 6986A>G Polymorphism in Graft Liver and Native Intestine on the Pharmacokinetics of Tacrolimus in Liver Transplant Patients: A Meta-Analysis*. Ther Drug Monit, 2013.
93. Gomez-Bravo, M.A., et al., *Impact of donor and recipient CYP3A5 and ABCB1 genetic polymorphisms on tacrolimus dosage requirements and rejection in Caucasian Spanish liver transplant patients*. J Clin Pharmacol, 2013. **53**(11): p. 1146-54.

94. Hershfield, M.S., et al., *Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing*. Clin Pharmacol Ther, 2013. **93**(2): p. 153-8.
95. Chen, D., et al., *Novel single nucleotide polymorphisms in interleukin 6 affect tacrolimus metabolism in liver transplant patients*. PLoS One, 2013. **8**(8): p. e73405.
96. Chen, D., et al., *Association of hemoglobin levels, CYP3A5, and NR1H3 gene polymorphisms with tacrolimus pharmacokinetics in liver transplant patients*. Drug Metab Pharmacokinet, 2013.
97. Ji, E., et al., *Combinational effect of intestinal and hepatic CYP3A5 genotypes on tacrolimus pharmacokinetics in recipients of living donor liver transplantation*. Transplantation, 2012. **94**(8): p. 866-72.
98. Muraki, Y., et al., *Impact of CYP3A5 genotype of recipients as well as donors on the tacrolimus pharmacokinetics and infectious complications after living-donor liver transplantation for Japanese adult recipients*. Ann Transplant, 2011. **16**(4): p. 55-62.
99. Uesugi, M., et al., *Effect of intestinal CYP3A5 on postoperative tacrolimus trough levels in living-donor liver transplant recipients*. Pharmacogenet Genomics, 2006. **16**(2): p. 119-27.
100. Rahsaz, M., et al., *Association between tacrolimus concentration and genetic polymorphisms of CYP3A5 and ABCB1 during the early stage after liver transplant in an Iranian population*. Exp Clin Transplant, 2012. **10**(1): p. 24-9.
101. Zhang, X., et al., *Impact of interleukin-10 gene polymorphisms on tacrolimus dosing requirements in Chinese liver transplant patients during the early posttransplantation period*. Eur J Clin Pharmacol, 2011. **67**(8): p. 803-13.
102. Provenzani, A., et al., *The effect of CYP3A5 and ABCB1 single nucleotide polymorphisms on tacrolimus dose requirements in Caucasian liver transplant patients*. Ann Transplant, 2009. **14**(1): p. 23-31.
103. Li, D., et al., *Polymorphisms of tumor necrosis factor-alpha, interleukin-10, cytochrome P450 3A5 and ABCB1 in Chinese liver transplant patients treated with immunosuppressant tacrolimus*. Clin Chim Acta, 2007. **383**(1-2): p. 133-9.
104. Wei-lin, W., et al., *Tacrolimus dose requirement in relation to donor and recipient ABCB1 and CYP3A5 gene polymorphisms in Chinese liver transplant patients*. Liver Transpl, 2006. **12**(5): p. 775-80.
105. Yu, S., et al., *Influence of CYP3A5 gene polymorphisms of donor rather than recipient to tacrolimus individual dose requirement in liver transplantation*. Transplantation, 2006. **81**(1): p. 46-51.
106. Rojas, L.E., et al., *Meta-analysis and systematic review of the effect of the donor and recipient CYP3A5 6986A>G genotype on tacrolimus dose requirements in liver transplantation*. Pharmacogenet Genomics, 2013. **23**(10): p. 509-17.
107. Durand, P., et al., *Tacrolimus dose requirement in pediatric liver transplantation: influence of CYP3A5 gene polymorphism*. Pharmacogenomics, 2013. **14**(9): p. 1017-25.
108. Goto, M., et al., *CYP3A5*1-carrying graft liver reduces the concentration/oral dose ratio of tacrolimus in recipients of living-donor liver transplantation*. Pharmacogenetics, 2004. **14**(7): p. 471-8.
109. Kuypers, D.R., et al., *Combined effects of CYP3A5*1, POR*28, and CYP3A4*22 single nucleotide polymorphisms on early concentration-controlled tacrolimus exposure in de-novo renal recipients*. Pharmacogenet Genomics, 2014. **24**(12): p. 597-606.

110. Bergmann, T.K., et al., *Population pharmacokinetics of tacrolimus in adult kidney transplant patients: impact of CYP3A5 genotype on starting dose*. Ther Drug Monit, 2014. **36**(1): p. 62-70.
111. Vannaprasaht, S., et al., *Personalized tacrolimus doses determined by CYP3A5 genotype for induction and maintenance phases of kidney transplantation*. Clin Ther, 2013. **35**(11): p. 1762-9.
112. de Jonge, H., et al., *Impact of CYP3A5 genotype on tacrolimus versus midazolam clearance in renal transplant recipients: new insights in CYP3A5-mediated drug metabolism*. Pharmacogenomics, 2013. **14**(12): p. 1467-80.
113. Ro, H., et al., *Impact of tacrolimus intraindividual variability and CYP3A5 genetic polymorphism on acute rejection in kidney transplantation*. Ther Drug Monit, 2012. **34**(6): p. 680-5.
114. Torio, A., et al., *Effect of CYP3A51/3 polymorphism on blood pressure in renal transplant recipients*. Transplant Proc, 2012. **44**(9): p. 2596-8.
115. de Jonge, H., et al., *In vivo CYP3A4 activity, CYP3A5 genotype, and hematocrit predict tacrolimus dose requirements and clearance in renal transplant patients*. Clin Pharmacol Ther, 2012. **92**(3): p. 366-75.
116. Elmachad, M., et al., *Frequencies of CYP3A5*1/*3 variants in a Moroccan population and effect on tacrolimus daily dose requirements in renal transplant patients*. Genet Test Mol Biomarkers, 2012. **16**(6): p. 644-7.
117. Garcia-Roca, P., et al., *CYP3A5 polymorphism in Mexican renal transplant recipients and its association with tacrolimus dosing*. Arch Med Res, 2012. **43**(4): p. 283-7.
118. Stratta, P., et al., *The interactions of age, sex, body mass index, genetics, and steroid weight-based doses on tacrolimus dosing requirement after adult kidney transplantation*. Eur J Clin Pharmacol, 2012. **68**(5): p. 671-80.
119. Passey, C., et al., *Dosing equation for tacrolimus using genetic variants and clinical factors*. Br J Clin Pharmacol, 2011. **72**(6): p. 948-57.
120. Tang, H.L., et al., *Lower tacrolimus daily dose requirements and acute rejection rates in the CYP3A5 nonexpressers than expressers*. Pharmacogenet Genomics, 2011. **21**(11): p. 713-20.
121. de Jonge, H., et al., *The P450 oxidoreductase *28 SNP is associated with low initial tacrolimus exposure and increased dose requirements in CYP3A5-expressing renal recipients*. Pharmacogenomics, 2011. **12**(9): p. 1281-91.
122. Li, L., et al., *Tacrolimus dosing in Chinese renal transplant recipients: a population-based pharmacogenetics study*. Eur J Clin Pharmacol, 2011. **67**(8): p. 787-95.
123. Glowacki, F., et al., *Influence of cytochrome P450 3A5 (CYP3A5) genetic polymorphism on the pharmacokinetics of the prolonged-release, once-daily formulation of tacrolimus in stable renal transplant recipients*. Clin Pharmacokinet, 2011. **50**(7): p. 451-9.
124. Pashae, N., et al., *CYP3A5 genotype is not related to the inpatient variability of tacrolimus clearance*. Ther Drug Monit, 2011. **33**(3): p. 369-71.
125. Wehland, M., et al., *Differential impact of the CYP3A5*1 and CYP3A5*3 alleles on pre-dose concentrations of two tacrolimus formulations*. Pharmacogenet Genomics, 2011. **21**(4): p. 179-84.
126. Ferrarresso, M., et al., *Association between CYP3A5 polymorphisms and blood pressure in kidney transplant recipients receiving calcineurin inhibitors*. Clin Exp Hypertens, 2011. **33**(6): p. 359-65.

127. Kniepeiss, D., et al., *The role of CYP3A5 genotypes in dose requirements of tacrolimus and everolimus after heart transplantation*. Clin Transplant, 2011. **25**(1): p. 146-50.
128. Wang, P., et al., *Using genetic and clinical factors to predict tacrolimus dose in renal transplant recipients*. Pharmacogenomics, 2010. **11**(10): p. 1389-402.
129. Satoh, S., et al., *CYP3A5 *1 allele associated with tacrolimus trough concentrations but not subclinical acute rejection or chronic allograft nephropathy in Japanese renal transplant recipients*. Eur J Clin Pharmacol, 2009. **65**(5): p. 473-81.
130. Press, R.R., et al., *Explaining variability in tacrolimus pharmacokinetics to optimize early exposure in adult kidney transplant recipients*. Ther Drug Monit, 2009. **31**(2): p. 187-97.
131. Ferrarresso, M., et al., *Influence of the CYP3A5 genotype on tacrolimus pharmacokinetics and pharmacodynamics in young kidney transplant recipients*. Pediatr Transplant, 2007. **11**(3): p. 296-300.
132. Cheung, C.Y., et al., *Influence of different allelic variants of the CYP3A and ABCB1 genes on the tacrolimus pharmacokinetic profile of Chinese renal transplant recipients*. Pharmacogenomics, 2006. **7**(4): p. 563-74.
133. Tada, H., et al., *Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients*. Transplant Proc, 2005. **37**(4): p. 1730-2.
134. Yanagisawa, R., et al., *Engraftment syndrome, but not acute GVHD, younger age, CYP3A5 or MDR1 polymorphisms, increases tacrolimus clearance in pediatric hematopoietic SCT*. Bone Marrow Transplant, 2011. **46**(1): p. 90-7.
135. Manvizhi, S., et al., *Combined approach with therapeutic drug monitoring and pharmacogenomics in renal transplant recipients*. Indian J Nephrol, 2013. **23**(1): p. 71-3.
136. Onizuka, M., et al., *Cytochrome P450 genetic polymorphisms influence the serum concentration of calcineurin inhibitors in allogeneic hematopoietic SCT recipients*. Bone Marrow Transplant, 2011. **46**(8): p. 1113-7.
137. Min, S.I., et al., *CYP3A5 *1 allele: impacts on early acute rejection and graft function in tacrolimus-based renal transplant recipients*. Transplantation, 2010. **90**(12): p. 1394-400.
138. Haufroid, V., et al., *CYP3A5 and ABCB1 polymorphisms and tacrolimus pharmacokinetics in renal transplant candidates: guidelines from an experimental study*. Am J Transplant, 2006. **6**(11): p. 2706-13.
139. Werk, A.N., et al., *Identification and characterization of a defective CYP3A4 genotype in a kidney transplant patient with severely diminished tacrolimus clearance*. Clin Pharmacol Ther, 2014. **95**(4): p. 416-22.
140. Rong, G., et al., *Influence of CYP3A5 and MDR1(ABCB1) polymorphisms on the pharmacokinetics of tacrolimus in Chinese renal transplant recipients*. Transplant Proc, 2010. **42**(9): p. 3455-8.
141. Mai, I., et al., *MDR1 haplotypes derived from exons 21 and 26 do not affect the steady-state pharmacokinetics of tacrolimus in renal transplant patients*. Br J Clin Pharmacol, 2004. **58**(5): p. 548-53.
142. Tanaka, K., et al., *Significant association between CYP3A5 polymorphism and blood concentration of tacrolimus in patients with connective tissue diseases*. J Hum Genet, 2014. **59**(2): p. 107-9.

143. Carcas-Sansuan, A.J., et al., *Conversion from Prograf to Advagraf in adolescents with stable liver transplants: comparative pharmacokinetics and 1-year follow-up*. Liver Transpl, 2013. **19**(10): p. 1151-8.
144. Storset, E., et al., *Improved prediction of tacrolimus concentrations early after kidney transplantation using theory-based pharmacokinetic modelling*. Br J Clin Pharmacol, 2014. **78**(3): p. 509-23.
145. Moes, D.J., et al., *Effect of CYP3A4*22, CYP3A5*3, and CYP3A Combined Genotypes on Cyclosporine, Everolimus, and Tacrolimus Pharmacokinetics in Renal Transplantation*. CPT Pharmacometrics Syst Pharmacol, 2014. **3**: p. e100.
146. Han, N., et al., *Prediction of the tacrolimus population pharmacokinetic parameters according to CYP3A5 genotype and clinical factors using NONMEM in adult kidney transplant recipients*. Eur J Clin Pharmacol, 2013. **69**(1): p. 53-63.
147. Zuo, X.C., et al., *Effects of CYP3A4 and CYP3A5 polymorphisms on tacrolimus pharmacokinetics in Chinese adult renal transplant recipients: a population pharmacokinetic analysis*. Pharmacogenet Genomics, 2013. **23**(5): p. 251-61.
148. Zhao, W., et al., *Population pharmacokinetics and pharmacogenetics of once daily prolonged-release formulation of tacrolimus in pediatric and adolescent kidney transplant recipients*. Eur J Clin Pharmacol, 2013. **69**(2): p. 189-95.
149. Zuo, X.C., et al., *Effect of CYP3A5*3 polymorphism on pharmacokinetic drug interaction between tacrolimus and amlodipine*. Drug Metab Pharmacokinet, 2013. **28**(5): p. 398-405.
150. Monchaud, C., et al., *Population pharmacokinetic modelling and design of a Bayesian estimator for therapeutic drug monitoring of tacrolimus in lung transplantation*. Clin Pharmacokinet, 2012. **51**(3): p. 175-86.
151. Xue, L., et al., *Population pharmacokinetics and pharmacogenetics of tacrolimus in healthy Chinese volunteers*. Pharmacology, 2011. **88**(5-6): p. 288-94.
152. Shi, X.J., et al., *Association of ABCB1, CYP3A4*18B and CYP3A5*3 genotypes with the pharmacokinetics of tacrolimus in healthy Chinese subjects: a population pharmacokinetic analysis*. J Clin Pharm Ther, 2011. **36**(5): p. 614-24.
153. Benkali, K., et al., *Population pharmacokinetics and Bayesian estimation of tacrolimus exposure in renal transplant recipients on a new once-daily formulation*. Clin Pharmacokinet, 2010. **49**(10): p. 683-92.
154. Zhao, W., et al., *Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients*. Clin Pharmacol Ther, 2009. **86**(6): p. 609-18.
155. Suzuki, Y., et al., *Impact of CYP3A5 genetic polymorphism on pharmacokinetics of tacrolimus in healthy Japanese subjects*. Br J Clin Pharmacol, 2008. **66**(1): p. 154-5.
156. Asberg, A., et al., *Inclusion of CYP3A5 genotyping in a nonparametric population model improves dosing of tacrolimus early after transplantation*. Transpl Int, 2013. **26**(12): p. 1198-207.
157. Dai, Y., et al., *Effect of CYP3A5 polymorphism on tacrolimus metabolic clearance in vitro*. Drug Metab Dispos, 2006. **34**(5): p. 836-47.
158. Fukudo, M., et al., *Impact of MDRI and CYP3A5 on the oral clearance of tacrolimus and tacrolimus-related renal dysfunction in adult living-donor liver transplant patients*. Pharmacogenet Genomics, 2008. **18**(5): p. 413-23.

159. Gerard, C., et al., *Determination of the most influential sources of variability in tacrolimus trough blood concentrations in adult liver transplant recipients: a bottom-up approach*. AAPS J, 2014. **16**(3): p. 379-91.
160. Li, D., et al., *Population pharmacokinetics of tacrolimus and CYP3A5, MDR1 and IL-10 polymorphisms in adult liver transplant patients*. J Clin Pharm Ther, 2007. **32**(5): p. 505-15.
161. Fukudo, M., et al., *Population pharmacokinetic and pharmacogenomic analysis of tacrolimus in pediatric living-donor liver transplant recipients*. Clin Pharmacol Ther, 2006. **80**(4): p. 331-45.
162. Miura, M., et al., *Pharmacogenetic determinants for interindividual difference of tacrolimus pharmacokinetics 1 year after renal transplantation*. J Clin Pharm Ther, 2011. **36**(2): p. 208-16.
163. Choi, J.H., et al., *Influence of the CYP3A5 and MDR1 genetic polymorphisms on the pharmacokinetics of tacrolimus in healthy Korean subjects*. Br J Clin Pharmacol, 2007. **64**(2): p. 185-91.
164. Niioka, T., et al., *Pharmaceutical and genetic determinants for interindividual differences of tacrolimus bioavailability in renal transplant recipients*. Eur J Clin Pharmacol, 2013. **69**(9): p. 1659-65.
165. Shilbayeh, S., *The impact of genetic polymorphisms on time required to attain the target tacrolimus levels and subsequent pharmacodynamic outcomes in pediatric kidney transplant patients*. Saudi J Kidney Dis Transpl, 2014. **25**(2): p. 266-77.
166. Thervet, E., et al., *Optimization of initial tacrolimus dose using pharmacogenetic testing*. Clin Pharmacol Ther, 2010. **87**(6): p. 721-6.
167. Provenzani, A., et al., *Unusual high dose of tacrolimus in liver transplant patient, a case report*. Int J Clin Pharm, 2012. **34**(2): p. 269-71.
168. Gijzen, V.M., et al., *CYP3A4*22 and CYP3A combined genotypes both correlate with tacrolimus disposition in pediatric heart transplant recipients*. Pharmacogenomics, 2013. **14**(9): p. 1027-36.
169. Santoro, A.B., et al., *CYP3A5 genotype, but not CYP3A4*1b, CYP3A4*22, or hematocrit, predicts tacrolimus dose requirements in Brazilian renal transplant patients*. Clin Pharmacol Ther, 2013. **94**(2): p. 201-2.
170. Zheng, S., et al., *Measurement and compartmental modeling of the effect of CYP3A5 gene variation on systemic and intrarenal tacrolimus disposition*. Clin Pharmacol Ther, 2012. **92**(6): p. 737-45.
171. Santoro, A., et al., *Pharmacogenetics of calcineurin inhibitors in Brazilian renal transplant patients*. Pharmacogenomics, 2011. **12**(9): p. 1293-303.
172. Kuypers, D.R., et al., *Tacrolimus dose requirements and CYP3A5 genotype and the development of calcineurin inhibitor-associated nephrotoxicity in renal allograft recipients*. Ther Drug Monit, 2010. **32**(4): p. 394-404.
173. Quaglia, M., et al., *Severe acute nephrotoxicity in a kidney transplant patient despite low tacrolimus levels: a possible interaction between donor and recipient genetic polymorphisms*. J Clin Pharm Ther, 2013. **38**(4): p. 333-6.
174. Metalidis, C., et al., *Expression of CYP3A5 and P-glycoprotein in renal allografts with histological signs of calcineurin inhibitor nephrotoxicity*. Transplantation, 2011. **91**(10): p. 1098-102.

175. Grenda, R., et al., *Evaluation of the genetic background of standard-immunosuppressant-related toxicity in a cohort of 200 paediatric renal allograft recipients--a retrospective study*. Ann Transplant, 2009. **14**(3): p. 18-24.
176. Woodahl, E.L., et al., *Pharmacogenomic associations in ABCB1 and CYP3A5 with acute kidney injury and chronic kidney disease after myeloablative hematopoietic cell transplantation*. Pharmacogenomics J, 2008. **8**(4): p. 248-55.
177. Klauke, B., et al., *No association between single nucleotide polymorphisms and the development of nephrotoxicity after orthotopic heart transplantation*. J Heart Lung Transplant, 2008. **27**(7): p. 741-5.
178. Yanagimachi, M., et al., *Influence of CYP3A5 and ABCB1 gene polymorphisms on calcineurin inhibitor-related neurotoxicity after hematopoietic stem cell transplantation*. Clin Transplant, 2010. **24**(6): p. 855-61.
179. Zhao, Y.J., et al., *Late, severe, noninfectious diarrhea after renal transplantation: high-risk factors, therapy, and prognosis*. Transplant Proc, 2013. **45**(6): p. 2226-32.
180. Elens, L., et al., *Impact of CYP3A4*22 allele on tacrolimus pharmacokinetics in early period after renal transplantation: toward updated genotype-based dosage guidelines*. Ther Drug Monit, 2013. **35**(5): p. 608-16.
181. Undre, N.A. and P.J. Stevenson, *Pharmacokinetics of tacrolimus in heart transplantation*. Transplant Proc, 2002. **34**(5): p. 1836-8.
182. Vincenti, F., et al., *One-year follow-up of an open-label trial of FK506 for primary kidney transplantation. A report of the U.S. Multicenter FK506 Kidney Transplant Group*. Transplantation, 1996. **61**(11): p. 1576-81.
183. Undre, N.A., et al., *Low systemic exposure to tacrolimus correlates with acute rejection*. Transplant Proc, 1999. **31**(1-2): p. 296-8.
184. Laskow, D.A., et al., *An open-label, concentration-ranging trial of FK506 in primary kidney transplantation: a report of the United States Multicenter FK506 Kidney Transplant Group*. Transplantation, 1996. **62**(7): p. 900-5.