Supplemental Material

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

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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]

[a]See Human Cytochrome P450 Allele Nomenclature Committee website (http://www.cypalleles.ki.se) for comprehensive haplotype definitions of CYP3A5 variant alleles and updated allele information.
[b]Nucleotide 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.
[c]rsID provided as it is catalogued in dbSNP (http://www.ncbi.nlm.nih.gov/snp/).
[d]Cannot 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*
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"	

Supplemental Table S3. Frequencies of *CYP3A5* alleles[1] in major race/ethnic groups[2]

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 *CYP3A5*1*, **3, *6* and **7* (rs776746, rs10264272 and rs41303343) genotype with phenotype

Type of experimental model *(in vitro, in vivo, 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] Provenzani et al. (2011) [45] Gijsen 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

		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] Satoh 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]	
Clinical	In kidney or heart transplant patients, no association was found between the CYP3A5 rs776746 genotype and dose-adjusted trough concentrations of tacrolimus.	Shilbayeh et al. (2013) [82] Boso et al. (2013) [83] Jordán de Luna et al. (2011) [84]	
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").	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]	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

		Cho et al. (2012) [43] Passey et al. (2011) [119] de Wildt et al. (2011) [44] Provenzani et al. (2011) [45] Gijsen 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] Pashaee 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]	
Clinical	In kidney or hematopoietic stem cell transplant patients, no association was found between CYP3A5 rs776746 genotype and dosage of tacrolimus.	Shilbayeh et al. (2013) [82] Yanagisawa et al. (2011) [134]	
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").	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]	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 hematopoeitic 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 Syndome 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 *CYP3A4* gene.	Werk et al. (2014) [139]	
Clinical	In kidney, heart and hematopoeitic 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]	Weak
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]	
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]	High

		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 hematopoeitic 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 (Cmax) 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 (Cmax) 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 (Cmax) 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 (Vd) 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 (C2/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 (Tmax) 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 (T1/2) 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 (T1/2) 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 seeen 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")	Gijsen 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 hematopoeitic 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 hematopoeitic 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

[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.

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 hematopoeitic stem cell transplant patients or ulcerative colitis patients can be found here: https://www.pharmgkb.org/views/viewClinicalAnnotation.action?clinicalAnnotationId=981203719

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

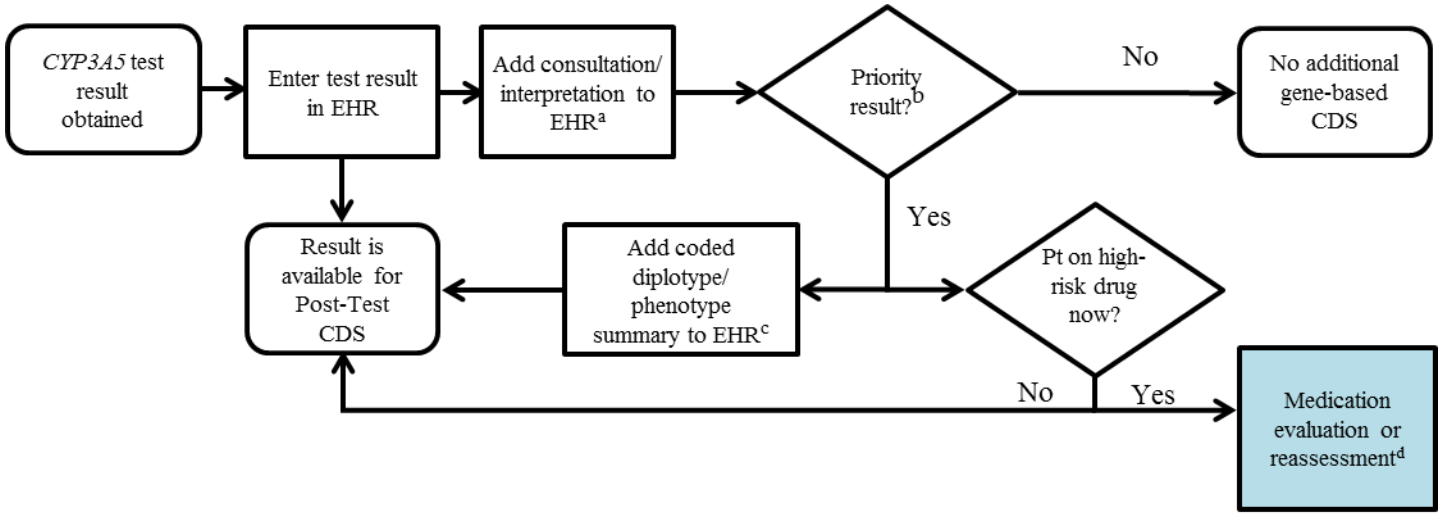
Supplemental Table S5. Drug(s) that pertain to this guideline.

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



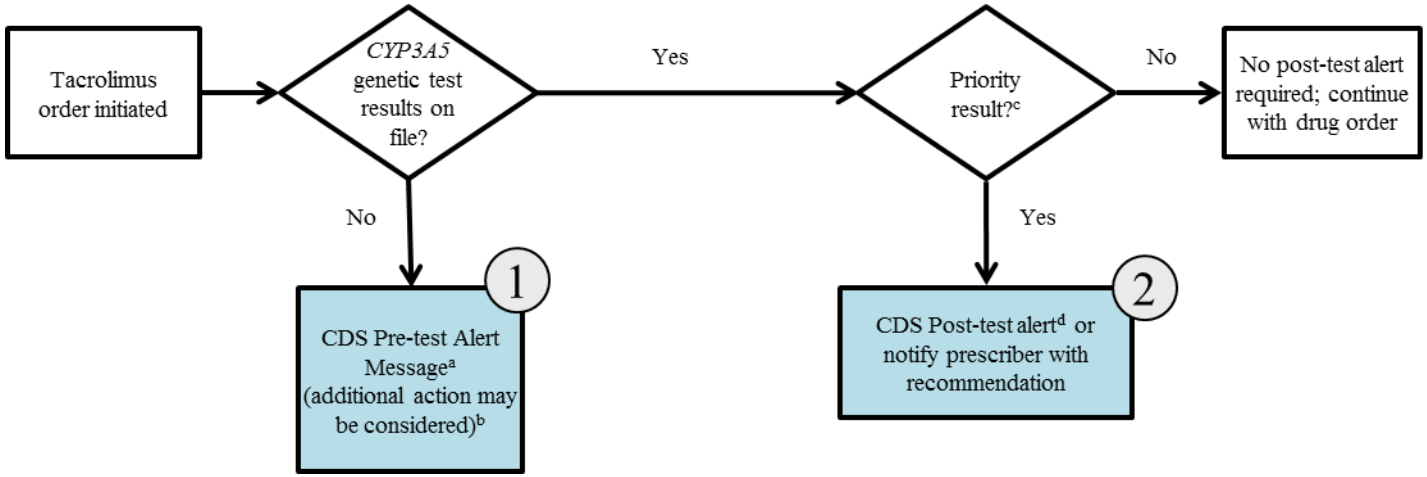
[a] See **Supplementary Table S8** for diplotype/phenotype specific example

[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 *CYP3A5*	Coded Diplotype/Phenotype Summary[b]	EHR Priority Result Notation[c]	Consultation (Interpretation) Text Provided with Test Result[d]
**1/*1*	CYP3A5 Extensive metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has two copies of a normal function allele (**1*). 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/*3*	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 (**3*). 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/*6*	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 (**6*). 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.

[a]A 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.

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

[c]For this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[d]The 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 *CYP3A5* result on file	*CYP3A5* results may be important for tacrolimus dosing. A *CYP3A5* 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	*CYP3A5* 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	*CYP3A5* 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.

[a]The specific wording of the alert text may differ among sites.
[b]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

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