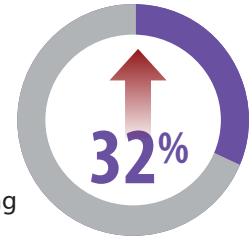
U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

Applying Pharmacogenomic (PGx) Testing to Tacrolimus Pharmacotherapy

Tacrolimus efficacy & *CYP3A5* function

Individuals with increased *CYP3A5* function have up to a **32% increased relative risk**† of acute kidney transplant rejection.[1]



†In a meta-analysis of 21 studies in over 2,100 kidney transplant patients comparing **extensive (or normal) or intermediate** to **poor *CYP3A5* metabolizers**. The follow-up among studies varied between ≤1 month to 12 months.[1]

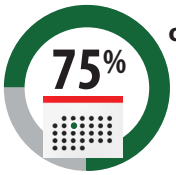
PGx testing confirms *CYP3A5* genetic variation and optimizes initial dosing regimens

- ☑ Tacrolimus is an immunosuppressant commonly used for prevention of liver, pancreas, kidney, heart, intestinal, lung, and hematopoietic stem cell transplant rejection.[2]
- ☑ Roughly 40 to 50% of the narrow therapeutic index and wide pharmacokinetic variability for tacrolimus is attributed to the cytochrome P450 3A5 ***(CYP3A5)*** enzyme.[2] Tacrolimus metabolism is also thought to be influenced by *CYP3A4* variation as well though this impact remains unclear.[3]
- ☑ Poor *CYP3A5* function is highly prevalent and informs current standard initial weight based tacrolimus dosing. Maintenance doses are adjusted by blood concentration levels.[2,3]
- ☑ Subtherapeutic tacrolimus blood levels are associated with **increased risk of rejection** and supratherapeutic levels increase the risk of adverse effects.[3,4]

Evidence for genotype-guided dosing

A prospective trial randomized 280 kidney transplant patients to receive either standard or ***CYP3A5* genotype-guided dosing** and found genotype-guided dosing resulted in the following benefits compared to standard dosing:[4]

More patients **achieved therapeutic tacrolimus levels after six oral doses** (43.2% v. 29.1%; p = 0.03).



of patients achieved target tacrolimus concentrations on **day eight** compared to day 25 (p = 0.001).

Fewer dose modifications (281 v. 420; p = 0.004).

Food & Drug Administration (FDA) PGx associations for tacrolimus and *CYP3A5*[5]

FDA therapeutic management recommendations

Extensive (or normal) or intermediate metabolizers **have lower systemic tacrolimus concentration, a lower probability of achieving target concentrations and likely a higher risk for rejection**. Measure drug concentrations and adjust dosage based on trough whole blood tacrolimus concentrations.

Utilize PGx testing to inform initial tacrolimus dosing post-transplant.

What should I know about genotype-guided tacrolimus dosing?

- ☑ Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines apply to kidney, heart, lung, and hematopoietic stem cell and liver transplants in which the donor and recipient have identical genotypes.[3]
- ☑ When selecting an initial tacrolimus dose, consider **drug-drug interactions, liver function, and other clinical conditions** in addition to *CYP3A5* genotype.[3]
- ☑ *CYP3A5* genotyping should **not** replace therapeutic drug monitoring (TDM). More evidence is needed to evaluate long-term transplant related clinical outcomes.[3]

Table 1. CPIC initial dosing recommendations for tacrolimus & *CYP3A5*[§3]

CYP3A5 Genotype	Diplotypes	*CYP3A5* Phenotype	Implication	Therapeutic Recommendations
Two functional alleles	*1/*1	Extensive (or normal) metabolizer[†] (expressor)	Lower dose-adjusted trough concentrations of tacrolimus and **decreased chance of achieving target concentrations**.	**Increase initial dose 1.5 to 2 times recommended starting dose**. Total starting dose should not exceed 0.3 mg/kg/day. Use TDM to guide dose adjustments.
One functional and one nonfunctional allele	*1/*3, *1/*6, *1/*7	Intermediate metabolizer (expressor)		
Two nonfunctional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7	Poor metabolizer (nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target concentrations.	Initiate therapy with standard recommended dose. Use TDM to guide dose adjustments.

[§]CPIC guidelines were published in 2015 and therefore, did not include data on extended-release formulations approved in the same year.
[†]Nomenclature varies between guidelines, literature, and reference laboratory reports. Extensive metabolizers or expressors are sometimes also referred to as normal metabolizers due to the high frequency of this phenotype.

A note on ancestry

While more prevalent in certain populations, *CYP3A5* variant alleles have been seen across most major ancestral groups.[6] **PGx testing is the only way to confirm the presence of a variant allele**.

Clinical pharmacist practitioners (CPP)

PGx and transplant CPPs can evaluate pharmacotherapy based on the PGx test results, provide therapy recommendations, and contact patients for follow-up education.

REFERENCES: 1. Rojas L, Neumann I, Herrero MJ, et al. Effect of *CYP3A5*3* on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. *Pharmacogenomics J*. Feb 2015;15(1):38-48. doi:10.1038/tpj.2014.38 **2.** Yu M, Liu M, Zhang W, Ming Y. Pharmacokinetics, Pharmacodynamics and Pharmacogenetics of Tacrolimus in Kidney Transplantation. *Curr Drug Metab*. 2018;19(6):513-522. doi:10.2174/1389200219666180129151948 **3.** Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing. *Clin Pharmacol Ther*. Jul 2015;98(1):19-24. doi:10.1002/cpt.113 **4.** Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin Pharmacol Ther*. Jun 2010;87(6):721-6. doi:10.1038/clpt.2010.17 **5.** Table of Pharmacogenetic Associations. 2022. **6.** Supplemental Table S3. Frequencies of *CYP3A5* alleles in major race/ethnic groups PharmGKB.