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Impact of *CYP3A5* Status on the Clinical and Financial Outcomes Among African American Kidney Transplant Recipients

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Background. Pharmacogenetic profiling of transplant recipients demonstrates that the marked variation in the metabolism of immunosuppressive medications, particularly tacrolimus, is related to genetic variants. Patients of African ancestry are less likely to carry loss-of-function (LoF) variants in the *CYP3A5* gene and therefore retain a rapid metabolism phenotype and higher clearance of tacrolimus. Patients with this rapid metabolism typically require higher dosing to achieve therapeutic trough concentrations. This study aims to further characterize the impact of *CYP3A5* genotype on clinical outcomes and financial expenditure. **Methods.** The CYP3A5 phenotype status was identified in 438 adult kidney transplant (KTx) recipients (96% were African American) using 3 LoF alleles (*CYP3A5*3*, **6* or **7*). Individuals were categorized as rapid metabolism phenotype without LoF alleles, intermediate phenotype for 1 LoF allele, and slow phenotype for 2 LoF alleles. KTx outcomes (patient/kidney survival and Medicare spending) were determined using linked transplant registry and claims data. **Results.** Among the cohort, 23% had a rapid, 47% intermediate, and 30% a slow metabolism phenotype based on genotype. At 3 y, the rate of death censored graft failure and all cause graft failure was highest in the rapid metabolism phenotype and lowest in the intermediate metabolism phenotype group. First-year Medicare reimbursement differed significantly by genotype (rapid: $79 535, intermediate: $72 796, slow: $79 346, $P = 0.03$). After adjustment for donor and recipient characteristics, care for patients with intermediate metabolism was $4790 less expensive ($P = 0.003$). **Conclusions.** Pharmacogenomic assessment of African American KTx recipients may be useful to guide therapy when as *CYP3A5* functional variants appear to be associated with differential outcome and spending after transplant.

(*Transplantation Direct* 2022;8: e1379; doi: 10.1097/TXD.0000000000001379).

INTRODUCTION

Pharmacogenomics assesses the impact of genotypic variation in key metabolic proteins on the metabolism of therapeutic pharmaceuticals. Tacrolimus, a calcineurin inhibitor that is the mainstay of immunosuppression in solid organ transplantation, is metabolized by the enzymes CYP3A4 and

Received 12 May 2022. Revision received 25 July 2022.

Accepted 26 July 2022.

[1] J.O. was supported by the National Heart, Lung and Blood Institute, National Institutes of Health, through grant R25-HL084665 while completing this work. K.L.L. is supported by the Mid-America Transplant/Jane A. Beckman Endowed Chair in Transplantation and receives research funding related to renal genetics from the Mid-America Transplant Foundation and the NIH (R01-DK120551). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or funding agencies.

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J.O., B.K., K.L., and D.A. did study design, data acquisition, data analysis, and article preparation. L.C. and H.X. did data acquisition and data analysis. M.A.S., Y.C., V.D., and R.M. did study design and critical review.

D.A., M.S., and K.L. received consulting for CareDx. D.A. received consulting for Talaris. V.D. received grant support from CareDx and honoraria from Atara, CareDx and IDMC, and MedPace/Akebia. The other authors declare no conflicts of interest.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001379

CYP3A5, with CYP3A5 being the more efficient catalyst.[1] The activity of the CYP3A5 enzyme is determined by genetic variation within the *CYP3A5* gene, a polymorphic gene that is well established to carry common loss-of-function (LoF) alleles.[2] The *CYP3A5*3* allele is the most common LoF variant resulting from an intronic single nucleotide polymorphism that creates a splicing defect and non-functional protein.[2] The *CYP3A5*6* allele is a missense mutation that results in a splicing defect, protein truncation, and absence of a subsequent functional protein. The *CYP3A5*7* allele is an insertion variant that results in a frameshift mutation causing a truncated and nonfunctional protein. Individuals without LoF alleles have normal CYP3A5 activity, which is designated *CYP3A5*1*. Individuals carrying 1 or 2 *CYP3A5*1* alleles metabolize tacrolimus at a higher rate, resulting in more rapid tacrolimus clearance, lower systemic exposure, and greater tacrolimus dose requirements relative to those who carry the LoF variants. Although not consistently reported, individuals with a rapid CYP3A5 metabolism phenotype appear to have a greater risk of acute rejection and graft failure following kidney transplantation (KTx).[3] Variability in tacrolimus metabolism can also leave patients susceptible to drug toxicity at high levels, which manifests as nephrotoxicity, neurotoxicity, and other metabolic derangements.[3] Although tacrolimus is dosed by trough level, patients can spend significant periods of time subtherapeutic or supratherapeutic because of time between dose adjustments and laboratory draws. Recent data show that kidney recipients with a rapid metabolism phenotype may consume greater healthcare resources because they require additional tacrolimus trough measurements and dose adjustments and have a lower estimated glomerular filtration rate at 6 mo posttransplant.[4]

African American (AA) KTx recipients have been found to have higher rates of graft loss after transplant and more frequent episodes of acute rejection.[5–7] These findings are undoubtedly multifactorial and heavily influenced by compounding racial inequities in the United States that lead to disproportionate access to healthcare providers, adequate insurance, and health education for people of color.[7–13] However, genome-wide association studies have also highlighted key pharmacogenomic differences between individuals of different ancestry.[3] AAs are much more likely to carry the *CYP3A5*1* allele and, consequently, have rapid metabolism, lower tacrolimus troughs, and higher dose requirements than individuals of European ancestry.[14,15] The *CYP3A5*3* allele is the most common in White individuals (79.7% among admixed Americans and 94.3% among individuals of European ancestry) compared with a frequency of only 18% among those of African ancestry.[16] Additional LoF variants occur exclusively in AAs, *CYP3A5*6* and *CYP3A5*7*, at a frequency of 15.4% and 10.3%, respectively.[2,16] Given that AAs are much more likely than White individuals to have a rapid metabolism phenotype that may affect tacrolimus immunosuppression, it is important to evaluate if and how these differences may impact the posttransplant care for AA KTx recipients.

Accurate characterization of interpatient variability of metabolism is crucial to understand given tacrolimus's narrow therapeutic index and impact on graft survival. As a result of phenotypic differences in pharmacokinetics, AA KTx patients have been reported to have lower 12-h trough concentrations than non-AA recipients (for patients with similar weight-based doses), which is correlated with higher rates of acute rejection.[15,17] There is a paucity of studies characterizing the impact of phenotypic differences in medication metabolism on healthcare expenditures. In this article, we gather pharmacogenetic data, transplant registry outcomes, and Medicare payment data to understand (1) the extent that *CYP3A5* genotype impacts the rate of clinical complications among AA KTx recipients and (2) the difference in overall transplant costs based on *CYP3A5* genotype. This study focuses on AAs specifically because it allows us to use the documented variability in *CYP3A5* genotype among individuals in this demographic to further dissect and understand known disparities in transplant outcomes.

MATERIALS AND METHODS

This was a retrospective study in collaboration with the University of Pennsylvania and Saint Louis University. Medical record and genomic data for all single organ, first-time AA KTx recipients transplanted at the Penn Transplant Institute between 2000 and 2016 with available *CYP3A5* genotype data, tacrolimus-based immunosuppression, and available Medicare claims data were included in this study. The *CYP3A5* variant allele (*3, *6, or *7) of the 438 adult AA KTx recipients who met these inclusion criteria was determined retrospectively using data gathered in prior genome-wide association studies at the University of Pennsylvania.[18] These patients were categorized as having 0 LoF mutations (rapid metabolizers or *CYP3A5*1* genotype), 1 mutation (intermediate metabolizers), or 2 mutations (slow metabolizers). Data regarding death censored graft failure (DCGF), all cause graft failure (ACGF), and death was obtained from the Scientific Registry of Transplant Recipients (SRTR).

Recipient and Donor Clinical Characteristics and Resource Utilization Data

National clinical, demographic, and Medicare claims for patients who received a KTx between 2002 and 2016 were obtained from a database linking SRTR KTx files with Medicare billing claims for this analysis. The SRTR system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight of the activities of the Organ Procurement and Transplantation Network and SRTR contractors. Medicare billing claims data include diagnostic and procedure codes for patients with Medicare fee-for-service primary or secondary insurance. After regulatory approvals, beneficiary identifier numbers from Medicare's databases were linked using Social Security number, sex, and birthdate to unique, anonymous registry identification numbers. Because of the large sample size, the anonymity of the patients studied, and the nonintrusive nature of the research, a waiver of informed consent was granted for the economic analyses per the Department of Health and Human Services Code of Federal Regulations (title 45, part 46, paragraph 46.116). Genetic analyses and data linkage for included patients was reviewed and approved by the University of Pennsylvania Institutional Review Board and Saint Louis University Institutional Review Board. Analyses were performed using Health Information Portability and

Accountability Act — compliant, limited datasets from which all direct identifiers were removed. Medicare claims were extracted for all patients with available genotypes and analyzed to assess total resource utilization after transplantation. Data on patient outcomes, such as sepsis, pneumonia, and UTIs (which are known as leading causes of posttransplant infections), were collected by identifying billing claims with corresponding ICD9 and ICD10 diagnosis codes as reported by prior studies of these events in the transplant population.[19,20] Patients lost to follow-up were censored from final analysis. Graft failure was considered a period cost and only factored into the cost analysis in the year that the graft failed.

Statistical Methods

Cox regression was used to assess the association between CYP3A5 metabolism phenotype and death, graft failure, ACGF, and the incidence of key posttransplant complications (such as sepsis and readmission) within 3 y. Outcomes were evaluated from the day of transplant to last follow-up with the patient or the end of the study period. Total Medicare payments were aggregated over the first 3 y after transplant. Multivariable linear regression was used to assess the impact of CYP3A5 metabolism phenotype on the cost of posttransplant care. The variables used in both the Cox and linear regression models were age, gender, time on dialysis (preemptive transplant, <25 mo, 25–60 mo, or >60 mo), panel reactive antibody, history of prior transplant, living versus deceased donor status, kidney donor profile index, and whether the recipient underwent induction. Data management and analyses were performed using SAS, version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Among this cohort of AA KTx recipients, 23% were rapid metabolizers, 47% were intermediate metabolizers, and 30% were slow metabolizers of tacrolimus (Table 1). At 3 y, the rate of DCGF and ACGF was highest in the rapid metabolizers and lowest in the intermediate metabolizers (Figure 1), although this difference did not reach statistical significance (rapid versus intermediate: DCGF $P=0.08$; death $P=0.88$; ACGF $P=0.35$; rapid versus slow: DCGF $P=0.41$; death $P=0.55$; ACGF $P=0.32$). In examining the adjusted hazard ratio of death and graft failure, rapid metabolizers and intermediate metabolizers had an increased risk of graft failure and death when compared with slow metabolizers, although this finding did not reach statistical significance (Figure 2). We also found that slow metabolizers had a lower unadjusted incidence of rejection, readmissions, pneumonia, urinary tract infection, and sepsis, the last of which reached statistical significance, $P<0.02$ (Figure 3).

First-year Medicare reimbursement was significantly different for patients who were rapid metabolizers ($79 535) compared with patients with intermediate metabolism ($72 796) (Figure 4). After adjustment for donor and recipient characteristics, intermediate metabolizers were $4790 less expensive than rapid metabolizers in the first-year following transplantation ($P=0.003$). AAs who were slow metabolizers were on average $1037 less expensive than rapid metabolizers, although this was not significant ($P=0.55$) (Table 2). Younger recipients of KTx age 18 to 30 were also found to have significantly higher healthcare costs than recipients in other age groups ($P=0.02$). Analysis of the mean cost of posttransplant clinical care revealed that patients with the slow metabolizer phenotype had lower spending than patients who are rapid metabolizers in the first 2 y following transplantation. Patients with intermediate metabolism phenotype appear to have less healthcare spending costs than both the rapid metabolizers in this time frame as well (Figure S1, SDC, http://links.lww.com/TXD/A451).

TABLE 1.

Distributions of clinical traits of kidney transplant recipients according to metabolizer status

Baseline characteristics	Rapid (n = 94) (%)	Intermediate (n = 210) (%)	Slow (n = 134) (%)
Age			
18–30	7.5	5.2	6.0
31–44	23.4	23.3	25.4
45–59	46.8	42.4	38.1
>60	22.3	29.1	30.6
Gender			
Male	63.8	55.7	61.2
Female	36.2	44.3	38.8
Duration of dialysis, mo			
None (pre-emptive)	3.2	7.6	10.5
>0–24	16.0	19.1	20.2
25–60	42.6	38.6	31.3
>60	35.1	31.4	33.6
Missing	3.2	3.3	4.5
Most current PRA level (%)			
<10	70.2	72.4	71.6
10–79	17.0	13.8	21.6
>80	12.8	13.8	6.7
Previous transplant			
Yes	12.8	14.3	14.93
No	87.2	85.7	85.07
Donor Type			
Living Donor	5.3	11.9	14.9
Deceased, KPDI <20	13.8	14.8	11.9
Deceased, KDPI 20–85	75.5	63.8	64.2
Deceased, KDPI >85	5.3	9.5	9.0
Induction at transplant		[a]	
Yes	94.7	86.7	91.0
No	5.3	13.3	9.0

Percentages are column percentages.
Chi-squared tests were performed.
Using *CYP3A5* variant allele (*3, *6, or *7), patients were categorized as Rapid (0 loss-of-function [LoF] mutations) Intermediate (1 LoF mutation), or Slow (2 LoF mutations).
[a]$P<0.05$–0.002.
KDPI, kidney donor profile index; PRA, panel reactive antibody.

DISCUSSION

In a cohort of AA KTx recipients, *CYP3A5* genotype(s) resulting in rapid tacrolimus metabolism was associated with statistically significant differences in healthcare spending for intermediate metabolizers and a trend to lower cost in slow metabolizers. Fast tacrolimus metabolism was also associated with higher DCGF and ACGF, although this did not reach statistical significance in adjusted or unadjusted analyses, in this pilot analysis. These findings are consistent with prior reports that demonstrate an increased risk of delayed graft function and acute rejection among AA who are rapid or intermediate metabolizers. In addition, the *CYP3A5 *1/*1* genotype has been associated with more frequent tacrolimus dose adjustments and toxicity.[17] This study differed from other studies by

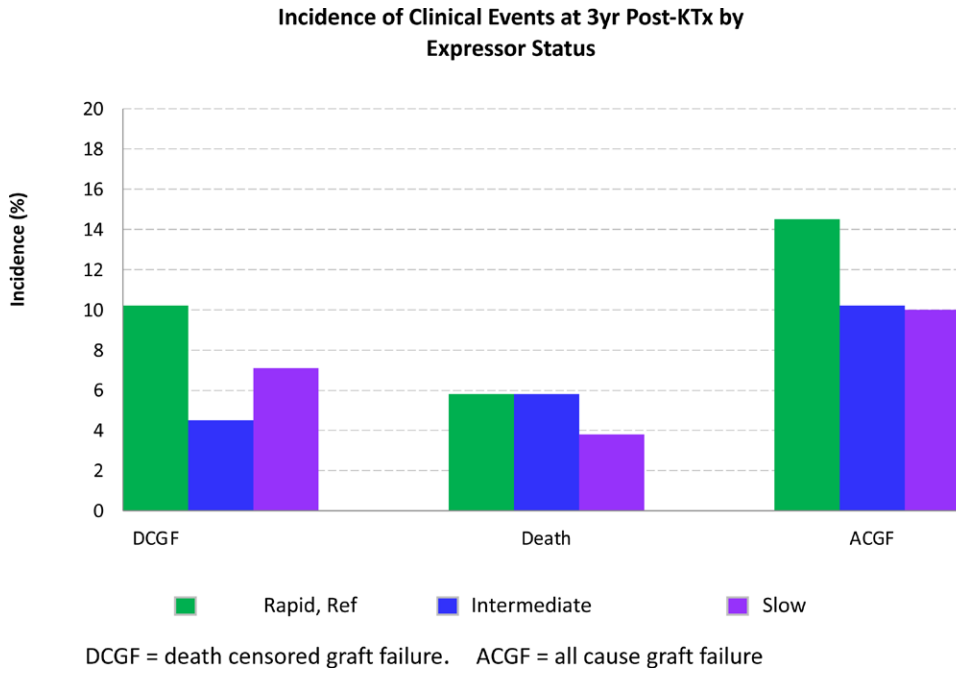

FIGURE 1. Incidence of clinical events at 3 y after kidney transplant. KTx, kidney transplantation.

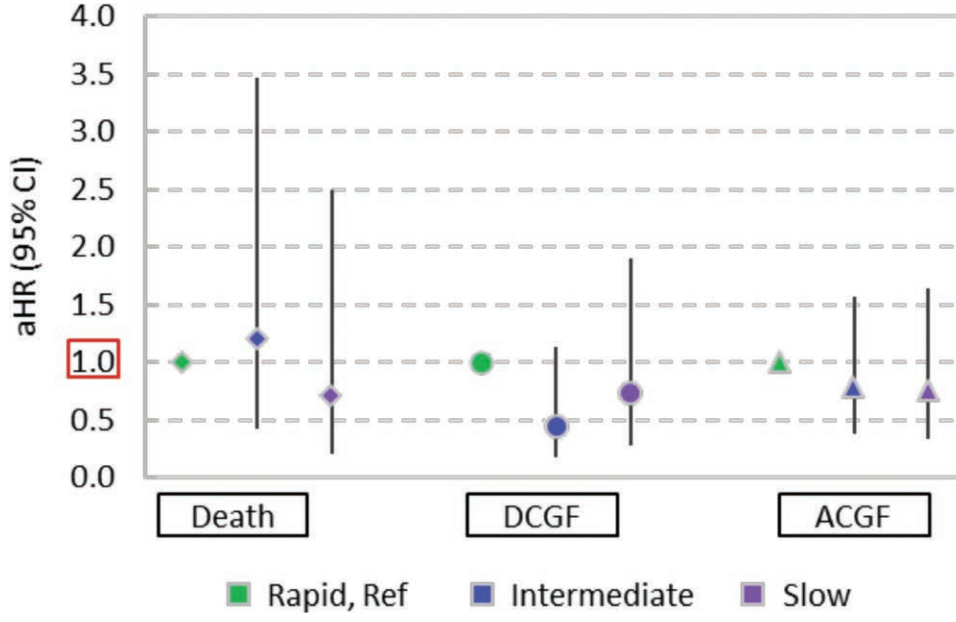

FIGURE 2. aHR of death and graft failure 3 y after kidney transplant in African Americans by CYP3A5 expression status. ACGF, all cause graft failure; aHR, adjusted hazard ratio; DCGF, death censored graft failure.

categorizing patients in 3 levels rather than just fast or slow, and limited sample size may account for the finding that only intermediate metabolizers had statistically significantly lower costs than rapid metabolizers in this data set.

Utilizing *CYP3A5* genotype to guide tacrolimus dosing may allow more accurate dose adjustment and decrease the risk of death and graft loss in this high-risk population. Knowledge of CYP3A5 status allows personalization of immunosuppression dose regimens based—such as proportionally increasing the initial tacrolimus dose given to a rapid metabolizer or utilizing long acting formulations, which are less impacted by rapid metabolism to limit peak concentration related drug toxicity.[2] Algorithms incorporating CYP3A5 and other factors using machine learning have been developed to allow clinicians to determine initial tacrolimus dosing more accurately, achieve target levels with fewer dose adjustments, and adjust long-term dosing to maintain goal tacrolimus exposure.[21,22] Drug exposure assessment using accurate, convenient, therapeutic drug monitoring may result in a reduction in the rates of acute rejection, delayed graft function, and graft failure, all of which have been correlated with increased intrapatient variability in C0 concentration.[23,24] Furthermore, TDM using C0 monitoring alone may be less accurate in fast metabolizers, as there are significant differences in the area under the curve based on

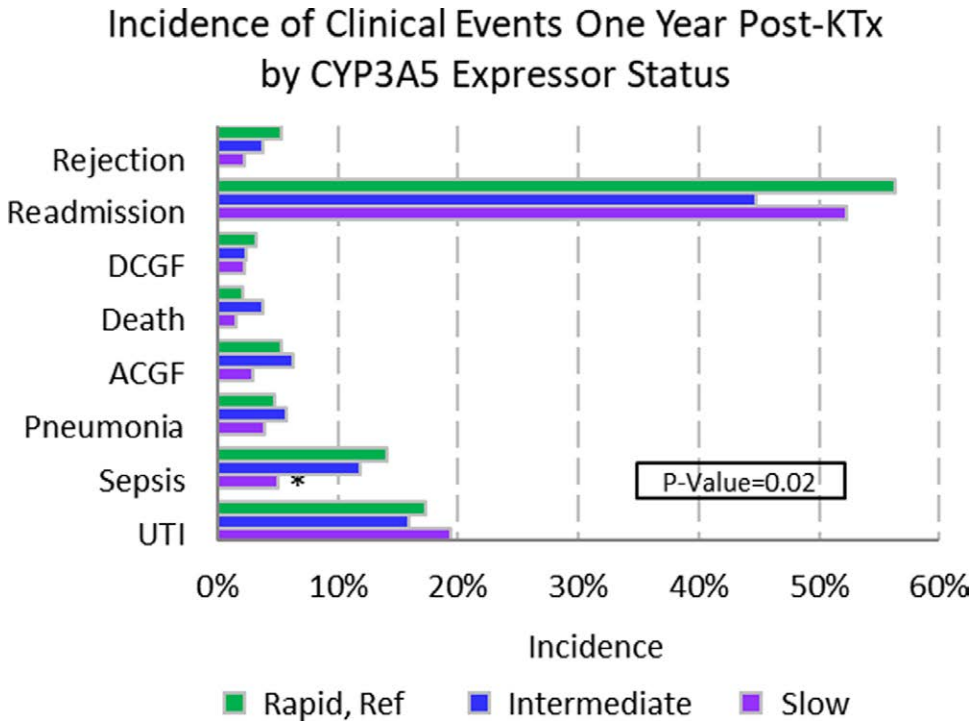

FIGURE 3. Incidence of postoperative complications by metabolism phenotype 1 y post-KTx. ACGF, all cause graft failure, DCGF, death censored graft failure; KTx, kidney transplant..

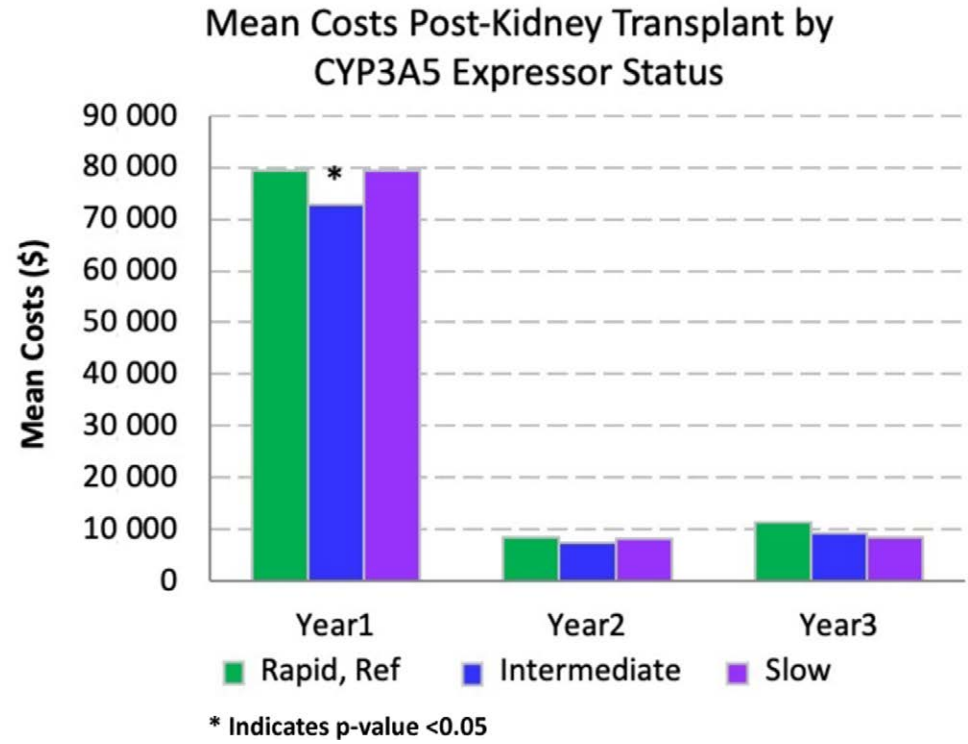

FIGURE 4. Mean costs after kidney transplantation by CYP3A5 expression status.

CYP34A genotype.[23] A change in immunosuppression management through better TDM and AI driven dose adjustment may result in decreased rejection and graft loss and should reduce the overall financial cost of kidney transplants for the healthcare system. Readmissions for adverse drug effects or the clinical sequelae of suboptimal immunosuppression likely contribute to the increased healthcare costs of faster metabolizers observed here. Although there could certainly be other explanations for readmissions, such as frailty, there was no significant difference in the ages, sex, or duration of dialysis for patients in the 3 phenotypic categories.

Machine learning–derived algorithms for tacrolimus dosing have already been developed and validated in the literature, with some studies focusing on the AA population

TABLE 2.

Linear regression data for Medicare spending costs among the study population

Characteristics	Estimate	Pr > Chi²
Intercept	82 924.9	<0.0001
Rapid metabolism phenotype	Ref	
Intermediate metabolism phenotype	−4789.5	0.003
Slow metabolism phenotype	−1037.2	0.55
Age 18–30	7192.8	0.02
Age 30–45	Ref	
Age 45–60	1998.5	0.22
Age >60	768.6	0.69
Female	−1774.6	0.20
Preemptive transplant	−11 598.5	0.01
Dialysis duration 0–25 mo	Ref	
Dialysis duration 25–60 mo	−271.6	0.89
Dialysis duration >60 mo	540.8	0.79
PRA <10	Ref	
PRA 10–79	1248.2	0.48
PRA >80	1309.8	0.57
Previous transplant	−1372.7	0.50
Living donor	1541.0	0.66
KDPI <20	−2676.7	0.15
KDPI 20–85	Ref	
KDPI >85	2526.0	0.29
Induction	−8497.9	0.0001

KDPI, kidney donor profile index; PRA, panel reactive antibody.

specifically.[25–28] These studies demonstrated improved time to therapeutic levels and lower risks of over- and underimmunosuppression when compared with clinician-guided dose adjustment. These genotype-informed algorithms could be expanded to include the entire KTx population given that *CYP3A5* genotype data would be useful to ascertain in all patients, regardless of race.[2] Standard use of genetic testing among all transplant recipients has the potential to improve established KTx outcome disparities given the differences in *CYP3A5* allele frequencies that preclude assessment based on phenotypic assessment alone and that may lead clinicians to inaccurately overdose of AAs who are not rapid metabolizers.[3]

In addition, this study also highlights a clear financial incentive for using precision medicine in the clinical transplant setting. As the cost of genetic sequencing continues to decrease and technologic advancements further facilitate the analysis of vast amounts of molecular data, opportunities arise to incorporate a patient's genetic data, metabolic environment, exposures, and behaviors into clinical practice.[29] The argument for precision medicine is often that it is the culmination of our advancements in basic science and translational and clinical research, allowing us to provide the most individualized care to patients. However, this work makes the argument that investing in precision medicine and rapid genotyping of transplant recipients could save thousands of dollars of healthcare expenditure per patient through more informed medication dose regimens.

This study is limited by the use of clinical data from a single institutional study and cost data from a single payer (Medicare). However, this is the largest published study of the impact of transplant pharmacogenomic analysis on cost in the literature and, specifically, on its impact on cost of care for AA patients. Furthermore, the majority of the AA patients transplanted during this time were Medicare beneficiaries, allowing accurate generalization to the non-Medicare population. Further work is needed to assess the economic benefits of pharmacogenomic- guided tacrolimus dosing in a representative multi-institutional cohort. However, these data are not currently obtained as part of the standard of care.

In the future, prospective studies are needed to determine if the use of genotype-guided tacrolimus dosing algorithms—and therefore decreased time to therapeutic trough concentrations and diminished intrapatient variability in tacrolimus concentration—translates to decreased clinic visits, healthcare visits, and overall costs. Such a study would be most impactful if performed among AA transplant recipients given the increased *CYP3A5* genetic variability within this population, as well as the established disparities in clinical outcomes. Larger studies would also be better powered to detect associations that did not reach statistical significance in this study.

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