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RESEARCH ARTICLE

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Survey of the utilization of genotype-guided tacrolimus management in United States solid organ transplant centers

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ABSTRACT

Introduction: Genotype-guided tacrolimus management is not routine in clinical practice despite the availability of Clinical Pharmacogenetics Implementation Consortium dosing guidelines. Prior surveys have evaluated patient and provider perspectives of pharmacogenetics (PGx) in transplant, but limited recent data exists on tacrolimus PGx implementation across United States transplant centers.

Methods: An electronic survey was distributed to transplant pharmacists regarding utilization of tacrolimus PGx, methods of implementing PGx, and barriers to clinical implementation. A survey response was requested for each organ program within the transplant center.

Results: A total of 90 programs from 69 transplant centers (28.1% of active U.S. transplant centers) responded to the survey. Tacrolimus PGx was utilized for patient care in 14 programs (15.6%). There was substantial variability in the implementation methods and application of tacrolimus PGx results among transplant programs. In programs that had not implemented tacrolimus PGx, common barriers for implementation included PGx testing cost and availability and lack of evidence for clinical utility.

Conclusion: Implementation of PGx guided tacrolimus in solid organ transplant centers remains limited with heterogeneity in the implementation approach. Additional research is needed to establish the clinical utility of PGx guided tacrolimus and education on reimbursement and testing resources may help to increase uptake.

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1. Introduction

Tacrolimus is one of the primary immunosuppressants used to prevent graft rejection in solid organ transplantation [1–3]. Its metabolism occurs in the intestine and liver by cytochrome P450 (CYP) 3A5 and CYP3A4 [4]. Genetic variation, particularly in *CYP3A5*, results in significant interpatient pharmacokinetic variability of tacrolimus. Individuals who carry at least one *CYP3A5* *1 allele, often called CYP3A5 expressers, have an active CYP3A5 enzyme resulting in higher tacrolimus metabolism and tacrolimus dose requirements than individuals who do not. This difference is most pronounced with the oral tacrolimus formulations where dose-controlled tacrolimus concentrations are 50–100% lower in CYP3A5 expressers compared to nonexpressers [5]. Given this association, the Clinical Pharmacogenetics Implementation Consortium (CPIC) published *CYP3A5* genotype-guided dosing guideline with a strong recommendation to increase the initial tacrolimus dose to 1.5-2× the standard dosing up to a maximum initial dose of 0.3 mg/kg/day when a patient is already known to be a CYP3A5 expresser [6].

The impact of *CYP3A5* genotype-guided dosing strategy has been studied prospectively. Some studies in transplant recipients concluded *CYP3A5* genotype-guided tacrolimus dosing improved the proportion of patients achieving a target tacrolimus through concentration and may decrease the number of dose adjustments required [7–9]. However, these results were not supported by another randomized controlled trial and no prospective studies demonstrated a difference in rejection outcomes for these patients [8–11]. Other investigators have identified increases in healthcare resource utilization in CYP3A5 expressers who did not receive genotype-guided dosing, suggesting implementation of this strategy could reduce healthcare costs, although this has not been prospectively studied [12–15].

Despite the availability of the CPIC guideline for *CYP3A5* genotype-guided tacrolimus dosing, the availability of clinical testing, and the evidence of potential benefit to reduce time to reach therapeutic tacrolimus concentrations and lower post-transplant management costs, the implementation of genotype-guided tacrolimus dosing within clinical practice is perceived to be limited. Only one institution has published on a clinical initiative for *CYP3A5* genotype-guided tacrolimus dosing [16]. General barriers to clinical pharmacogenetics (PGx) implementation such as information technology, scientific limitations, education, and reimbursement may provide further explanation for the limited clinical uptake of tacrolimus PGx [17]. When considering PGx

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Article highlights

- The utilization of pharmacogenetics to guide tacrolimus dosing in solid organ transplant in the U.S. has not been specifically evaluated
- Approximately 15% of responding programs are using genotype-guided tacrolimus strategies for initial dose selection and/or tacrolimus dose titration. The majority of these sites do not use clinical decision support demonstrating feasibility of implementation regardless of informatics infrastructure.
- The primary barriers to implementation of genotype-guided tacrolimus are the cost of testing and the unclear clinical utility of this approach compared to standard therapeutic drug monitoring.
- Further research is needed to demonstrate clinical utility of genotype-guided tacrolimus dosing across different transplant populations and education about reimbursement strategies could help overcome the current implementation barriers.

implementation, clinicians must plan for information storage and integration in the electronic health record, timing, and logistics of genotype testing, testing method (e.g., panel vs single-gene), costs and payment, as well as stakeholder buy-in from clinicians, laboratory, and informatics personnel [17–19]. Prior surveys and interviews of clinician and patient perspectives on PGx testing in solid organ transplant have demonstrated these barriers are consistent for this population [20,21]. However, these surveys were completed several years ago and there is limited data on the current state of implementation of tacrolimus PGx within solid organ transplant centers across the United States (U.S.). The objectives of this study were to determine the current state of implementation of PGx testing for tacrolimus management in the U.S. solid organ transplant centers and to assess implementation approaches as well as perceived barriers to clinical PGx implementation.

2. Methods

A 33-question electronic survey was created using the Qualtrics Platform (Qualtrics, Provo, UT). The survey included a brief invitation, 14 free-text response questions and 19 multiple-choice or select-all-that-apply questions (Supplementary Information). Following baseline characteristic questions, branching logic was utilized to ask respondents questions relevant to the indicated PGx implementation status of their transplant program. If respondents indicated that their program did not utilize PGx testing or only used it for research, they were asked questions pertaining to barriers their institution faced regarding clinical implementation of PGx guided tacrolimus. If respondents indicated that their program did utilize PGx testing, then further questions were asked regarding the implemented gene(s), testing methods, application of services, and billing considerations. Pilot testing of the survey was performed by a small group of transplant pharmacists identified by the study team. Questions were revised for clarity based on feedback prior to being finalized and disseminated. This study was reviewed and determined to be exempt by the local institutional review board (HUM00247254).

The survey was distributed to the e-mail listservs of the American College of Clinical Pharmacy (ACCP) Transplant Practice & Research Network and the American Society of Transplantation (AST) Transplant Pharmacy Community of Practice. Pharmacist members were asked to complete the survey once for each kidney, pancreas, heart, and lung transplant program at their transplant center. All responses that answered whether the program was using PGx testing were included in the analysis. Responses for liver transplant programs, those with unknown transplant center, and duplicate submissions from programs were excluded from the survey results. The survey was open for a four-week response period from 22 January 2024 to 19 February 2024. Two reminder messages were sent prior to the survey closing. Results for the survey were primarily evaluated descriptively. A *post hoc* assessment of the indicated barriers from programs that were not using *CYP3A5* genotype-guided testing was performed via Chi-squared tests to evaluate if barriers differed among programs that were exploring implementation, had explored but did not implement, and those who had not explored implementing.

3. Results

A total of 98 survey responses were received, of which eight responses were excluded (two unknown transplant center and six duplicate program responses). The included responses came from 69 unique transplant centers, representing 28.1% of 245 active U.S. transplant centers with non-liver transplant programs. Out of the 90 responding programs, 15 (16.7%) were pediatric transplant programs. Fifty-six responses (62.2%) were for kidney transplant, followed by 18 (20%) for heart transplant, 8 (8.9%) for lung transplant, and 8 (8.9%) for pancreas transplant. Tacrolimus PGx was implemented into patient care at 14 programs (15.6%) and PGx testing was utilized only for research at one program (1.1%). Of the 14 programs that had implemented clinical PGx testing, the majority were adult kidney or adult heart transplant (35.7% and 28.6%, respectively). Characteristics of the responding programs are summarized in Table 1.

3.1. Programs utilizing clinical tacrolimus PGx

Table 2 summarizes the current approaches of clinical tacrolimus PGx among the 14 programs who indicated they had implemented clinical PGx testing. Thirteen (92.9%) of the responding programs indicated that PGx testing is initiated for patients prior to transplant specifically for planned tacrolimus use post-transplant. Four were pediatric programs. Six programs (42.9%) indicated PGx results were ordered or available for nearly all patients (>90%) prior to initiation of tacrolimus. The majority of programs (57.1%) reported using a PGx panel test for the genotype-guided tacrolimus implementation and half of the programs sent testing to an external laboratory. The most reported payment model for testing was billing the patient's insurance (50%); however, three sites noted if the test was denied the cost would be covered by an institutional grant or the healthcare system. The majority of these sites (64.2%) also reported having a PGx pharmacist to assist with genotype-guided dosing implementation.

Eleven programs (78.5%) reported using PGx to guide the initial dose of tacrolimus with all indicating *CYP3A5* genotypes were considered for the dosing decision, and two

Table 1. Characteristics of survey responding transplant programs.

	No PGx ($n = 75$)	Clinical PGx ($n = 14$)	Research PGx ($n = 1$)	Total ($n = 90$)
Adult Kidney	43 (57.3%)	5 (35.7%)	0 (0%)	48 (53.3%)
Pancreas	8 (10.7%)	0 (0%)	0 (0%)	8 (8.9%)
Adult Heart	8 (10.7%)	4 (28.6%)	1 (100%)	13 (14.4%)
Adult Lung	5 (6.7%)	1 (7.1%)	0 (0%)	6 (6.7%)
Pediatric Kidney	6 (8.0%)	2 (14.3%)	0 (0%)	8 (8.9%)
Pediatric Heart	3 (4.0%)	2 (14.3%)	0 (0%)	5 (5.6%)
Pediatric Lung	2 (2.7%)	0 (0%)	0 (0%)	2 (2.2%)

PGx = pharmacogenetics.

Table 2. Current approaches to clinical tacrolimus pharmacogenetics.

Prompt	Number of Participants ($n = 14$)
PGx test available *prior* to tacrolimus:	
Ordered or already available for nearly all patients (>90%)	6 (42.9%)
Ordered or already available for most patients (>50–90%)	2 (14.3%)
Ordered or already available for select patients (10–50%)	5 (35.7%)
Ordered or already available rarely for patients (<10%)	0
No response	1 (7.1%)
Genotype Test:	
PGx Panel	8 (57.1%)
CYP3A5 and CYP3A4	4 (28.6%)
CYP3A5 only	1 (7.1%)
No response	1 (7.1%)
Genotype test sent to external laboratory	7 (50.0%)
PGX billing methods:	
Patient Insurance	7 (50.0%)
Bundled with transplant cost	3 (21.4%)
Covered PGx program	1 (7.1%)
Unsure	2 (14.3%)
No response	1 (7.1%)
Initial tacrolimus dosing:	
Individual patient initial dose determined by pharmacist considering PGx	5 (35.7%)
Individual patient initial dose determined by physician considering PGx	1 (7.1%)
Protocolized dosing based on PGx	3 (21.4%)
Other	2 (14.3%)
No response	3 (21.4%)
Initial doing references:	
CPIC guidelines only	2 (14.3%)
Internal data only	1 (7.1%)
CPIC and institutional data	6 (42.9%)
Primary literature	2 (14.3%)
No response	3 (21.4%)
Tacrolimus PGx Utilization:	
Initial dosing only	3 (21.4%)
Initial dosing and adjustment of tacrolimus dose based on prior troughs	1 (7.1%)
Initial dosing, adjustment of tacrolimus dose based on prior troughs, and assessment of nontherapeutic trough or side effects	7 (50%)
Adjustment of tacrolimus dose based on prior troughs, and assessment of nontherapeutic trough or side effects	1 (7.1%)
Adjustment of tacrolimus based on prior trough and dose adjustment after stopping azoles	1 (7.1%)
No response	1 (7.1%)

PGx = pharmacogenetics.

programs indicating *CYP3A4* genotypes were also considered. Three of these programs (27.2%) reported having a protocol-based genotype-guided tacrolimus dose, while the remaining eight programs indicated initial dosing was determined for each patient by the pharmacist or physician. CPIC guidelines were reported as a resource for determining initial dosing for ten of the eleven programs; seven programs reported using institutional data and four programs reported primary literature review as other resources for determining initial dosing. Documenting the genotype-guided dose in a clinical note was the method of communicating the initial tacrolimus dosing recommendation (six programs) followed by a clinical note and a verbal recommendation (two programs), with one program reporting only a verbal recommendation and only one site reporting use of a clinical decision support tool.

Ten programs (71.7%) reported utilizing PGx for tacrolimus dose adjustments or monitoring. Nine of these programs indicated PGx was used for assessment of nontherapeutic troughs or side effects, and one program indicated PGx was used to guide dose adjustments after stopping azoles. Similar to the initial dose recommendations, all programs reported using *CYP3A5* genotypes with two programs also considering *CYP3A4* genotypes for tacrolimus maintenance dosing adjustments. Only one program indicated dose adjustments were performed according to a dosing protocol, while other programs indicated dose titration was modified considering the therapeutic drug monitoring and genetic result(s).

3.2. Programs not utilizing clinical tacrolimus PGx

Of the 76 programs with no clinical PGx implementation or PGx for research only, 8 (10.5%) reported that they had explored PGx but

Table 3. Perceived barriers to clinical implementation of tacrolimus pharmacogenetics.

Barrier	All ($N = 76$)	Exploring PGx ($N = 8$)*	Explored but did not implement ($N = 9$)*	Have not explored ($N = 53$)*	p-value
Genotype testing not covered by insurance or too expensive	41 (53.9%)	3 (37.5%)	6 (66.7%)	32 (60.4%)	0.44
Evidence/perceived benefit of using genotype guided dosing over current TDM approach is too limited	35 (46.1%)	4 (50%)	3 (33.3%)	28 (52.8%)	0.56
Genotype testing not available at institution	30 (39.5%)	1 (12.5%)	1 (12.5%)	28 (52.8%)	0.01
Lack of solid organ transplant specific practice guidelines that recommend pharmacogenetic testing	28 (36.8%)	3 (37.5%)	2 (22.2%)	23 (43.4%)	0.48
Provider buy-in for genotype testing is limited	26 (34.2%)	1 (12.5%)	4 (44.4%)	21 (39.6%)	0.30
Turnaround time for genotype test result is too long	24 (31.6%)	0 (0%)	2 (22.2%)	22 (41.5%)	0.05
Workload burden of genotype testing is too much	19 (25.0%)	0 (0%)	4 (44.4%)	15 (28.3%)	0.11
Clinician knowledge/education for genotype guided tacrolimus dosing is limited	18 (23.7%)	2 (25%)	3 (33.3%)	13 (24.5%)	0.85
Pharmacist buy-in for genotype testing is limited	9 (11.8%)	0 (0%)	0 (0%)	9 (17.0%)	0.19
Storage of pharmacogenetic test results in EMR is challenging	5 (6.6%)	2 (25%)	0 (0%)	3 (5.7%)	0.10
Prevalence of relevant genetic variants are rare in institution's transplant population	3 (3.9%)	0 (0%)	0 (0%)	3 (5.7%)	0.61
Unclear which genetic test(s) to use for genotype guided tacrolimus dosing	2 (2.6%)	1 (12.5%)	0 (0%)	1 (1.9%)	0.21

*6 programs with no PGx or PGx only for research left this section blank.
EMR = electronic medical record, PGx = pharmacogenetics, TDM = therapeutic drug monitoring.

did not implement, 9 (11.8%) were currently in the process of exploring genotype-guided tacrolimus dosing, while 53 (69.7%) programs had not explored genotype-guided tacrolimus dosing. Six programs did not identify their attempt of PGx implementation. The reported barriers to PGx implementation for tacrolimus for these sites are shown in Table 3. The top four reported barriers were that genotype testing was not covered by insurance or too expensive (53.9%), evidence or perceived benefit of using genotype guided dosing over current therapeutic drug monitoring approach was too limited (46.1%), genotype testing was not available at the institution (39.5%), and solid organ transplant specific practice guidelines that recommend pharmacogenetic testing was lacking (36.8%). Programs that had not explored PGx implementation for tacrolimus were more likely to indicate that genotype testing was not available at their institution ($p = 0.01$) and that the turnaround time for testing is too long ($p = 0.05$) than programs that have or are currently exploring PGx implementation but have not implemented. Although not statistically different, a higher proportion of programs that explored PGx but did not implement indicated the workload burden of genotype testing as a barrier for implementation (44.4% vs 28.3%).

Responses were similar when comparing kidney transplant programs to non-kidney transplant programs, as well as when comparing responses for adult programs to pediatric programs (not reported).

4. Discussion

The results of this survey confirm that there is currently limited implementation of clinical tacrolimus PGx in solid organ transplant programs in the U.S. We have also identified the current barriers limiting PGx implementation for tacrolimus as well as summarized the current methods of tacrolimus PGx. These findings can be used to inform future education or research initiatives to address the existing barriers to implementation and provide clinicians who are interested in implementing tacrolimus PGx with a summary of methods that other sites have utilized.

A 2019 survey of medical and surgical directors of U.S. transplant centers asked about their perspectives on PGx testing in solid organ transplantation [20]. A primary barrier noted in this study was that greater than 50% of the respondents indicated a lack of confidence in PGx knowledge or ability to apply a PGx result. This contrasts with our study where fewer than a quarter of the responding centers without clinical tacrolimus PGx indicated clinician knowledge/education for genotype guided tacrolimus was a barrier to implementation. Although this survey was only sent to pharmacists, this generally suggests that education for PGx has improved. In the prior survey, although 46.1% of respondents reported that PGx testing was available for clinical practice in their institution, *TPMT* was the most commonly ordered test (66.5%), while *CYP3A5* was ordered only by 26.6% of respondents, and 37.6% of respondents had ordered a PGx test <10 times over the prior year [20]. Although our survey only asked about testing for tacrolimus PGx, our findings suggest that transplant programs are testing patients for *CYP3A5* more frequently as over half of the sites indicated >90% of patients have genotype results after tacrolimus is initiated.

Barriers to implementation that remained consistent with the prior surveys include unclear clinical value of a PGx-guided dosing approach compared to current standard of care approaches as well as concerns regarding the cost of testing [20,21]. The majority of clinical trials evaluating genotype-guided tacrolimus dosing were performed in adult kidney transplant recipients and most indicated *CYP3A5* genotype-guided tacrolimus dosing achieved therapeutic exposure more quickly and decreased the monitoring burden in regard to dosing adjustments [7,8]. However, there are also negative studies and limited prospective evidence that this strategy improves clinical outcomes such as rejection [10,11]. Given the differences in immunosuppression strategies and overall rejection risk among transplant types, it is difficult to conclude *CYP3A5* genotype-guided tacrolimus dosing would not be beneficial for any transplant population but there remains a paucity of data for other transplant populations and further studies are needed to address this barrier. Although cost of testing remains a concern,

recent evidence suggests that utilization of genotype-guided dosing could help reduce discrepancies in the post-transplant tacrolimus monitoring burden for patients and providers and potentially treatment costs [12,15,22]. Additionally, coverage for *CYP3A5* genotype testing is increasing in the U.S., with ten of the twelve Medicare Administrative Contractors having approved local coverage determinations for PGx testing [18]. One site in Indiana has determined that <0.5% of claims for *CYP3A5* genotype testing for tacrolimus prior to transplant were denied [16]. Although we did not ask the price of PGx testing in this survey, of the programs that had implemented testing, some absorb the cost if not covered by insurance or bundle the cost of PGx testing with the transplant costs, suggesting the actual cost of the PGx test is perceived to be small in comparison to the perceived benefit of a potential reduction in monitoring costs.

Lack of availability of genotype testing within the institution was the third most reported barrier in this study. The Genetic Testing Registry is available for laboratories to voluntarily report their available clinical genetic tests. Interested clinicians could identify stakeholders within their pathology departments and use this resource to evaluate and select a laboratory to allow for testing at their institution. Others have described additional considerations for assessing pharmacogenetic testing and there are guidelines for assessing the quality of *CYP3A5* and *CYP3A4* genotype tests through the Association of Molecular Pathologists to help centers further guide test selection [23,24]. Notably, the majority of programs that implemented genotype-guided tacrolimus dosing reported having a pharmacogenetics pharmacist to assist with implementation. Multidisciplinary collaboration and pharmacist expertise have been noted to be essential aspects for implementation of pharmacogenetic services [18–20], and the inclusion of this pharmacy expertise within clinical teams may help to develop strategies to overcome the barriers discussed above.

Despite the general consensus that PGx results and prescribing recommendations should be integrated into the electronic health record (EHR) [18], the majority of programs that have implemented genotype-guided tacrolimus dosing did not utilize clinical decision support tools for dosing recommendations. This potentially highlights the limitations of current clinical decision support tools to account for the complexity of dosing considerations for tacrolimus given the potential for post-transplant instability, drug–drug interactions, or other patient characteristics that are also known to impact tacrolimus dose requirements. However, it also demonstrates that although full integration of results and recommendations is ideal, implementation of PGx for tacrolimus is feasible without these components in place so that institutions without substantial informatics infrastructure could still deploy personalized tacrolimus dosing.

A main strength of this survey was that it captured the utilization of PGx guided dosing at the transplant program level, whereas prior studies had surveyed providers or patients, which allows for an evaluation of the utilization across all solid organ transplant centers in the U.S. This study is limited by the low response rate, with just under a third of eligible transplant centers responding. This may be attributed to the distribution strategy as it is possible pharmacists as some centers may not be members of these groups. When evaluating the reported barriers to implementation, it is also important to note that these are from the pharmacist perspective and could differ from other providers. The respondents were also more likely to work in adult transplant or kidney transplant which could bias the results, although this is concordant with the composition of transplant programs across the country.

5. Conclusions

This was a pharmacist-based survey that evaluated the current use of tacrolimus PGx in solid organ transplant programs in the United States. Fifteen percent of responding programs had implemented PGx testing for tacrolimus; however, there was substantial variability in implementation methods and application of results in tacrolimus dosing decisions. Most programs did not utilize PGx testing for clinical dosing of tacrolimus; lack of clear evidence for clinical utility of testing and cost of testing were the primary reported barriers for implementation. These findings support the fact that use of PGx testing for tacrolimus has increased over the last decade but highlights the continued need for evidence demonstrating the utility of this approach.

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Ethical disclosure

This study was reviewed and determined to be exempt by the local institutional review board (HUM00247254).

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