Implementation of Standardized Clinical Processes for TPMT Testing in a Diverse Multidisciplinary Population: Challenges and Lessons Learned

Kristin W. Weitzel  
*University of Florida*

D. M. Smith  
*University of Florida*

Amanda R. Elsey  
*University of Florida*

Benjamin Q. Duong  
*University of Florida*

Benjamin Burkley  
*University of Florida*

*See next page for additional authors*

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Implementation of Standardized Clinical Processes for TPMT Testing in a Diverse Multidisciplinary Population: Challenges and Lessons Learned

Kristin W. Weitzel1,2,*, D. Max Smith1,2, Amanda R. Elsey1,2,3, Benjamin Q. Duong1,2, Benjamin Burkley2, Michael Clare-Salzler4,5, Yan Gong2, Tara A. Higgins6, Benjamin Kong7,†, Taimour Langae2, Caitrin W. McDonough2, Benjamin J. Staley6, Teresa T. Vo8,†, Dyson T. Wake9,†, Larisa H. Cavallari1,2 and Julie A. Johnson1,2

Although thiopurine S-methyltransferase (TPMT) genotyping to guide thiopurine dosing is common in the pediatric cancer population, limited data exist on TPMT testing implementation in diverse, multidisciplinary settings. We established TPMT testing (genotype and enzyme) with clinical decision support, provider/patient education, and pharmacist consultations in a tertiary medical center and collected data over 3 years. During this time, 834 patients underwent 873 TPMT tests (147 (17%) genotype, 726 (83%) enzyme). TPMT tests were most commonly ordered for gastroenterology, rheumatology, dermatology, and hematology/oncology patients (661 of 834 patients (79.2%); 580 outpatient vs. 293 inpatient; \( P < 0.0001 \)). Thirty-nine patients had both genotype and enzyme tests (\( n = 2 \) discordant results). We observed significant differences between TPMT test use and characteristics in a diverse, multispecialty environment vs. a pediatric cancer setting, which led to unique implementation needs. As pharmacogenetic implementations expand, disseminating lessons learned in diverse, real-world environments will be important to support routine adoption.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ Clinical implementation of TPMT genotyping testing has been described primarily in pediatric cancer populations.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ Do differences in TPMT test ordering and use exist between a diverse, multidisciplinary patient population as compared with a pediatric cancer population that may lead to unique clinical implementation needs?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
✔ Limited data are available regarding implementation of TPMT testing in diverse patient populations. Our study found that TPMT test ordering and use characteristics differed between a diverse, multidisciplinary patient population vs. a pediatric cancer population. In addition, there were meaningful differences between this diverse multidisciplinary pharmacogenetics implementation as compared with our initial implementation of CYP2C19 testing in an inpatient, cardiac catheterization setting.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
✔ As pharmacogenetics is increasingly translated into practice, dissemination of real-world experiences and lessons learned with different types of implementations in diverse settings is essential for adopting clinical pharmacogenetics across a wide range of settings.

Thiopurines (i.e., azathioprine, mercaptopurine, and thioguanine) are used as antimetabolite cytotoxic and immunosuppressive drugs for treatment of several types of malignant (e.g., acute lymphoblastic leukemia (ALL)) and nonmalignant conditions, particularly in autoimmune disorders such as inflammatory bowel disease (IBD).1–3 Although thiopurines achieve a treatment response in up to 70% of patients with nonmalignant conditions, their use is limited by the potential for significant toxicity, including gastrointestinal (GI) effects, rash, and the possibility of severe or life-threatening
myelosuppression.\textsuperscript{4,5} In IBD, for example, more than 20% of patients discontinue thiopurines because of drug-related toxicities.\textsuperscript{4}

The thiopurine S-methyltransferase (TPMT) enzyme, which is encoded by the \textit{thiopurine S-methyltransferase} (TPMT) gene, is responsible for inactivating thiou嘌ine drugs, with an inverse relationship between TPMT enzyme activity and formation of cytotoxic thioguanine nucleotide metabolites with resultant toxicities.\textsuperscript{6} TPMT enzyme activity is affected by polymorphisms in the \textit{TPMT} gene, with the three most common inactive TPMT alleles, TPMT*2, *3A, and *3C, accounting for ~90% of all variants. Nearly all patients who inherit two inactive TPMT alleles (e.g., *2/*3A, *2/*3C; poor metabolizers) experience severe or life-threatening myelosuppression with usual doses due to accumulation of toxic thiopurine drug metabolites.\textsuperscript{7–9} Patients who inherit one inactive TPMT allele (e.g., *1/*2, *1/*3A; intermediate metabolizers) have higher levels of thioguanine nucleotide metabolites and increased risk of myelosuppression as compared with patients who are homozygous for wildtype TPMT alleles (*1/*1; normal metabolizers). TPMT enzyme function can also be assessed using an enzymatic assay (i.e., TPMT genotyping) that measures the rate at which methylated products (6-mMP (methyl-mercaptopurine) or 6-mTGN (methyl-thioguanine)) are formed in erythrocytes.\textsuperscript{10} For initial assessment, providers may order one or both tests, keeping in mind instances in which a specific test may be inappropriate, such as TPMT genotyping in patients who have undergone liver transplant or TPMT phenotyping in patients who have received a recent blood transfusion.

Prospective trials in pediatric patients with ALL have demonstrated that TPMT genotype-guided therapy is associated with reduced thiopurine toxicity with reduction in efficacy.\textsuperscript{11,12} In patients with IBD and other nonmalignant conditions, genotype-guided thiopurine dosing has also been shown to reduce adverse drug events, with up to a 10-fold decrease in hematologic toxicities in patients who have a TPMT variant as compared with nonvariant carriers.\textsuperscript{5} In addition to its routine inclusion in pediatric cancer treatment protocols, treatment guidelines for multiple nonmalignant conditions recommend preemptive use of TPMT genotyping and/or phenotyping to guide thiopurine dosing.\textsuperscript{13–15}

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines provide detailed recommendations for use of TPMT genotype data to guide thiopurine dosing in clinical practice.\textsuperscript{8} These guidelines align well with implementation of TPMT genotyping in cancer treatment settings, in which the genotype test is used nearly exclusively in the inpatient setting due to the presence of disease and treatment factors in this population that decrease the accuracy of phenotyping.\textsuperscript{16} Published descriptions of TPMT genotyping implementations in specialized cancer and/or pediatric practice settings also exist.\textsuperscript{17–21} However, the current practice-based guidance and/or published experience descriptions provide little guidance for clinicians implementing TPMT genotype and/or phenotype testing in diverse, multispecialty (primarily noncancer) populations.\textsuperscript{22} Practical guidance for implementation of TPMT testing is especially important for a variety of reasons. These include that in noncancer populations, thiopurine dosing is variable for different conditions (and therefore differing needs for TPMT-based dose adjustments). Additionally, prescribers may not be familiar with TPMT testing and there may be confusion about choosing between the TPMT genotype and/or phenotype assay testing in these populations. Although TPMT phenotype testing has historically been the predominant method to assess TPMT enzyme function in noncancer settings, we anticipate that TPMT genotyping will be increasingly adopted outside of the pediatric cancer population as testing costs decrease and pharmacogenetic implementations become increasingly common.\textsuperscript{23,24} It is important to identify practice-based barriers and clinician needs with implementation of routine ordering and interpretation of TPMT testing in diverse, multispecialty populations.

The University of Florida (UF) Health Personalized Medicine Program (PMP), a multidisciplinary clinical implementation initiative, was established in 2012 with implementation of CYP2C19 genotyping to guide antiplatelet therapy in patients undergoing percutaneous coronary intervention.\textsuperscript{23,25} Although TPMT genotyping and/or phenotyping were performed in individual specialty practices at UF Health prior to 2012, a system-wide approach to coordinate test ordering and interpretation did not exist. In 2014, the UF Health PMP developed and implemented a standardized process for TPMT testing that included discipline-specific provider education; guidance on TPMT test ordering and interpretation (for genotype and/or phenotype testing); clinical decision support within the electronic health record (Epic); and standardized patient education materials. We hypothesized that because of differences in practice settings and providers, frequency of TPMT genotype test vs. phenotype (enzymatic) assay ordering, and clinical use of thiopurines, unique needs would emerge for system-wide implementation of a TPMT testing program in a diverse, multidisciplinary noncancer practice environment as compared with implementation in a specialized pediatric hematology/oncology setting. In this article, we describe the process for system-wide implementation of TPMT testing in our institution, compare the use of TPMT genotyping and phenotyping in diverse multidisciplinary practice settings vs. a pediatric hematology/oncology setting, and examine the concordance between TPMT genotype and phenotype test results in patients who underwent both tests.

**METHODS**

**Development of TPMT testing service**

UF Health Shands Hospital is a 1,692-bed tertiary academic medical center affiliated with the University of Florida and UF Physicians Outpatient Clinics. The health system’s areas of excellence include cancer specialties, heart care, women and children’s services, neuromedicine specialties, and transplant services and houses the UF Health Shands Cancer Hospital and UF Health Shands Children’s Hospital. TPMT genotype and phenotype test ordering and reporting procedures have historically varied among different practice settings. In most cases, TPMT tests were ordered by individual providers through Prometheus Laboratories (San Diego, CA), with a test turnaround time of 7 to 14 days (including refrigerated sample shipping time plus test turnaround time of 2–3 days from time of sample receipt). Prometheus
test results were faxed to the provider and scanned into the “media” section of the electronic health record (EHR) by nursing staff. The Prometheus laboratory results reported TPMT genotype using star-allele nomenclature with assignment of phenotype (e.g., normal enzyme activity) and TPMT enzyme assay results reported numerically, in EU (enzyme units) with reference ranges, and graphically, in a visual representation of TPMT enzyme activity along a spectrum of low, intermediate, or normal ranges.

Development of a standardized system-wide approach to TPMT ordering and interpretation began in August 2013. At the time, the UF Health Shands Hospital Pharmacy and Therapeutics (P & T) Committee provided oversight to a PMP subcommittee and regulatory governance for clinical pharmacogenetic implementations. As a first step for this implementation, we identified clinical services that commonly ordered TPMT testing (i.e., pediatric hematology/oncology, gastroenterology, rheumatology, neurology, and internal medicine). Individual meetings were then conducted with prescribers and nursing staff on these services to determine current TPMT ordering procedures and obtain feedback on clinical needs to improve the TPMT testing process. Prescribers from all disciplines were invited to participate in PMP subcommittee meetings to develop therapeutic recommendations (Figure 1) and clinical decision support (CDS) language.

Therapeutic recommendations and CDS alert language were approved by the P & T Committee in November 2013, although strategies for CDS alerts and clinical follow-up continued to evolve throughout the study period. An Epic Best Practice Advisory (BPA, Figure 2) was built to fire in the presence of an actionable TPMT genotype in the EHR and a new order for a thiopurine for all clinical services. A pretest alert triggered by a new thiopurine order in a patient without a known TPMT genotype result was built for pediatric hematology/oncology services only (subsequent alerts were not suppressed after initially firing for all alerts). When a CDS alert fired, the PMP pharmacogenetics resident was notified via an Epic in-basket message and provided a written or verbal consultation for actionable results, depending on the clinical service. During the study period, PMP created additional Epic in-basket messages to notify the pharmacogenetics resident about phenotype test orders and/or results. If a phenotype-related in-basket message was received, the resident contacted the prescriber by email to determine if a clinical consult was needed. If so, the resident provided recommendations according to the prescriber’s preferred communication method (e.g., verbal consultation, email consultation, or written note).

In addition to previous outreach and consultations with individual providers, UF Health PMP pharmacists conducted individual or group (e.g., grand rounds) educational sessions with clinical staff and prescribers prior to the launch of the clinical implementation in February 2014. Provider education was individualized based on discipline-specific guideline recommendations for testing and treatment with thiopurines, historical use of TPMT genotype or phenotype testing within each setting, current clinical workflow and test-ordering procedures, and differences in patient populations. Written patient education materials were provided to prescribers and staff and were available in PDF form accessible through a hyperlink in the BPA in Epic.

**Genotyping**

UF Health PMP worked with the UF Health Pathology Laboratory (UFHPL), a College of American Pathologists-accredited Clinical Laboratory Improvement Amendments-licensed (CAP/CLIA) clinical laboratory to develop and validate TPMT genotype testing (enzymatic testing was not offered by UFHPL). The TPMT assay is a laboratory-developed test using quantitative polymerase chain reaction (qPCR) through the Viia7 Real-Time PCR System (Applied Biosystems by Life Technologies, Foster City, CA) to determine gene variants based on analysis of genomic DNA extracted from either peripheral blood or buccal cells. Development and validation of genotyping for TPMT*2, *3A, *3B, *3C alleles was completed in January 2014. TPMT genotype results expressed as phenotypes were provided in the BPA based on CPIC guidelines, with patients classified as TPMT “normal metabolizers” (i.e., *1/*1), “intermediate metabolizers” (e.g., *1/*2, *1/*3A), or “poor metabolizers” (e.g., *2/*3A, *2/*3C).

**Data collection and analysis**

A standardized institutional process for TPMT testing and clinical decision support was launched on 3 February 2014, throughout the health system. TPMT tests (genotype and/or phenotype) are performed in all settings as clinical test(s), consistent with the established standard of care within that practice setting. UF Health PMP is alerted via Epic to TPMT genotype and phenotype orders and provides written pharmacogenetic consultations for patients. Electronic data collection included number and type of TPMT tests ordered, test turnaround time, discipline/practice setting of ordering prescriber, patient status at the time of order (inpatient vs. outpatient), and demographics of patients who underwent TPMT testing. For patients who had both genotype and phenotype results, manual data collection was performed to identify factors that could affect the accuracy of the TPMT enzyme test (i.e., sample age, history of allogeneic bone marrow transplant, red blood cell (RBC) transfusions within 90 or 120 days, uremia, indication, and drug interactions). Chi-square and Fisher’s exact test were used for categorical variables, as appropriate. The Wilcoxon rank-sum test compared TAT between the genotype and enzyme tests. Data collection processes were approved by the University of Florida Institutional Review Board.

**RESULTS**

Between 3 February 2014, and 3 February 2017, 834 patients underwent 873 TPMT tests, consisting of 147 (17%) genotype tests and 726 (83%) enzyme tests (Table 1). As expected based on the use characteristic of thiopurines in the study populations, patients on the hematology/oncology service were younger than those on non-hematology/oncology services. Sex, race, and ethnicity also differed between patients on the hematology/oncology service vs. nonhematology/oncology services. The clinical services that most commonly ordered a TPMT genotype or
phenotype test were gastroenterology, rheumatology, dermatology, hematology/oncology, and allergy/immunology (Table 2). Overall, the enzyme assay was ordered most often to assess TPMT metabolism phenotype. However, there were notable differences in the type of test ordered by service. Patients assigned to the hematology/oncology service were more likely to have genotype testing alone as compared with those on other clinical services: 95% (39 of 41) of hematology/oncology patients vs. 9% (69 of 793) of nonhematology/oncology; \( P < 0.0001 \). In contrast, among patients tested by the gastroenterology, rheumatology, or dermatology services, 87% (542 of 620 patients) had only enzyme testing ordered. Both a genotype and enzyme test were ordered for 39 patients, with dual-test orders occurring most frequently on the gastroenterology service (\( n = 24 \) of 39 patients; 62%). TPMT testing was ordered more often in the outpatient setting as compared with the inpatient setting overall (580 outpatient orders vs. 293 inpatient orders; \( P < 0.0001 \)). However, hematology/oncology service providers ordered TPMT genotype testing more frequently in the inpatient setting; 95% of tests from hematology/oncology vs. 60% of tests from other providers were for inpatients; \( P < 0.0001 \).

Among genotyped patients, 88% (\( n = 130 \)) were normal metabolizers, 12% (\( n = 17 \)) intermediate metabolizers (\( n = 7 \) hematology/oncology service, \( n = 5 \) GI service, and \( n = 5 \) other services), and none were poor metabolizers. Phenotype frequencies based on enzyme testing were consistent with frequencies based on genotype testing, with 85% (\( n = 617 \)) of patients classified as having normal enzyme activity and the remaining 15% (\( n = 109 \)) as low, intermediate, or abnormal activity (result reporting nomenclature...
Test order rate was calculated as the sum of patients with any TPMT test ordered by a service divided by 36 months (3 February 2014 to 3 February 2017).
providers prior to TPMT implementation. In addition, we observed discipline-specific differences in CDS development and clinical support needs. For malignant conditions, prescribers preferred a pretest alert and written consult note with each actionable genotype, but requested that BPA language refer to the patient’s chemotherapy treatment protocol instead of CPIC recommendations due to minor differences between CPIC- and protocol-recommended genotype-guided dosing. For nonmalignant conditions, prescribers supported CPIC-recommended dose adjustments. However, due to concerns about workflow efficiency, alert fatigue, and differences in Epic documentation of genotype and phenotype test results, these prescribers opted not to have a TPMT pretest alert or written consultation notes from PMP with each actionable genotype. Instead, they requested outreach by PMP upon actionable genotype results, with case-by-case determination of the level of clinical support needed. We also observed areas of concordance among the varying specialties in CDS development. Because of BPA space limits and a universal prescriber preference to minimize BPA text, prescribers worked together to reach consensus on essential information to include in the BPA. In addition, all specialties supported not suppressing subsequent alerts after the initial firing due to the anticipated rarity of an alert firing and identification of instances in which it would be desirable for it to fire multiple times (e.g., provider orders thiopurine but is unaware of an existing TPMT result linked to a previous date/patient encounter in the EHR).

In addition to discipline-specific needs that emerged, the predominant use of phenotyping vs. genotyping in nonhematology/oncology patients also impacted the implementation process. Within our institution, phenotype results are ordered from a variety of commercial laboratories with variable reference ranges and most often documented as scanned media files vs. discrete variables. Because of this, we were not able to link CDS alerts to an “actionable” phenotype result. Instead, PMP used the in-basket messaging system to detect TPMT phenotype orders and provide clinical support as needed, such as assisting with test interpretation or identifying inappropriate use of phenotyping (e.g., recent blood transfusion).

Finally, this wide range of clinical specialties translated to diverse provider education needs. To address this, we developed different educational strategies based on practice needs and aligned with historic use of TPMT testing. Identified provider educational gaps included inconsistent knowledge of discipline-specific evidence-based recommendations for thiopurine dosing, unfamiliarity with TPMT genotyping (as compared with predominant use of phenotyping in nonhematology/oncology patients), confusion regarding which TPMT test to order and how to interpret discordant test results, and variable needs for support staff education with workflow changes in TPMT test ordering and resulting processes.

We also experienced differences in this implementation as compared with our initial development of CYP2C19 testing in an inpatient, cardiac catheterization setting.25 The TPMT implementation’s inclusion of both inpatient and outpatient settings required engagement of two distinct CDS approval and build processes, vs. an inpatient-only process with CYP2C19 implementation. We also observed differences in regulatory oversight. Within our institution, the P & T committee regulates inpatient medication use processes only, so while this group was sufficient to oversee CYP2C19 implementation, support of TPMT testing required PMP to engage with outpatient Medication Safety and Epic committees. Our regulatory structure has since been formally revised to accommodate subsequent pharmacogenetic implementations, with the PMP Committee now existing as a standalone institutional committee with inpatient and outpatient representation.

These findings and lessons learned have important implications as clinical pharmacogenetic testing is implemented with increased frequency in diverse, multidisciplinary environments across a range of specialties and settings. Within our institution, changes to the clinical implementation process that were developed with TPMT laid the groundwork for our program to meet a wide range of future needs for subsequent pharmacogenetic implementations, including CYP2D6 testing for opioids in pain management, CYP2D6 and CYP2C19 testing for SSRI therapy in psychiatry, and CYP2C19 testing to guide proton pump inhibitor and voriconazole use across multiple specialty populations. As pharmacogenetic implementations become more widespread within diverse, multispecialty institutions, these considerations can inform the development of other pharmacogenetic implementations.

CONCLUSION

This study revealed significant diversity in the use and application of TPMT testing to thiopurine dosing within a large, multidisciplinary population that included cancer and noncancer patients and revealed unique CDS, regulatory, and provider education needs for pharmacogenetic implementations within our institution. As pharmacogenetic implementations become increasingly common among diverse practice settings, disseminating unique characteristics and lessons learned regarding diverse implementations will be essential to support routine adoption of clinical pharmacogenetics.


Conflict of Interest. The authors declared no competing interests for this work.

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Implementation of Standardized Clinical Processes

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