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ARTICLE

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

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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 certain 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

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[†]At the time of program implementation and/or data collection, author was a postgraduate trainee with the UF Health Personalized Medicine.
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myelosuppression.[4,5] In IBD, for example, more than 20% of patients discontinue thiopurines because of drug-related toxicities.[4]

The thiopurine S-methyltransferase (TPMT) enzyme, which is encoded by the *thiopurine S-methyltransferase* (*TPMT*) gene, is responsible for inactivating thiopurine drugs, with an inverse relationship between TPMT enzyme activity and formation of cytotoxic thioguanine nucleotide metabolites with resultant toxicities.[6] TPMT enzyme activity is affected by polymorphisms in the *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.[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 phenotyping) that measures the rate at which methylated products (6-mMP (methyl-mercaptopurine) or 6-mTGN (methyl-thioguanine)) are formed in erythrocytes.[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 without reduction in efficacy.[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.[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.[13–15]

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines provide detailed recommendations for use of *TPMT* genotype data to guide thiopurine dosing in clinical practice.[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.[16] Published descriptions of *TPMT* genotyping implementations in specialized cancer and/or pediatric practice settings also exist.[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.[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.[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.[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.[23] 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, dermatology, 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*).[6,26]

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).[9,16,21,27–29] 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

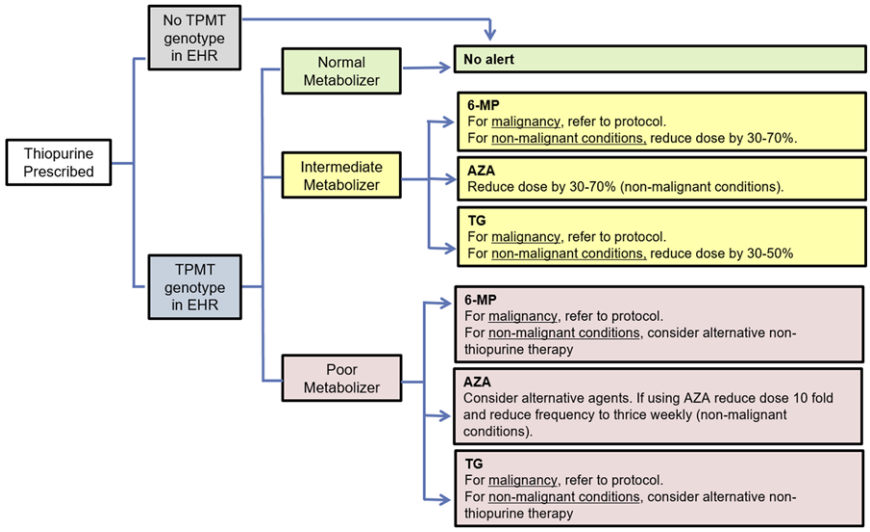

Figure 1 Clinical decision support algorithm for *TPMT* genotyping. AZA, azathiopurine; EHR, electronic health records; 6-MP, mercaptopurine; TG, thioguanine; TPMT, thiopurine methyltransferase.

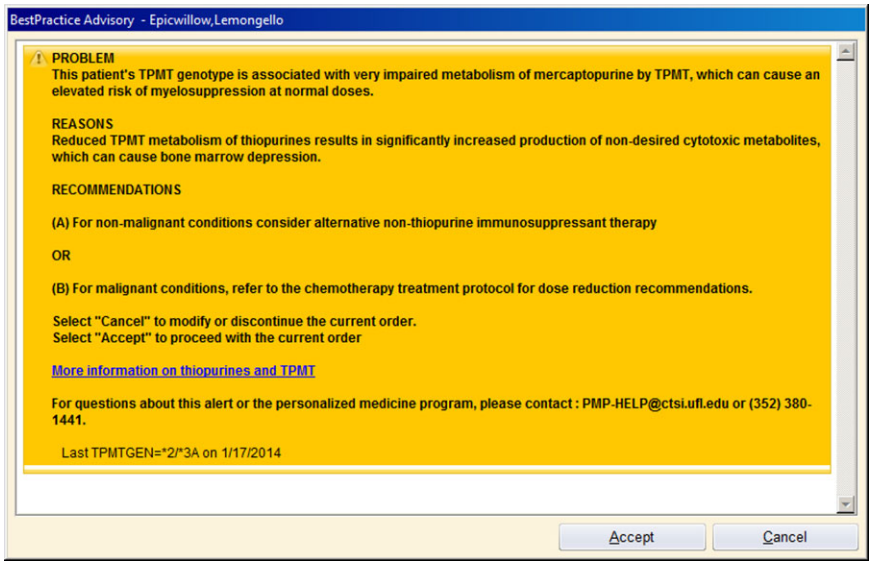

Figure 2 Sample Epic best practice advisory alert for *TPMT* genotype testing. TPMT, thiopurine methyltransferase.

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

Table 1 Characteristics of patients on the hematology/oncology service vs. other services who had TPMT testing

Characteristic[b]	Hem/Onc ($n = 41$[a])	Non -Hem/Onc ($n = 793$[a])
Age, median (IQR), years	5.28 (3.28, 10.77)	37.99 (24.06, 55.67)
Sex, *n* (%)		
Male	28 (68.29)	259 (32.66)
Race, *n* (%)		
White	21 (51.2)	592 (74.7)
Black	9 (22.0)	147 (18.5)
Other	10 (24.4)	47 (5.9)
Unknown	1 (2.4)	7 (0.9)
Ethnicity, *n* (%)		
Not Hispanic	29 (70.7)	736 (92.8)
Hispanic	12 (29.3)	49 (6.2)
Unknown	0	8 (1.0)

IQR, interquartile range.
[a]Reflects total number of patients tested; 39 patients received both tests ($n = 873$ TPMT tests ordered for 834 patients).
[b]$P < 0.0001$.

differed by laboratory). Test turnaround time was shorter for genotyping than phenotyping (5 days (IQR 3–7 days) vs. 6 days (IQR 5–8 days)); $P < 0.0001$). Of the 39 patients who underwent both genotyping and phenotyping, test results were discordant in two (5%) patients. Both discordant patients were male, treated on the gastroenterology service, genotyped as *TPMT* *1/*1, and classified as intermediate metabolizers according to phenotype assay results. At the time of enzyme testing, concomitant medications in patients with discordant test results included naproxen for one patient and mesalamine and hydrocortisone for the other patient.

Fifty-four percent of patients who underwent TPMT testing ($n = 450$ of 834 patients) received a thiopurine during the 3-year data collection period. Conversely, out of 1,323 patients who received a thiopurine between 3 February 2014, to 31 December 2016 (data unavailable for entire study period), 807 (61%) underwent TPMT testing. In patients who received a thiopurine, mercaptopurine was used most often in hematology/oncology patients ($n = 33$ of 38; 87%), while azathioprine was used most frequently on other clinical services ($n = 356$ of 412; 86%). For all patients on the hematology/oncology service with an actionable *TPMT* genotype, thiopurines were appropriately dose-adjusted based on genotype according to the patient's chemotherapy treatment protocol, as directed in the BPA (similar data are unavailable for nonhematology/oncology patients due to EHR limitations).

DISCUSSION

The above results demonstrate significant differences in the ordering and use of the *TPMT* genotype test vs. phenotyping assay within a diverse, multispecialty patient population as compared with TPMT testing characteristics in a primarily pediatric cancer population. Over a 3-year period, the majority of TPMT tests in our institution were ordered by nonhematology/oncology providers in the outpatient setting, with patients more likely to undergo TPMT phenotype testing as compared with *TPMT* genotyping. Genotype–phenotype discordance was observed at a rate of 5% in patients who underwent both tests, which is consistent with discordance studies in large populations.[30,31] Both patients who had discordant test results were also taking medication(s) that could potentially inhibit the TPMT enzyme, although data are conflicting regarding the clinical relevance of drug-induced TPMT enzyme inhibition.[21,32,33] At the end of the study period, one discordant patient received azathioprine with a genotype-guided dose and the other patient did not receive a thiopurine. Use of genotype to guide thiopurine dosing in discordant patients is consistent with study findings that support increased accuracy of the *TPMT* genotype test as compared with the phenotype assay. In a large analysis of genotype–phenotype discordance, researchers found *TPMT* genotyping to be more reliable than phenotyping and recommended its use over the TPMT phenotype assay if only one test could be performed.[30]

The predominance of TPMT orders by nonpediatric hematology/oncology providers observed in our study is consistent with TPMT testing data in a diverse pediatric patient population from Manzi *et al.* at Boston Children's Hospital, who reported that over a 2-year period, nearly 90% (317 of 355) of TPMT test orders in their institution were placed by GI specialists.[19] This finding supports the need to engage both hematology/oncology and nonhematology/oncology

Table 2 TPMT test orders for patients by specialty

	Genotype only, *n* ($n = 108$)	Phenotype only, *n* ($n = 687$)	Genotype and phenotype, *n* ($n = 39$)	TPMT test order rate, mean test(s)/month
Gastrointestinal	42	425	24	14
Rheumatology	11	61	0	2
Dermatology	1	56	0	1.6
Hematology/oncology	39	1	1	1.2
Allergy/immunology	2	35	1	1.1
Hospitalist	1	18	4	0.75
Internal medicine	3	18	1	0.64
Neurology	1	14	4	0.64
Pulmonary/critical care	1	11	1	0.4
Others	7	48	3	1.7

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.

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