Institutional Profile

Pharmacogenomics

Institutional profile: University of Florida Health Personalized Medicine Program

The University of Florida (UF) Health Personalized Medicine Program launched in 2012 with *CYP2C19* genotyping for clopidogrel response at UF Health Shands Hospital. We have since expanded *CYP2C19* genotyping to UF Health Jacksonville and established the infrastructure at UF Health to support clinical implementation for five additional gene–drug pairs: *TPMT*–thiopurines, *IFNL3* (*IL28B*)–PEG IFN-α-based regimens, *CYP2D6*–opioids, *CYP2D6*/*CYP2C19*–antidepressants and *CYP2C19*–proton pump inhibitors. We are contributing to the evidence based on outcomes with genotype-guided therapy through pragmatic studies of our clinical implementations. In addition, we have developed a broad array of educational programs for providers, trainees and students that incorporate personal genotype evaluation to enhance participant learning.

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The University of Florida (UF) Health Personalized Medicine Program (PMP) was created in the spring of 2011 with a focus on pharmacogenetics. We described our program in an Institutional Profile in 2013 and provide an update in the current review [1]. The PMP is housed within the UF Clinical and Translational Sciences Institute and led by a multidisciplinary team including pharmacists, physicians, informaticians and others. As detailed previously, the guiding principles of our program include the need for informatics support within the electronic health record (EHR) for the application of genotype results to prescribing decisions, with back-up support provided by expert clinical pharmacists. In addition, we continue to believe that the most efficient manner of implementation is through a broad, pre-emptive genotyping chip, such that information can be generated at one time and used across the patient's lifespan. However, at present, the most clinically realistic approach, mainly from a reimbursement standpoint, is to genotype reactively in response to a drug order. Nonetheless, our ultimate goal is to overcome reimbursement and other barriers that hinder adoption of pre-emptive testing. In order to support sustainability of pharmacogenetic implementation, we also recognize the importance of generating data on metrics and clinical outcomes with pharmacogenetic implementation, and educating providers on appropriate interpretation and application of genotype results.

CYP2C19-clopidogrel implementation

Our initial implementation was launched in June 2012 with *CYP2C19* testing to predict clopidogrel response in patients undergoing percutaneous coronary intervention (PCI)

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at UF Health Shands Hospital (Figure 1). The rationale, process and infrastructure for this implementation have been described [1,2]. In line with our guiding principles, we initially genotyped for *CYP2C19* as part of a larger pharmacogenetic panel [3]. The test was incorporated into the routine clinical care for patients undergoing left heart catheterization so that genotype results would be available in the event that the patient proceeded to PCI. Genotype results were entered into the EHR, and additional genotypes were stored in a data repository for potential future clinical use. However, because there is no reimbursement model for preemptive pharmacogenetics testing, this approach was not sustainable when we began clinically billing for testing in 2013.

While institutional and grant support was used to establish program infrastructure, *CYP2C19* genotyping is now part of routine clinical care. The test order resides on the post-PCI order set, with testing performed in the UF Health Pathology Laboratory and results available within the EHR in 2–3 days. Clinical decision support provides a 'Best Practice Advisory' (BPA) when an order for clopidogrel is entered in the EHR for a patient with a *CYP2C19* nonfunctional allele, notifying the physician of potentially reduced clopidogrel effectiveness and recommending alternative therapy [2]. In the event that genotype results are returned after patient discharge, a clinical pharmacist communicates with the physician to discuss alternative therapy in those with a nonfunctional allele.

In spring 2016, we expanded testing to UF Health Jacksonville. Consistent with early implementation at UF Health Shands, genotyping is done for patients undergoing left heart catheterization, and testing is paid for with research funding. Testing is done using a rapid genotyping platform (Spartan RX, Spartan Biosciences Inc., ON, USA), with results available in approximately 1 h and entered into the EHR. The rapid availability of test results allows physicians to immediately prescribe genotype-informed antiplatelet therapy.

Additional implementations

We have since implemented the following gene-drug pairs: *TPMT*–thiopurines, *IFNL3* (*IL28B*)–PEG–IFN-α-based regimens, *CYP2D6*–opioids, *CYP2D6/CYP2C19*–antidepressants and *CYP2C19*–proton pump inhibitors (PPIs). Launch dates are shown in Figure 1. In each case, implementation followed physician requests for genotyping to inform prescribing decisions. Genotype tests for all but *IFNL3* were established by the UF Health Pathology Laboratories, and all genotype results are entered into the laboratory section of the EHR.

With the exception of *CYP2C19* testing for PPIs, CPIC guidelines are available for each implementation and genotype-guided recommendations provided to UF Health physicians are consistent with these guidelines [4–7]. In the absence of CPIC guidelines for *CYP2C19*–PPIs, we carefully reviewed the evidence and felt it to be sufficient to support genotype-guided PPI dosing recommendations. In particular, the efficacy of PPIs, which are metabolized by CYP2C19, is highly dependent on plasma concentration [8]. Compared with CYP2C19 poor and intermediate metabolizers, rapid and ultrarapid metabolizers have lower PPI plasma concentrations, lesser gastric acid suppression and an increased risk for treatment failure with usual PPI dosing [9,10]. A recommendation for a dose increase is provided for rapid and ultrarapid metabolizers. Clinicians are advised that usual PPI doses are expected to be effective for normal metabolizers and that lower doses may be sufficient for symptom management in PMs.

Best Practice Advisories were built in the UF Health Epic system for *TPMT* and *CYP2D6* genotypes relative to thiopurines and opioids, respectively, and additional BPAs are in process to support the *CYP2D6/CYP2C19*-selective serotonin reuptake inhibitor implementation. Collectively the approach with BPAs is that they are only triggered when the patient carries a genotype that warrants an alternative approach. For *TPMT*, the BPA

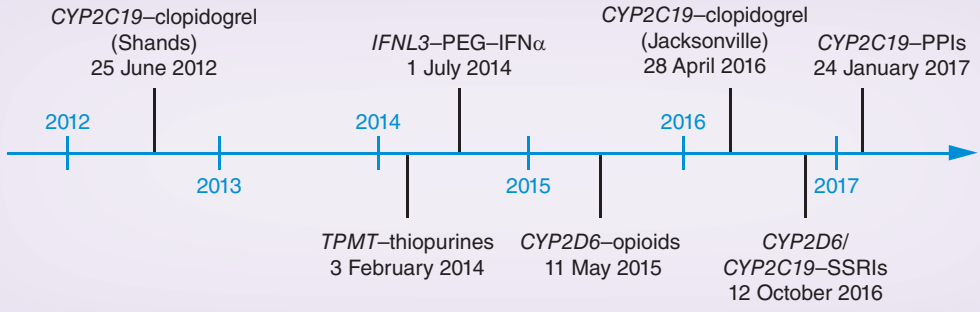

Figure 1. Timeline of launch of pharmacogenetic implementations at University of Florida Health.

Table 1. Pharmacogenetic tests ordered at University of Florida Health.

Test	Drug	Number of tests†	Ordering service
CYP2C19	Clopidogrel	1694	Cardiology, UF Health Shands
		634	Cardiology, UF Health Jacksonville
		13	Neurology, neurosurgery
TPMT	Thiopurines	43	Hematology/oncology
		67	Gastroenterology
		42	Other (e.g., dermatology, rheumatology, neurology, internal medicine, family medicine, surgery, neurology)
IFNL3	PEG–IFN-α-based regimens	96	Gastroenterology
CYP2D6	Opioids	202	Family medicine
		33	Internal medicine
		34	Chronic Pain Clinic
		3	Adult oncology
CYP2D6	SSRIs	12	Psychiatry
CYP2C19	SSRIs	13	Psychiatry
CYP2C19	Proton pump inhibitors	No data yet available	Gastroenterology

†Number of orders through 31 December 2016. All tests are available clinically, and the number of orders reflects both those ordered in association with research protocols and those ordered for routine clinical care. All orders for *CYP2C19*–clopidogrel, *TPMT* and *IFNL3* tests at UF Health in Gainesville are for routine clinical care.
ALL: Acute lymphoblastic leukemia; GERD: Gastroesphogeal reflux disease; PCI: Percutaneous coronary intervention; SSRI: Selective serotonin reuptake inhibitor.

recommends lower thiopurine doses for those with a single nonfunctional allele and either lower doses or consideration of alternative therapy for those homozygous for two nonfunctional alleles. For *CYP2D6* genotype, the BPA is in response to a codeine or tramadol order for a patient with a genotype associated with poor or ultrarapid metabolism. The advisory warns about the risk for reduced effectiveness for poor metabolizers or risk for toxicity for ultrarapid metabolizers and suggests that an alternative opioid that does not rely on CYP2D6 metabolism be prescribed. The clinical pharmacist also tracks those with actionable *CYP2D6* genotypes relative to other pain medications (e.g., oxycodone, hydrocodone) and may also recommend alternative treatment approaches. For *IFNL3* testing, pharmacists are alerted to the test order by the EHR and follow-up with the ordering provider to give guidance on test interpretation and application.

Table 1 shows the number of genotype tests ordered through December 2016 for each implementation described above. PMP pharmacists are also alerted via the EHR to inpatient and outpatient genotypes ordered outside of a clinical implementation (e.g., *CYP2C19* testing for clopidogrel response by neurology). For these, PMP pharmacists consult with the ordering clinician to provide recommendations for interpreting and applying the genetic test results in the patient's care plan.

Building evidence for sustainability of pharmacogenetics implementation

Our view is that evidence of clinical utility from randomized controlled trials is not required prior to clinical pharmacogenetic implementation. Rather, we believe that strong and consistent genotype associations with drug response and the availability of alternative therapy or dosing for patients with genotypes predictive of poor response or increased toxicity to traditional therapy are sufficient to support implementation. However, recognizing that evidence that genotype-guided therapy positively impacts outcomes is important for sustainability of the program, we have taken a pragmatic approach to examining patient outcomes with several of our implementations.

CYP2C19–clopidogrel

After the first 2 years of program launch, we examined the occurrence of major adverse cardiovascular events in patients undergoing PCI and *CYP2C19* testing. We found that, among patients with a nonfunctional allele, the risk for the composite outcome of death, myocardial infarction, stroke or stent thrombosis was significantly lower among patients treated with alternative therapy (e.g., prasugrel or ticagrelor) versus clopidogrel [11]. More recently, we collaborated with six other institutions as part of the NIH-funded IGNITE Network Pharmacogenetics Working Group to examine

outcomes with *CYP2C19* genotype-guided antiplatelet therapy in a larger population. Results were consistent with our earlier observation and reported at the 2016 American Heart Association Scientific Sessions [12].

CYP2D6–opioids

Outcomes with genotype-guided opioid prescribing are being evaluated in two separate studies. In one study, adult patients with chronic pain are recruited from primary care clinics, serving as implementation or control sites (ClinicalTrials.gov identifier: NCT02335307). Patients from implementation sites undergo *CYP2D6* genotyping, with results placed in the EHR and genotype-guided recommendations provided by a pharmacist via a consult note. The other study focuses on cancer-related pain and is being conducted in collaboration with H Lee Moffitt Cancer Center and Research Institute in Tampa, Florida. Patients with advanced cancer are randomized to genotype-guided versus traditional pain management (ClinicalTrials.gov identifier: NCT02664350). Genotype results for the genotype-guided arm are placed in the EHR and accompanied by recommendations for consideration of opioids that are not metabolized by CYP2D6 for poor, intermediate and ultrarapid metabolizers. The primary end point for both studies is patient-reported pain-related outcomes, with the hypothesis that genotype-guided pain management will lead to better pain control compared with usual pain management. The studies are expected to be completed in late 2017.

CYP2C19–PPIs

A comparative effectiveness study, in collaboration with Nemours Children's Hospital in Orlando, Florida, is testing the hypothesis that genotype-supported treatment of gastroesophageal reflux disease and dyspepsia will lead to better symptom control compared with conventional treatment (ClinicalTrials.gov Identifier: NCT02930824). Patients who are being started on a PPI or who have continued symptoms on current PPI therapy are randomized to a genotype-supported strategy, with *CYP2C19* genotype information integrated into treatment decisions, versus conventional management. We expect to complete data collection for the target population of 180 patients by mid-2017.

CYP2D6/*CYP2C19*–antidepressants

Within the pediatric psychiatry clinic, we are conducting a prospective randomized trial to examine the feasibility and acceptability of *CYP2D6* and *CYP2C19* testing to guide treatment of depression. Children and adolescents with major depression, anxiety or obsessive compulsive disorders are randomized to receive pharmacogenetic testing prior to starting or changing antidepressant medication or to usual treatment. Both clinician and parent understanding and acceptance of pharmacogenetic testing will be assessed, as will outcomes related to comfort with initiating medications and medication adherence.

Educational initiatives

The PMP's educational initiatives for providers incorporate principles of active learning and use of personal genotype information. Provider education for an implementation starts with a small group of key stakeholder clinicians and focuses on evidence review and developing the clinical recommendations for specific gene–drug pairs. We then expand educational efforts to include large provider groups (such as at departmental grand rounds presentations), trainees, nursing and administrative staff, to educate target audiences and support uptake and operationalizing of the clinical implementation. In addition, practice-based resources (e.g., genotype-guided dosing charts, patient education materials) are created for providers to assist with drug therapy changes and patient education within each implementation. On a broader scale, the PMP hosted the first UF Precision Medicine Conference in 2016 to reach providers across the nation, which will be offered again in 2017. To date, 249 providers have participated in PMP educational programs that included personal genotype evaluation.

The PMP has also developed educational offerings for post-graduate trainees and students. We currently offer one of only two accredited Post-graduate Year Two yearlong pharmacist training programs in pharmacogenetics, which has graduated five residents to date. Five additional postgraduate trainees have completed 4-week rotations in clinical pharmacogenetics. The PMP has also reached student pharmacists, with the development of a novel elective course currently in its fourth year that incorporates student genotype evaluation. Teaching approaches used in this course led to improved clinical pharmacogenetics knowledge and an increased student understanding of pharmacogenomics based on having undergone genotyping [13]. To date, 135 students have participated in these courses, including personal genotyping. Research efforts in this area are ongoing to further examine various teaching methods and use of personal genotype evaluation in broader multidisciplinary provider audiences.

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