University of Florida Health Personalized Medicine Program

1. Abstract

Rationale. There is significant evidence supporting incorporation of genotype data into drug prescribing decisions. However, barriers such as uncertainty about when to order genotyping, how to act on results, and the paucity of data on outcomes with pharmacogenetic testing have hindered clinical uptake of pharmacogenetics. The University of Florida (UF) Health Personalized Medicine Program (PMP) was formed in 2011 to overcome these barriers and facilitate clinical adoption of pharmacogenetic testing with the ultimate goal of the improving patient outcomes through better informed prescribing decisions.

Methods. The UF Health PMP's first clinical implementation began 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 (mercaptopurine, azathioprine, thioguanine), *IFNL3* (*IL28B*)–PEG IFN-α-based regimens, *CYP2D6*–opioids, *CYP2D6/CYP2C19*–selective serotonin reuptake inhibitors, and *CYP2C19*–proton pump inhibitors. We are generating data on clinical outcomes with pharmacogenetic testing through pragmatic clinical trials and investigations of our clinical implementations. In addition, we recently established a pharmacist-led Pharmacogenetics Consultation Clinic to optimize drug therapy plans for referred patients based on genotype results. We also provide educational programs for providers, trainees, and students that incorporate personal genotype evaluation to enhance participant learning and have one of only two ASHP-accredited PGY2 residencies in pharmacogenetics.

Results. To date, over 4,600 clinical pharmacogenetic tests have been ordered at UF Health, with testing in children, adults, inpatients, and outpatients. This includes 31 tests ordered for patients referred to our recently established Pharmacogenetics Consultation Clinic. Among patients undergoing *CYP2C19* genotyping at the time of percutaneous coronary intervention, we found significantly fewer major adverse cardiovascular events among patients with a loss-of-function allele treated with alternative antiplatelet therapy versus clopidogrel (1.5% vs 10.3%, adjusted p value=0.034). These data led to a larger, multi-site trial that confirmed our initial finding. In a pragmatic trial of *CYP2D6* genotype-guided opioid management versus usual care in patients with chronic pain, we observed a greater reduction in pain intensity among genotyped patients with the poor or intermediate metabolizer phenotype taking tramadol, codeine, or hydrocodone at baseline (-1.09±1.53, or 16% reduction versus -0.28±1.17 or 2% reduction, adj p=0.016). In terms of our educational initiatives, six residents have completed our PGY2 residency, and we have offered a personalized medicine elective course in the Pharm.D. curriculum that includes personal genotype evaluation for 4 consecutive years to over 220 students. We have also hosted a CPE- and CME-accredited Precision Medicine Conference for the third consecutive year, with over 490 total attendees from 32 states and 5 countries.

Conclusion. We have successfully implemented pharmacogenetics in practice for a number of gene-drug pairs and developed a broad array of programs to educate and train current and future providers on how to integrate genotype data into prescribing decisions. Data from our pharmacogenetic implementations support improved clinical outcomes with both *CYP2C19* genotype-guided antiplatelet therapy and *CYP2D6* genotype-guided opioid prescribing. Such data, in addition to educational efforts, are important for supporting broader uptake and sustainability of pharmacogenetics in practice.

2. Medication-Use System Initiative/Scope. Medication safety problem or challenge**.** Adverse drug effects are associated with significant morbidity, mortality, and healthcare costs.[1] Genotype influences the risk for adverse drug effects. For example, *TPMT* genotype is well documented to influence risk for hematologic toxicity with thiopurines.[2] Similarly, *CYP2D6* genotype is predictive of risk for life-threatening respiratory depression with select opioids and also influences the likelihood for adverse drug effects from certain selective serotonin reuptake inhibitors (SSRIs).[3,4] In the case of *CYP2C19* genotype and clopidogrel, approximately 30% to 60% of the population inherits a deficiency in CYP2C19 which reduces the effectiveness of clopidogrel in preventing major adverse cardiovascular effects, including death, myocardial infarction, and stroke.[5] The FDA has highlighted this risk through a boxed warning. Despite evidence supporting incorporation of genotype data into drug prescribing decisions to reduce the occurrence of adverse drug effects and improve patient outcomes, barriers such as uncertainty about when to order genotyping and how to act on results have hindered clinical uptake of pharmacogenetics. The University of Florida (UF) Health PMP was formed in 2011 to overcome these barriers and facilitate clinical adoption of pharmacogenetic testing with the ultimate goal of the improving patient outcomes and reducing adverse drug effects through better informed prescribing decisions.

Scope of medication safety improvement initiative. The UF Health PMP is housed within the UF Clinical and Translational Science Institute (CTSI) and is a pharmacist-led multidisciplinary team effort focused on integrating genotype results as part of routine care to guide prescribing decisions. There are several guiding principles of the program, as we have previously described.[6,7] First, there is a need for clinical decision support within the electronic health record (EHR) and clinical pharmacist consults for the translation of genotype results into appropriate prescribing decisions. Second, we believe that ultimately the most efficient means of pharmacogenetic implementation is through the use of a pre-emptive genotyping chip, so that genetic information can be generated once and used throughout a patient's life. However, primarily because of reimbursement issues, reactive genotyping at the time of a drug order is the most realistic approach at present. Our goal, therefore, is to overcome barriers, including reimbursement, that hinder pre-emptive testing.[8] In fact, we are currently validating a platform for pre-emptive multi-gene testing. Third, we recognize that data on outcomes with pharmacogenetic testing are necessary for broader adoption and sustainability. Finally, an educated workforce is necessary to ensure appropriate interpretation and application of genotype results to prescribing decisions.

Components of medication safety improvement initiative. The first clinical implementation launched in June 2012 with *CYP2C19* genotyping to predict clopidogrel response in patients undergoing percutaneous coronary intervention (PCI) at UF Health Shands Hospital, and we have described the rationale, process, and infrastructure of this implementation.[6] We have since expanded *CYP2C19* testing to our Jacksonville campus and established the infrastructure to support implementation of five additional gene–drug pairs **(Figure 1)**. **In line with one of the priority areas for the ASHP program, this includes *CYP2D6* genotyping to better inform opioid prescribing.** Pharmacists have integral roles in each step of the implementation process, from selection of gene-drug pairs for implementation to providing genotype-guided recommendations and monitoring for implementation metrics and clinical outcomes, as detailed in Section 4. **Through collaboration with physicians on the leadership team and within each implementation area, in addition to genotyping experts, informaticians, and others, we have successfully implemented testing across the health system, with over 4,600 pharmacogenetic tests ordered at UF Health to date, including testing in children, adults, inpatients, and outpatients.** We also recently established a pharmacist-led Pharmacogenetics Consultation Clinic to optimize drug therapy plans for referred patients based on genotype

results. We also provide educational programs for providers, trainees, and students that incorporate personal genotype evaluation[9] and have one of only two ASHP-accredited PGY2 residencies in pharmacogenetics.

3. Pharmacist Leadership. The leadership team structure is shown in **Figure 2**. Julie Johnson, PharmD, Distinguished Professor and Dean of the College of Pharmacy serves as Director of the PMP and has an international reputation in pharmacogenetics, particularly in the areas of hypertension, heart failure, and anticoagulation. Kristin Weitzel, PharmD and Larisa Cavallari, PharmD serve as Associate Directors of the PMP. Dr. Weitzel, Clinical Professor of Pharmacotherapy and Translational Research, is a leader in genomic medicine education and director of the PGY2 Pharmacogenetics Residency. Dr. Weitzel has played a critical role in the program since 2013 and led the launch of several of the pharmacogenetic implementations at UF Health in Gainesville, including *TPMT* genotyping for thiopurine dosing. [10] She also chairs the PMP Advisory Committee, which consists of pharmacists, physicians, and genetic experts, and serves to review the evidence supporting genetic associations with drug response and provide recommendations for implementation priorities and procedures. In addition, she works closely with the pharmacogenetic resident to review genotype results and provide recommendations for genotype-guided therapies. Dr. Cavallari, Associate Professor of Pharmacotherapy and Translational Research, has a long record of research in pharmacogenetics and an extensive record in warfarin pharmacogenetics in minority populations and in heart failure pharmacotherapies. She led the implementation on genotype-guided warfarin dosing in her previous position at the University of Illinois at Chicago.[11] Since joining UF in 2014, she led implementation of *CYP2D6* testing for opioids and *CYP2C19* testing for PPI dosing. She also leads many of the research initiatives within the PMP, including the investigation of outcomes with *CYP2C19*-guided antiplatelet prescribing, *CYP2D6*-guided pain management, and *CYP2C19*-guided PPI dosing.[12-15] Other members of the leadership team include Dr. David Nelson, Professor of Medicine, Assistant Vice President for Research, and Director of the CTSI, Dr. Michael Clare-Salzler, Professor of Medicine and Director of Molecular Pathology, and Amanda Elsey, MHA, Assistant Director of the program.

Many more individuals are involved in each implementation, including physicians on services where testing is implemented, clinical pharmacy staff, and experts in ethical and regulatory issues, genetics, and informatics. Most notably, Meghan Arwood, PharmD, directs the newly established Pharmacogenetics Consult Clinic, and Benjamin Staley, PharmD, leads the integration of pharmacogenetic clinical decision support tools into the EHR. We further describe pharmacist roles in PMP initiatives in Section 4 and metric and outcome data in Section 5.

4. Planning and Implementation. Pharmacy leadership and level of involvement**.** Pharmacy leadership roles in each implementation step are shown in **Figure 3**. Each implementation required a multi-disciplinary team approach. The leadership team (described in section 3) engages physicians in the area of interest, experts in genetics, and health informaticists for each implementation. In most cases, physician interest in obtaining genotype data to assist with prescribing decisions sparked pharmacogenetic implementation. For example, implementation of *CYP2D6* genotyping was primarily driven by primary care physicians requesting genetic data to guide opioid prescribing in patients with chronic pain and antidepressant prescribing in children.

Team-based approach. The implementation process has been published.[6] Following evidence evaluation and consultation with the PMP Advisory Committee, pharmacists on the leadership team work with Molecular Pathologists at UF Health to establish genotyping procedures. Dr. Michael Clare-Salzler is a Molecular Pathologist on the PMP Leadership Team who facilitates

communication with the pathology group. PMP pharmacists also engage experts in health informatics to build electronic clinical decision support tools, and Ben Staley, PharmD, serves a critical role in this regard. A major component of each implementation is provider education, which is led by Dr. Weitzel and delivered in a variety of formats as described below. Finally, led by Drs. Cavallari and Johnson and facilitated by Dr. Almut Winterstein, Chair of the Department of Pharmaceutical Outcomes and Policy, procedures are established for pharmacists to track implementation metrics and clinical outcomes. Important implementation success metrics tracked include the following:

- % of patients eligible for the genotype test who have it ordered by the physician
- % of patients with a clinical genotype successfully reported
- turnaround time from sample collection to population of genotype data in the EHR
- % of patients with a genotype leading to a recommendation for alternative therapy
- % of patients in whom a genetic-guided recommendation is accepted by the clinician

Two papers describing implementation metric data have been published to date,[6,10] with a third (describing the *CYP2C19*-clopidogrel implementation at UF Health Jacksonville) in press and a fourth (describing the *CYP2D6*-opioid implementation) in progress. Pharmacists serve as first authors on all of these, with additional pharmacists in contributing author roles.

Pharmacogenetic Implementations. *CYP2C19-clopidogrel implementation at UF Health Shands Hospital*. For our initial *CYP2C19*-clopidogrel implementation, the genotype test was first 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. Consistent with our guiding principles, *CYP2C19* was genotyped as part of a larger panel of pharmacogenes. *CYP2C19* genotype results were entered into the EHR, and additional genotypes were stored in a data repository for potential future clinical use. However, we encountered barriers with this approach after the initial year of the program in that no reimbursement model existed for preemptive pharmacogenetic testing. Therefore, when we began clinically billing for testing in 2013, we could only bill for *CYP2C19* testing for patients undergoing PCI. At that time, the genotype test order was moved to the post-PCI order set, with results available within the EHR in 2 to 3 days. Patients can access their genotype results through the patient portal of the EHR, and education materials are available through the program's website (http://personalizedmedicine.ufhealth.org). Problems with the genotyping chip led us to switch from panel based testing to *CYP2C19* testing without additional genotypes. However, we are in the process of validating a new chip in order to return to panel based testing.

CYP2C19 intermediate metabolizers (IMs) and poor metabolizers (PMs), with one or two loss-of-function alleles, respectively, have impaired ability to bioactivate clopidogrel, lower concentrations of the pharmacologically active metabolite, and lesser inhibition of platelet aggregation with clopidogrel. Studies have consistently demonstrated reduced clopidogrel effectiveness at preventing adverse cardiovascular events, including death, myocardial infarction, and stroke, after PCI in PMs and IMs.[5,16] Thus, a clinical pharmacist reviews each genotype result and follows up with providers to recommend alternative antiplatelet therapy (prasugrel or ticagrelor) after PCI for IMs and PMs in the absence of contraindications. In addition, we built electronic clinical decision support in the form of a "Best Practice Advisory" or BPA in the EHR, which appears if clopidogrel is ordered for a patient with the PM or IM phenotype, notifying the physician of potentially reduced clopidogrel effectiveness and recommending alternative therapy.[6]

CYP2C19-clopidogrel implementation at UF Health Jacksonville. We expanded *CYP2C19* testing to UF Health Jacksonville in the Spring 2016, with testing done using a rapid genotyping platform for patients undergoing left heart catheterization. Results are available in approximately one hour, allowing physicians to immediately prescribe genotype-informed antiplatelet therapy.

Other implementations. Once the *CYP2C19*-clopidogrel implementation infrastructure was in place, it facilitated implementation of additional gene-drug therapies **(Figure 1)**. The populations receiving pharmacogenetic testing and locations of testing are shown in **Table 1**. Genotype tests for all but *IFNL3* were established by the UF Health Pathology Laboratories, with all genotype results entered into the laboratory section of the EHR. To date, BPAs have been built for the *TPMT*-thiopurines, *CYP2D6*-opioids, and *CYP2D6/CYP2C19*-SSRI implementations. For each, BPAs only trigger when the patient carries a genotype that warrants an alternative drug or dosing approach. For *TPMT*, the BPA recommends lower thiopurine doses for patients with a single loss-of-function allele and either lower doses or consideration of alternative therapy for those homozygous for two loss-of-function alleles to minimize risk for hematologic toxicity. A manuscript describing the *TPMT*-thiopurine implementation was recently published.[10] For *CYP2D6* genotype, the BPA triggers in response to a codeine or tramadol order for a patient with a genotype associated with poor or ultra-rapid metabolism. The advisory warns about the risk for reduced effectiveness for PMs, who cannot convert codeine or tramadol to its active metabolite responsible for analgesic effects, and risk for toxicity for ultra-rapid metabolizers (UMs) and suggests that an alternative opioid that does not rely on CYP2D6 metabolism be prescribed.

We have overcome unique challenges with each implementation, with examples provided below:

- Because there are no phlebotomists in most clinics, we validated *CYP2D6* and *CYP2C19* testing from buccal cells to facilitate genotype collection in the outpatient setting. This was particularly important with our implementation of *CYP2D6/CYP2C19* testing to guide antidepressant prescribing in children and adolescents in the Pediatric Psychiatry Clinic in that children are particularly adverse to needle sticks.
- The *CYP2D6/CYP2C19*-SSRI implementation was also challenging from an electronic clinical decision support perspective in that variants in two genes had to be considered for multiple drugs.
- An ongoing challenge with the *CYP2D6* genotype implementation is that a number of drugs inhibit the CYP2D6 enzyme and can essentially convert patients with a normal *CYP2D6* genotype to poor or intermediate metabolizers. Thus, genotype has to be considered in the context of drug interactions when providing recommendations. To address this challenge, clinical pharmacists provide consult notes to the prescribing physician that take both genotype and interacting medications into account.

Pharmacogenetic Consultation Clinic. In September 2017, the PMP launched the outpatient Pharmacogenetics Consultation Clinic at the UF Health Internal Medicine clinic at Tower Hill (IMTH), in which IMTH providers refer patients for a face-to-face consult with Dr. Meghan Arwood leading this effort. As part of a collaborative practice agreement with IMTH physicians, Meghan Arwood, PharmD, verifies the need for pharmacogenetic testing, orders appropriate pharmacogenetic test(s), provides pharmacogenetics-based drug therapy recommendations to the referring provider, and educates patients and providers on implications of pharmacogenetic test results for a variety of therapeutic areas (e.g., psychiatry, gastroenterology, pain management, cardiology). By integrating the use of pharmacogenetic data into routine primary care practice, this innovative clinic aims to improve quality of care by reducing the trial-and-error approach to prescribing, and ultimately to improve drug-related outcomes.

The Pharmacogenetics Consult Clinic has been well received thus far by patients, one of whom stated, “this is the future of medicine.” Based on preliminary results of patient survey data, 13/14 (93%) patients agreed/strongly agreed that they would recommend pharmacogenetic testing to others based on their experience in this clinic. Notably, approximately 10% (2/21) of patient referrals to date have been due to word of mouth from previous patients, supporting patients’ high level of satisfaction with the clinic. Of the 21 referred patients, 16 patients have been genotyped, 1 patient had previous genotype results, 2 patients did not receive genotyping (inappropriate indication), and 2 patients have future scheduled visits.

Educational initiatives. Recognizing the critical importance of educating current and future providers on clinical use of genotype data to guide prescribing, the PMP has conducted a number of educational initiatives for pharmacists, physicians, nurses, students, and trainees. At a local level, educational efforts include traditional approaches, such as grand rounds and nursing in-services, and novel approaches, including CPE- and CME-accredited programs that incorporate personal genotyping and pharmacogenetic case conferences. On a broader scale, the PMP hosts the UF Precision Medicine Conference to reach providers nationally and internationally. The first conference took place in Orlando March 2016 and has occurred annually since then. Attendees are mailed genotyping kits ahead of the conference, and those desiring personal genotyping are provided with their results at the conference to facilitate case-based discussions and active learning. To date, over 490 total attendees from 32 states and 5 countries have attended the Precision Medicine Conference.

The PMP offers one of only two accredited PGY2 pharmacogenetics residency programs, which has graduated six residents to date. A recent NIH-funded Precision Medicine T32 Training Program will enhance the two decades-long record of training post-PharmD fellows in pharmacogenetics within our group. The PMP has also reached student pharmacists, with the development of a novel elective course currently in its fifth year that incorporates student genotype evaluation. Teaching approaches used in this course led to improved clinical pharmacogenetics knowledge and an increased student understanding of pharmacogenetics based on having undergone genotyping.[9] To date, over 220 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.

5. Measurable Outcomes and Impact. CYP2C19-clopidogrel implementation at UF Health Shands Hospital. Metrics with our initial implementation were published and showed that 84% of PCI patients were genotyped, with approximately 30% having the IM or PM phenotype. Seventy percent of IMs/PMs were switched to prasugrel or ticagrelor.[6] After the first 2 years of program launch, we investigated the occurrence of major adverse cardiovascular events (MACE) in patients undergoing PCI and *CYP2C19* testing. Kaplan-Meier analysis and Cox regression modeling adjusting for propensity scores were performed to compare MACE between loss-of-function (LOF) genotype carriers prescribed prasugrel or ticagrelor versus clopidogrel. We found that among patients with a loss-of-function allele, the risk for MACE, defined as the composite of death, myocardial infarction, stroke, or stent thrombosis, was significantly higher among patients treated with alternative antiplatelet therapy (e.g., prasugrel or ticagrelor) versus clopidogrel (10.3% vs 1.5%, p=0.012) and remained lower after multivariable Cox regression (p=0.034). These data were presented by Dr. Cavallari at the 2015 American Heart Association Scientific Sessions.[12]

These data prompted a multi-institutional study of outcomes with *CYP2C19*-guided antiplatelet therapy, led by Drs. Cavallari and Johnson. This study was done as part of the NIH-funded Implementing Genomics in Practice (IGNITE) Network Pharmacogenetics Working Group, led by Dr. Cavallari.[17] Results were consistent with our earlier observation and reported by Dr. Cavallari as a Late Breaking Clinical Special Report at the 2016 American Heart Association Scientific Sessions and were recently published in *JACC Cardiovascular Interventions*.[13] Specifically, among 1,815 patients who underwent PCI and *CYPC19* genotyping at 7 institutions across the U.S., 31.5% had a loss-of-function allele. The risk for MACE (defined as death, myocardial infarction, and stroke) was significantly higher in patients with a loss-of-function allele prescribed clopidogrel versus alternative antiplatelet therapy (23.4 vs. 8.7 per 100 patient-years; adjusted hazard ratio: 2.26; 95% confidence interval: 1.18 to 4.32; p=0.013; **Figure 4**]. Similar results were observed among 1,210 patients with an acute coronary syndrome at the time of PCI (adjusted hazard ratio: 2.87; 95% confidence interval: 1.35 to 6.09, p=0.013). There was no difference in MACE between patients without a loss-of-function allele and loss-of-function allele carriers prescribed alternative therapy (adjusted hazard ratio: 1.14, 95% confidence interval: 0.69 to 1.88, p=0.60)**.**

We also helped lead a multi-site *CYP2C19* guided antiplatelet therapy implementation strategies manuscript and an economic analysis of *CYP2C19* testing based on the outcomes data presented above.[18] The economic analysis showed that a genotype-guided strategy to antiplatelet therapy after PCI was cost savings compared with both universal alternative antiplatelet therapy and universal clopidogrel use. These results were presented at the 2017 meeting of the Society of Medicine Decision Making,[19] with a manuscript in process.

CYP2C19-clopidogrel implementation at UF Health Jacksonville*.* After the first year of genotyping patients at UF Health Jacksonville undergoing left heart catheterization using the Spartan RX™ system, we examined testing metrics, provider acceptance of testing and response to genotype results, and antiplatelet therapy over the 6 months following genotyping. In the first year, 931 patients, including 392/505 (78%) total patients undergoing PCI, were genotyped. The median genotype test turnaround time was 96 minutes. Genotype results were available for 388 (99%) PCI patients prior to discharge. Of 336 genotyped PCI patients alive at discharge and not enrolled in an antiplatelet therapy trial, 1/6 (17%) PMs, with 2 loss-of-function alleles, 38/93 (41%) IMs, with one loss-of-function allele, and 119/237 (50%) patients without a loss-of-function allele were prescribed clopidogrel (p=0.110). Six months later, among patients with follow-up data, clopidogrel was prescribed in 0/4 (0%) PMs, 33/65 (51%) IMs, and 115/182 (63%) patients without a loss-of-function allele (p=0.008 across groups; p=0.020 for PMs versus those without a loss-of-function allele). These data demonstrate that rapid genotyping is clinically feasible at a high volume cardiac catheterization facility and allows informed chronic antiplatelet prescribing, with lower clopidogrel use in PMs at 6 months. A manuscript describing these data is in press in the *Journal of Translational Medicine*.

CYP2D6-opioid implementation. When we implemented *CYP2D6* testing clinically, we simultaneously initiated a pragmatic clinical trial to assess effects of *CYP2D6* genotype-guided opioid prescribing on patient-reported pain outcomes in adults with chronic pain (≥3 months pain) (ClinicalTrials.gov Identifier: NCT02335307). Patients were recruited from primary care clinics in the UF Health or affiliated OneFlorida Network, serving as implementation (n=5) or control (n=4) sites. Of 480 total study patients, 320 from implementation sites underwent *CYP2D6* genotyping, with results available about 7 days after the baseline clinic visit and placed in the EHR. Patients were defined as CYP2D6 UMs, NMs, IMs or PMs based on their *CYP2D6* genotype and use of strong or moderate CYP2D6 inhibitors. A clinical pharmacist-written consult note was provided on all patients with an actionable (PM, IM, or UM) and non-actionable

(NM) phenotype. Strong recommendations were made in IMs and PMs against tramadol and codeine, where the impact of CYP2D6 is clear. Recommendations against oxycodone and hydrocodone were more moderate. Acceptance of the recommended changes was at the physician's discretion. The remaining 160 enrolled patients (controls) received usual pain management during the study and were genotyped at the end. Change in pain intensity was assessed via the NIH-developed and validated Patient Reported Outcomes (PRO) Measures Information System (PROMIS) pain measures at baseline and 3 months and compared between genotyped and control patients.

Average baseline pain score was 6.7/10 in both groups indicating most had poorly controlled pain. A total of 438/480 (91%) patients were taking an opioid at baseline, with 90% taking tramadol, hydrocodone, codeine, or oxycodone. When considering CYP2D6 phenotype, based on genotype and drug interactions, 28% were IMs or PMs. 69 patients had a PM or IM phenotype and were receiving codeine, tramadol, or hydrocodone at baseline. We would expect these patients to have little to no pain relief from their opioid therapy. In these patients, we observed significant reductions in multiple measures of pain intensity in the genotype versus control group **(Figure 5)**, supporting improved patient reported outcomes with genotype-guided opioid prescribing. A clinically meaningful 30% reduction in pain score was observed in 16% of genotype guided versus 0% of usual care patients (p=0.10). Trends were also observed for sleep disturbance (p=0.076) and physical functioning (p=0.11), with patients in the genotype-guided arm doing better in each case. When limiting the analysis to IMs and PMs on codeine or tramadol, a 30% reduction in pain score was observed in 23% of genotype-guided versus 0% of usual care patients (p=0.04). No differences were observed in pain measures by study arm for oxycodone, suggesting CYP2D6 may be less important for oxycodone than for codeine, tramadol, and hydrocodone. These data were presented at the American Society of Clinical Pharmacology and Therapeutics meeting in March 2018,[14] with a manuscript expected to be submitted by mid-2018.

Ongoing trial of CYP2D6-guided pain management for cancer patients. A second pragmatic clinical trial evaluating outcomes with *CYP2D6* genotype-guided management of cancer-related pain is ongoing at UF Health in Gainesville and being conducted in collaboration with H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida (ClinicalTrials.gov Identifier: NCT02664350). A paper describing the rationale and design of the trial was recently published.[15] Briefly, patients with advanced cancer are randomized to genotype-guided versus traditional pain management. Similar to the study in chronic pain, genotype results for the genotype-guided arm are available within approximately 7 days and placed in the EHR. For PMs, IMs, and UMs, a clinical pharmacist provides an electronic consult note with recommendations to consider alternative opioids that are not metabolized by CYP2D6. The primary endpoint is patient-reported pain-related outcomes, with the hypothesis that genotype-guided pain management will lead to better pain control compared to usual pain management. The study is expected to be completed in late 2018.

Pharmacogenetic Consult Clinic Data. Of the 17 clinic patients with genotype results to date, 76% (13/17) had at least one actionable genotype, which is much more frequent than would be expected based on population data. For instance, of patients tested for *CYP2D6*, 19% have been PMs, which is at least twice as high as the population frequency (5-10% of the population are PMs). Thus far, most referrals have been for patients with genotypes that make "normal dosing" less than optimal. And although the providers do not know the patient's genotype before referring, they appear to be correctly identifying patients who may be difficult to treat based on genotype. This argues that not only has our education to the providers been successful on the

types of patients to refer to our clinic, but that by getting patients' genotypes earlier, we can reduce the trial-and-error approach to prescribing.

Next steps. Based on our positive data in chronic pain patients, we are planning to implement *CYP2D6* testing to guide opioid prescribing for patients with acute pain. This will initially be piloted in patients undergoing arthroplastic surgery. These patients have two pre-operative visits, providing an opportunity to obtain a sample for genotyping prior to surgery so that results may be available at the time of the procedure to inform post-operative pain management.

6. Innovation and Generalizability. Innovation**.** Our pharmacist-led program is innovative in several respects. First, we have substantial engagement from stakeholders, including pharmacists, physicians, patients, and UF Health administrators. Second, it includes testing across age groups and inpatient/outpatient settings for multiple gene-drug pairs **(Table 1)**. Third, we have developed innovative educational programming with personal genotyping offered both within and outside the UF Health setting and across multiple disciplines, settings, and levels of trainees/clinicians. Fourth, we were the first to report on outcomes with genotype-guided antiplatelet prescribing and genotype-guided opioid prescribing. In both cases, outcomes were improved with genotype-guided approaches. Fifth, we have launched a comprehensive, referral-based Pharmacogenetics Consult Clinic, in which we have integrated pharmacogenetic testing into routine outpatient practice in the primary care setting, an endeavor that only a handful of sites across the country have taken on.

Sustainability. Our clinical program has been in existence since 2012, with *CYP2C19* testing after PCI being the most mature. *CYP2C19* testing for clopidogrel continues to be paid for by UF Health Shands Hospital under the Diagnosis Related Group based on our evidence that genotyping and prescribing alternative therapy versus clopidogrel after PCI reduces the risk for adverse cardiovascular events.[12,20] Importantly, we observed that the majority of events occurred in the first 30 days following PCI, which has important implications given the Center for Medicare and Medicaid Services Hospital Readmission Reduction Act in which hospitals can be penalized for readmissions in the 30 days following discharge. Tests conducted in the outpatient setting can be billed to third party payers, and our data show that 85% of tests billed are reimbursed on some level.[6]

Adoption in other hospitals. We have implemented *CYP2C19* genotyping in the cardiac catheterization laboratories of two hospitals in Gainesville in Jacksonville. While they both carry the UF Health brand, and the physicians are UF faculty, UF Health Jacksonville is otherwise a unique entity. Specifically it has its own dean of medicine, a different faculty group practice, their own clinical operations, financial structure and revenue streams among many other things that are unique and independent from the operations at UF Health Shands Hospital in Gainesville. There are also differences in patient populations. Whereas Gainesville is a suburban, college town with a mostly white, higher income patient population, the downtown urban core of Jacksonville, where this hospital is located, has the largest number of minorities, lowest household income and level of education, and highest unemployment rate in the city. UF Health Jacksonville is a state designated safety-net hospital for the medically underserved, and a high percentage of patients served are Medicaid recipients or uninsured. We also used a different genotyping approach in Jacksonville, with a rapid turn-around genotyping approach, allowing results to be available before discharge, and in some cases, before the patient leaves the catheterization laboratory.

We have learned important lessons from our experience with *CYP2C19*-guided antiplatelet therapy at the two hospitals as summarized below:

- Delays in obtaining genotype results can create significant disruptions in workflow that can be minimized when genotype results are available early after PCI.
- Rapid genotyping is feasible for sites where the cardiac catheterization laboratory is in close proximity to the clinical pathology laboratory.
- Genotype is important to inform switches from clopidogrel to prasugrel or ticagrelor in patients with a loss-of-function allele.
- Genotyping can also inform de-escalation from more potent $P2Y_{12}$ inhibitors to clopidogrel in patients without a non-functional allele.
- Clinical pharmacist and electronic decision support is important in settings where return of genotype results is delayed.
- Clinical pharmacist and/or electronic decision support may be necessary in settings where rapid genotyping is available to assist with decisions regarding antiplatelet therapy in the acute setting as well as decisions to de-escalation of chronic antiplatelet therapy.

Adoption in other health systems. We have also demonstrated the feasibility of implementing pharmacogenetic testing outside of UF Health. As part of our pragmatic trial of *CYP2D6*-guided opioid therapy, we implemented *CYP2D6* testing at two primary care clinics in the Orlando area. With each of these, buccal cell samples were collected and sent to UF for genotyping, with results returned to the clinic in approximately 7 days. Prior to implementation, we visited each site to provide education on *CYP2D6* genotype, its implications for opioid therapy, and appropriate alternative therapy in patients with the PM, IM, or UM phenotype. Physicians were also offered *CYP2D6* genotyping as part of the educational program.

Use of resources. As our program has expanded to include a number of gene-drug pairs, and the workload by our clinical pharmacists to provide genotype-based recommendations has increased, we have sought alternative approaches to providing pharmacogenetic support. This led to establishment of the Pharmacogenetics Consultation Clinic, and we are exploring innovative models for reimbursement of the pharmacist services in the clinic. We are also working toward building more automated methods of providing clinical decision support

7. Sustaining and Advancement. In addition to continuing current efforts, we are examining outcomes with *CYP2C19*-guided PPI dosing and working toward an initiative to implement genotype-guided prescribing to improve opioid use and safety for patients with acute pain. Funding provided through this award would be used to support continued efforts to advance medication safety within our institution, including partial financial support of our ASHP-accredited PGY2 Pharmacogenetics Residency program, collection and dissemination of additional outcomes data, and conducting an institutional needs assessment to identify new areas for program development to improve patient safety.