Published in final edited form as:

Pharmacogenomics. 2013 May ; 14(7): 723–726. doi:10.2217/pgs.13.59.

University of Florida and Shands Hospital Personalized Medicine Program: clinical implementation of pharmacogenetics

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Abstract

The University of Florida and Shands Hospital recently launched a genomic medicine program focused on the clinical implementation of pharmacogenetics called the Personalized Medicine Program. We focus on a preemptive, chip-based genotyping approach that is cost effective, while providing experience that will be useful as genomic medicine moves towards genome sequence data for patients becoming available. The Personalized Medicine Program includes a regulatory body that is responsible for ensuring that evidence-based examples are moved to clinical implementation, and relies on clinical decision support tools to provide healthcare providers with guidance on use of the genetic information. The pilot implementation was with *CYP2C19*-clopidogrel and future plans include expansion to additional pharmacogenetic examples, along with aiding in implementation in other health systems across Florida.

Completion of the human genome project in 2001 led to predictions about the medical benefits that would arise from the effort. These included the use of information to aid in the prediction of disease risk, to better stratify disease and to guide treatment decisions. While the advances have perhaps been slower than was anticipated in 2001, there is recent evidence that the predictions of medical benefits for patients are becoming a reality, particularly in guiding treatment or pharmacogenetics. There have also been remarkable technical advances since that time, considering that the human genome project took 13 years and cost nearly US\$3 billion for a composite genome, while a whole genome can now be sequenced in approximately a day for under US\$1000.

The low cost of genome sequencing makes predictions that whole-genome sequences of patients will be increasingly available seem possible. However, generation of the genetic information is just the first step, and many other challenges remain to the actual clinical use of genetic information to guide treatment decisions. The University of Florida (UF) and Shands Hospital's Personalized Medicine Program (PMP) was launched in 2011 as a translational, clinical implementation program within the UF Clinical and Translational

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Science Institute. The goal of the PMP is to begin to solve the challenges that face genomic medicine, including how to store and utilize genomic data for clinical use, define genetic data that are sufficiently robust for clinical use, develop clinical decision support to guide clinicians in the use of genomic data, among other considerations. In the process we place the UF in a leadership position within the genomic medicine community and prepare our health system for the use of genomic data. Our early efforts are focused on clinical implementation of pharmacogenetics, although long-term goals include the addition of disease risk prediction and disease stratification to the program. Pharmacogenetics was selected as the starting point because:

- In many cases the effect sizes are larger than for disease genetics;
- There are many examples of regulatory backing for use of pharmacogenetic data based on US FDA drug labeling;
- The clinical actions to be made based on the genotype are relatively straightforward in many cases;
- Most of the pharmacogenetic examples are not associated with disease risk and so the challenging ethical, legal and social issues, for example, discrimination based on genetic information, are believed to be less of an issue with pharmacogenetics than disease genetics.

These issues made pharmacogenetics a more tractable starting point down the genomic medicine road.

Guiding principles of the UF & Shands PMP

There are several guiding principles that are essential to the UF & Shands PMP.

Pre-emptive, chip-based genotyping

In order to help define the challenges of storing and using genomic data, the program has a pre-emptive genotyping focus, with chip-based genotyping. This allows generation of multiple, clinically actionable genotypes, along with creation of the informatics and other systems that define how and where to store genetic information that might not be clinically useful at present, but might be of value in the future.

Regulatory body to define clinically actionable pharmacogenetics cases

For an evidence-based approach to clinical implementation, and to provide oversight to the program, it was essential that there be a regulatory body responsible for assessing and evaluating the literature, and then approving relevant clinical usages within the institution. Because the current focus is on pharmacogenetics, the most appropriate regulatory body was the hospital's existing Pharmacy and Therapeutics (P&T) Committee, and a PMP sub committee was formed to support this function of the P&T committee.

Support genetic data with clinical decision support

Clinicians told us they would be too busy to learn or remember all the specifics of genetics and pharmacogenetics examples, thus it was essential that genetic information be presented to the clinician in a manner that provides interpretation and clinical recommendations.

Program elements for clinical implementation

PMP subcommittee to the P&T Committee

The PMP subcommittee is charged with evaluating the pharmacogenetics literature to define the examples for which the literature is sufficiently robust to warrant clinical implementation. Once a case has been selected as clinically actionable the committee evaluates the literature to define the specific genetic polymorphisms that will be utilized clinically for the pharmacogenetics recommendations. If the example is a drug-metabolizing enzyme, the genotypes need to be collapsed to predicted metabolism phenotypes. These phenotype recommendations are also made by the committee based on the literature. Finally, the PMP subcommittee formulates the recommendations for how the genetic information will be utilized, the alternative therapy to be recommended, if relevant, and the wording presented by the clinical decision support tools. These recommendations are then taken to the P&T committee for approval, after which any patient tested on the pharmacogenetic chip will have those genotypes reported into their medical record, regardless of whether they are on a relevant drug.

Platform & custom chip selection & clinical genotyping

In order to utilize genetic information in the clinical setting, the test must be performed in a College of American Pathologists-accredited, Clinical Laboratory Improvement Amendments-licensed clinical laboratory. The genetic data for the UF and Shands PMP is being generated in the UF pathology laboratories, a diagnostic reference laboratory. We evaluated a variety of options for chip-based genotyping, including the commercial arrays marketed by Affymetrix and Illumina. Owing to chip costs, configuration, turnaround time, and the ability to have custom defined, flexible content, we chose to utilize the Life Technologies Quant Studio™ Open Array technology. In collaboration with investigators of PharmGKB at Stanford University we selected 256 SNPs for inclusion on the custom array [1]. This included the drug-metabolizing enzyme and transporter SNPs common on the commercial drug metabolism and transporter panels, and includes additional SNPs with a strong body of evidence that might see clinical utility in the near future. Details of the chip, and our selection process for the system, and the SNPs included have been previously published [1]. The custom chip approach allows us to react quickly to the literature and add SNPs with potential future clinical relevance, an opportunity for which we have already taken advantage.

Clopidogrel *CYP2C19* pilot

Our pilot implementation project was *CYP2C19* and clopidogrel. Clopidogrel is a prodrug that requires two-step bioactivation, for which *CYP2C19* plays a major role. The gene for *CYP2C19* contains several loss-of-function SNPs that are common in the population and data suggest that patients carrying a loss-of-function allele have decreased efficacy with clopidogrel. In particular, patients undergoing percutaneous coronary intervention (PCI) are at increased risk of adverse cardiovascular events and marked increased risk for stent thrombosis [2]. These data resulted in the addition of a boxed warning to the FDA product label for clopidogrel, and Clinical Pharmacogenetic Implementation Consortium guidelines are available to guide use of genetic information with clopidogrel [2]. We selected clopidogrel-*CYP2C19* as our pilot project because: genotype-guided treatment has the potential to prevent major adverse cardiovascular events; there is regulatory support based on the boxed warning; and it allowed us to focus on a relatively small physician group for the initial implementation (interventional cardiologists) while being able to impact a reasonably large number of patients. The cardiologists had never previously ordered a *CYP2C19* pharmacogenetic test through an outside reference laboratory, but agreed to add the pharmacogenetic test panel to the standing order set for patients undergoing left heart

catheterization. Based on the preemptive nature of the program, we aim to genotype all patients getting left heart catheterization to rule out coronary disease, not just those who get a PCI. Our program launched in June 2012 and as of March 2013, *CYP2C19* genotypes have been reported to the medical record for nearly 800 patients.

Because *CYP2C19* genotyping has been added as a standard procedure in our cardiac catheterization laboratory, consent for that testing is covered under the clinical consent. We are additionally seeking research informed consent, which allows us to:

- Potentially use the genetic information from the additional 248 SNPs on the chip for their future clinical care (eight of the 256 SNPs are currently used to infer the *CYP2C19* diplotype/predicted phenotype);
- Use the SNP data for research purposes, linked with data in their electronic health record;
- Store their biological sample in the Clinical and Translational Science Institute biobank for future research;
- Allow for the recontacting of patients for future research. Those patients who are not invited to consent for the research or who refuse research consent have all data about the remaining 248 genotypes destroyed.

For patients who undergo a PCI, have an actionable genotype (defined as intermediate or poor metabolizer) and have an order placed for clopidogrel, an electronic clinical decision support alert will be sent to the ordering physician alerting them that the patient's *CYP2C19* genotype suggests they are at risk of reduced efficacy with clopidogrel and an alternative antiplatelet is recommended. Additionally, the cardiovascular clinical pharmacist gets electronic alerts on all patients with an actionable genotype (regardless of PCI status) and follows up with the cardiologist to evaluate need for alternative therapy. This clinical support is particularly important for those patients who are discharged prior to the genotype being available, which is common for PCI patients who had their procedure performed as an outpatient.

Future perspective

We have successfully launched a clinical implementation program for pharmacogenetics at the UF. Future plans include expansion to a variety of other practice settings (e.g., pediatric hematology/oncology) with additional pharmacogenetics examples that also have Clinical Pharmacogenetic Implementation Consortium guidelines [3–5]. We also plan to work collaboratively with private practice cardiology groups across the state of Florida to implement the clopidogrel–*CYP2C19* program into their institutions. We seek to continue to work at the cutting edge of genomic medicine implementation, with the goal of improving care for the patients we serve, while also providing data and approaches that will lead to clinical translation of this important clinical tool in other healthcare settings.

Acknowledgments

This work is supported in part by NIH grants: U01 GM074492, U01 HL105198 and UL1 TR000064.

No writing assistance was utilized in the production of this manuscript.

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Highlights

- The University of Florida and Shands Hospital has launched a clinical genomic medicine program presently focused on the clinical implementation of pharmacogenetics.
- Guiding principles of the program include the importance of pre-emptive genotyping on a chip-based platform, regulatory oversight to ensure implementation of evidence-based examples, and clinician support of the information through clinical decision support tools and interaction with a clinical pharmacist.
- We elected to implement the program utilizing the Life Technologies Quant Studio™ Open Array technology, which allows us to define the SNPs included in the array, and respond to the literature as it evolves and add new SNPs as needed.
- The pilot implementation project was with clopidogrel–*CYP2C19*, for which the interventional cardiologists made the test a part of the standing order set for patients undergoing cardiac catheterization. The clinical program launched in June 2012.
- Patients with an actionable *CYP2C19* genotype (inferred intermediate or poor metabolizer phenotype) and a prescription for clopidogrel have an alert sent to the physician recommending alternative antiplatelet therapy.
- *CYP2C19* genotype is tested under clinical consent. Patients are additionally invited to provide research informed consent, which allows potential future clinical use of data on the chip beyond the *CYP2C19* genotype.