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Implementing Personalized Medicine: Development of a Cost-Effective Customized Pharmacogenetics Genotyping Array

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Abstract

Although there is increasing evidence to support the implementation of pharmacogenetics in certain clinical scenarios, the adoption of this approach has been limited. The advent of preemptive and inexpensive testing of critical pharmacogenetic variants may overcome barriers to adoption. We describe the design of a customized array built for the personalized-medicine programs of the University of Florida and Stanford University. We selected key variants for the array using the clinical annotations of the Pharmacogenomics Knowledgebase (PharmGKB), and we included variants in drug metabolism and transporter genes along with other pharmacogenetically important variants.

Over the past decade, as described in the literature, there have been substantial advances in understanding the influence of genetic variability on drug efficacy, toxicity, and pharmacokinetics. There are an increasing number of reports of widely replicated gene–drug associations and of genotype–phenotype relationships of a sufficiently large effect size as to be clinically actionable. Based on the growing literature, the Clinical Pharmacogenetics Implementation Consortium (CPIC)[1] has developed guidelines for areas in which the body of evidence is strong enough to warrant use of the pharmacogenetic information in the clinical setting. These guidelines, which summarize the literature and provide specific recommendations regarding the use of genetic information to guide treatment with a specific drug or drugs, are available at PharmGKB (http://www.pharmgkb.org).

Despite a growing literature base in pharmacogenetics, US Food and Drug Administration labeling on a variety of drugs (including black box warnings in some cases), and CPIC guidelines, the clinical implementation of pharmacogenetics has been minimal. Potential barriers to clinical implementation are listed in Table 1.

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SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

CONFLICT OF INTEREST

The authors declared no conflict of interest.

There have also been astounding advances in genotyping and sequencing technologies in the past decade. For example, Life Technologies recently announced the introduction of a sequencing technology that can sequence the entire human genome for less than $1,000. Based on these advances, it is likely that increasing amounts of patient-specific genomic information will be available, and that genetic information will therefore be available to clinicians preemptively and when it is needed. Such an approach obviates many of the current barriers described in Table 1 and moves the discussion away from “should I order the pharmacogenetic test” to “can I ignore use of pharmacogenetic information in this patient when I already have it?” Availability of large amounts of genetic information probably represents the future, and generation of larger amounts of genetic information for future use is more cost-effective than testing for one gene or one single-nucleotide polymorphism (SNP) at a time. As such, some institutions that are undertaking clinical implementation of pharmacogenetics are genotyping on a broader panel of SNPs so that most of the information will be available when needed.

The University of Florida and Stanford University were funded under a National Institutes of Health Clinical Translational Science Award administrative supplement to pilot (at the University of Florida) and replicate (at Stanford) a clinical pharmacogenetics implementation. We are initially targeting clopidogrel therapy and its association with *CYP2C19* genotype, but we are genotyping a broader array of genetic variants so as to allow for future “when needed” use of pharmacogenetics information. Genotypes from the chip beyond *CYP2C19* will be moved to the patient’s medical record once the pharmacy and therapeutics committee at each participating hospital approves the addition of the relevant gene–drug pair, regardless of whether the patient is actually taking the relevant drug at the time. This allows the genotype to be available if/when the relevant drug is being considered for use in the patient.

Six key factors considered in selecting a genotyping approach included (i) turnaround time from isolated DNA to genotype, (ii) the labor involved in generating the genotype, (iii) the number of samples per array, (iv) the cost of the array, (v) the content of the array, and (vi) the flexibility to adjust the content. Turnaround time is important because, although the broader panel represents preemptive genotyping, the *CYP2C19* genotype is needed immediately for guiding clopidogrel therapy in patients undergoing percutaneous coronary intervention. It is therefore important to select a system that provides next-day genotype data. We considered several commercial arrays but did not select them because of array costs, the labor involved, longer turnaround times from DNA to genotype data, and lack of content other than the drug metabolizing enzymes and transporters. Although many of the currently actionable genotypes are in genes covered by commercially available arrays, there is increasing evidence for the importance of genes outside this group. For example, three hepatitis C drugs contain product labeling that suggests the genotyping of a genetic marker on *IL28* to guide therapy (http://www.pharmgkb.org/gene/PA134952671).

These issues make the concept of a customized array appealing. We built such an array, utilizing the Life Technologies QuantStudio 12K Flex system with OpenArray technology. This platform meets all the key elements that we deemed important for clinical application of the genotyping information. Specifically, the turnaround time from DNA to genotype is only 5 h. The QuantStudio system requires minimal technical support time. It relies on TaqMan chemistry, and millions of TaqMan assays are available. Also, because each SNP genotype is run in a separate reaction, new SNPs can be substituted into the array based on new data, thus providing substantial flexibility. Chips on the open array can be designed in any combination of 3,072 SNPs (e.g., 12 samples × 256 SNPs; 24 samples × 128 SNPs). On the basis of the curated evidence in PharmGKB, we selected the 12 sample × 256 SNP format. We determined that this format would not only provide complete coverage of the

currently actionable pharmacogenetics examples and extensive coverage of the major drug metabolizing and drug transporter genes but also include genes for which there is a growing body of evidence that may be moving toward clinically actionable status, as well as some SNPs of local interest. Finally, the array was deemed cost-effective for our clinical program, at ~$42 per sample, or 16¢ per SNP on a 256-SNP array (with discounts available), which is 10–20% of the per-sample costs for the commercial arrays. This represents array and reagent costs only; it does not include costs for labor, sample processing, data storage, report generation, and performance of the necessary ongoing assay quality control to meet Clinical Laboratory Improvement Amendments/College of American Pathologists standards. Labor costs would be lower than those for the other commercial platforms because of the ease of use, whereas the other costs would be similar across platforms.

The genotype data were validated to ensure accuracy and reproducibility. First, 94 Coriell DNA samples were run in triplicate on the array, and the results were compared across runs and to data available in HapMap and the 1000 Genomes Project. In addition, genotypes for *CYP2C19* were validated using GenMark's eSensor platform. Given the rarity of some of the *CYP2C19* star (*) alleles, these were validated using a commercially available kit with synthetic DNA for each allele (Maine Molecular Quality Control, Scarborough, ME).

SNP selection for this panel relied heavily on the curated pharmacogenetics data and clinical annotations in PharmGKB.[2] The PharmGKB clinical annotations are literature-based synopses of the clinical impact of key pharmacogenetics variants on drug response phenotype. Each annotation provides a succinct interpretation for each genotype of each variant, indicating in what way it influences the efficacy, toxicity, or dose requirement of a particular drug or drug class. The clinical annotations are manually curated from the primary literature. Each clinical annotation is assigned a level of evidence to indicate the strength of the association. These levels of evidence are level 1 (replicated data with clinical implementation or replicated data with preponderance of evidence showing significant association); level 2 (reasonably strong evidence from several cohorts but some discrepancy in the literature); level 3 (single study or conflicting evidence); level 4 (a case report; a study that did not achieve significance but is biologically plausible; or *in vitro*, molecular, or functional assay evidence).[2]

The variants on the University of Florida custom chip were chosen on the basis of one or more of the following criteria: (i) availability of PharmGKB clinical annotations (selection from this group was based on the level-of-evidence rating, most examples being at levels 1 and 2, with a few SNPs at level 3); (ii) existence of functional SNPs for key pharmacogenetics genes (or genes of significant pharmacogenetic importance) (VIPs); (iii) knowledge of tagging SNPs for important pharmacogenetics haplotypes (e.g., HLA-B *1501); and (iv) specific interest to the collaborating research groups.

The array includes SNPs from 120 genes, including 25 drug metabolism genes and 12 drug transporter genes. There are 252 "pharmacogenetics SNPs," two sex markers, and two SNPs included as quality-control duplicates, for a total of 256. Table 2 shows the genes on the chip. The details of the SNPs included on the array, along with links to their curated data (and, in most cases, clinical annotations) on PharmGKB, are available in Supplementary Table S1 online. The content of this array may be of interest to those who are considering implementing a preemptive genotyping approach. Importantly, we excluded SNPs with a reasonable body of evidence for disease risk prediction because the discovery of these might be actionable or cause patient/provider anxiety. For example, APOE (apolipoprotein E) polymorphisms associated with Alzheimer's disease have been excluded, although there are some pharmacogenetics data for those same SNPs in the context of statins and warfarin. The exclusion of known disease markers allows us to learn from pharmacogenetics

implementation before having to deal with the thornier ethical and legal issues that may surround clinical implementation of disease genetics.

At the announcement of completion of the Human Genome Project in 2001, the use of pharmacogenetics in clinical medicine was seen as a primary example of the utility of genomic information in improving patient care. Although we may be arriving at the clinical implementation goal a bit later than was expected at the turn of the millennium, it appears that we have arrived. The use of a broad pharmacogenetics panel, such as the one in our customized array, will not only advance clinical utilization of pharmacogenetics data but will also enable health systems to prepare for the larger opportunities associated with implementation of genomic medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Potential barriers to clinical implementation that can be overcome with a preemptive genotyping approach

Barrier	Overcome by preemptive genotyping?
Uncertainty about when to order the pharmacogenetic test	Yes—particularly if genotype data are presented to the clinician at time of relevance based on CDS tools
Turnaround time	Yes
Cost of the genotyping test	Partially—costs for preemptive SNP array more cost-effective than multiple single tests over patient's life span
Clinician discomfort with information delivered in usual laboratory report format (e.g., nucleotide genotype, star (*)allele genotype)	Yes—if laboratory report is supported by CDS tools within the EMR
Clinician uncertainty about how to act on the genetic information	Yes—if supported with CDS tools within the EMR
Uncertainty about relevance of clinical implementation in absence of randomized controlled trial data	No
Concerns about genetic data being available and liability of ignoring or missing the information once it is in the medical record	No

CDS, clinical decision-support; EMR, electronic medical record; SNP, single-nucleotide polymorphism.

Table 2

Genes included in University of Florida and Stanford University Personalized Medicine Program Custom Array

A1BG	CYP2D6	LUC7L2
ABCB1	CYP3A4	MTHFR
ABCC1	CYP3A5	MUC21
ABCC2	CYP4B1	NAT1
ABCC4	CYP4F2	NAT2
ABCC6	DPYD	NOS3
ABCG2	DRD2	NPPA
ACE	DRD3	NQO1
ADORA2A	DTNBP1	NR1I2
ADRB1	EDN1	OPRM1
ADRB2	EPHX1	P2RY1
AGTR1	ESR1	P2RY12
AKT1	ESR2	PCSK9
ALOX5	F7	PON1
AMPD1	FKBP5	PRKCA
APOA4	FLOT1	RGS4
APOB	FTO	SCN1A
APOC3	G6PD	SELE
APOE	GLCCI1	SELP
ARG1	GNB3	SERPINE1
BDKRB1	GRK4	SIGLEC12
BDKRB2	GRK5	SLC14A2
CACNA1C	GSTP1	SLC22A1
CACNB2	HMGCR	SLC22A16
CACNG2	HTR1A	SLCO1B1
CALU	HTR2A	SLCO1B3
CDA	HTR2C	SLCO2B1
CES1	IL1B	TCF7L2
CHRNA4	IL28B	TH1L
CHST3	IMPDH1	TNF
COMT	KCNJ11	TOMM40
CRHR1	KCNJ6	TPH2
CRHR2	KCNMB1	TPMT
CYP1A2	LDLR	UGT1A locus
CYP1B1	LEP	UGT2B7
CYP2A6	LPA	USP24
CYP2B6	LPIN1	USP9Y

CYP2C19	LTA	VDR
CYP2C8	LTA4H	VKORC1
CYP2C9	LTC4S	ZBTB42