



ARTICLE

Implementation of preemptive DNA sequence–based pharmacogenomics testing across a large academic medical center: The Mayo-Baylor RIGHT 10K Study



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ABSTRACT

Purpose: The Mayo-Baylor RIGHT 10K Study enabled preemptive, sequence-based pharmacogenomics (PGx)-driven drug prescribing practices in routine clinical care within a large cohort. We also generated the tools and resources necessary for clinical PGx implementation and identified challenges that need to be overcome. Furthermore, we measured the frequency of both common genetic variation for which clinical guidelines already exist and rare variation that could be detected by DNA sequencing, rather than genotyping.

Methods: Targeted oligonucleotide-capture sequencing of 77 pharmacogenes was performed using DNA from 10,077 consented Mayo Clinic Biobank volunteers. The resulting predicted drug response–related phenotypes for 13 genes, including *CYP2D6* and *HLA*, affecting 21 drug–gene pairs, were deposited preemptively in the Mayo electronic health record.

Results: For the 13 pharmacogenes of interest, the genomes of 79% of participants carried clinically actionable variants in 3 or more genes, and DNA sequencing identified an average of 3.3 additional conservatively predicted deleterious variants that would not have been evident using genotyping.

Conclusion: Implementation of preemptive rather than reactive and sequence-based rather than genotype-based PGx prescribing revealed nearly universal patient applicability and required integrated institution-wide resources to fully realize individualized drug therapy and to show more efficient use of health care resources.

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Introduction

Pharmacogenomics (PGx) is the study of genetically determined variation in individual response to drugs.^{1–3} PGx variants may affect either pharmacokinetics, processes such as drug metabolism or transport that influence the concentration

of a drug reaching its target, or pharmacodynamics, variation in the target itself or processes downstream of the target.^{1,2}

Although many DNA sequences are known to influence drug response,^{1–3} PGx has not yet achieved broad clinical implementation. More recently, there have been multiple efforts to move toward that goal, from studies conducted by

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single institutions⁴ to those involving multiple institutions and multiple countries such as the Ubiquitous Pharmacogenomics Consortium that extends across the European community.⁵ There are numerous reasons for this slow pace of implementation, including a requirement to educate providers, limited insurance reimbursement in the United States, and a relative lack of prospective comparisons of preemptive test results vs reactive testing.

Numerous entities such as the Pharmacogenetics Knowledgebase (PharmGKB)⁶ and Pharmacogene Variation Consortium (PharmVar)⁷ have been established to serve as database repositories to collect PGx variants and provide underlying information, including allele frequencies, metabolic pathways, and the strength of associations between variants and clinical effects. Further resources, including the Clinical Pharmacogenetic Implementation Consortium (CPIC),⁸ the Dutch Pharmacogenetic Working Group (DPWG),⁹ and others, are dedicated to the establishment of peer-reviewed clinical dosing guidelines based on diplotype-driven predictions of resulting drug response phenotypes. Various government entities such as the US Food and Drug Administration (FDA)¹⁰ both publish dosing guidelines and exercise regulatory authority over testing and return of results. All of these databases catalog genomic variants that are relatively common, where there is sufficient data to support statistically robust conclusions as to their effect. However, over the past decade, it has been shown that rare variants are both greater in number and often show larger effect sizes than many common variants.¹¹ A number of studies aimed at genes known to be involved in PGx also show that both common and rare variants are prevalent and influence clinical outcomes and that variants and allele frequencies vary across populations, suggesting that individual use of these data might have a broad and significant effect on drug prescribing practices worldwide.

A number of health care systems have begun to integrate alerts for PGx drug–gene pairs into their electronic health records (EHRs).^{12–14} Those alerts have sometimes been designed to inform the prescriber of the availability of PGx testing for the drug being prescribed, as is the case at the Mayo Clinic for a subset of drug–gene pairs (Table 1). However, this reactive approach requires that the prescriber order the PGx test and then wait for the result, a delay that could be avoided if genomic information for that patient had already been deposited in the EHR. Ideally, a preemptive test would integrate PGx seamlessly into the clinical workflow, would only fire alerts for patients whose genomes carry the variant(s) of interest, would avoid delays in the initiation of drug therapy, and would provide the prescriber with information for all sequence variants in the gene(s) of interest rather than merely a small number of commonly genotyped single nucleotide variants (SNVs) or structural variants such as insertions or deletions and copy number variants.

As a feasibility test and to identify challenges associated with the application of this approach to the clinical implementation of PGx guidance and—eventually—as a tool to study the clinical utility and economic benefit of preemptive

sequence-based PGx, the Mayo Clinic and the Baylor College of Medicine Human Genome Sequencing Center (BCM-HGSC) collaborated to generate DNA sequence data for 77 known or candidate pharmacogenes using a capture panel and DNA from 10,077 patients who received their health care from the Mayo Clinic. Specifically, drug response phenotypes predicted for gene variants included in drug–gene pairs for which alerts currently fire at the Mayo Clinic, were deposited in the EHR to determine whether preemptive sequence-based PGx testing might represent a step toward the broader incorporation of this aspect of clinical genomics into patient care. The DNA sequence information was generated under College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) standards. This effort was also designed to make it possible to stimulate PGx research studies by taking advantage of clinical drug response information present in the Mayo Clinic EHR. Table 1 lists the 21 drug–gene pairs for which PGx alerts fired across the Mayo Clinic system during the study as well as the year of their implementation. The 77 pharmacogenes that were sequenced for this study are listed in Table 2, with genes highlighted for which gene-related predicted phenotype status (eg, poor metabolizer) were deposited preemptively in the EHR. We chose to clinically implement the data for only those drug–gene pairs that had already undergone rigorous internal peer review for clinical utility—as described subsequently in the Materials and Methods—with the remaining genes being available for inclusion in future research studies to assess their potential clinical utility. The Mayo-Baylor RIGHT 10K Study also made it possible to identify significant institutional infrastructural and educational challenges associated with the implementation of this important aspect of clinical genomics.

Materials and Methods

Study participants

The 10,077 Mayo-Baylor RIGHT 10K Study participants were volunteers who had donated biospecimens and health information to the Mayo Clinic Biobank for research purposes. Details regarding the design of the study have been described elsewhere.¹⁵ Demographic information for the study cohort is provided in Table 3.

DNA sequencing

Blood was collected and genomic DNA was extracted at the Mayo Clinic for target-enriched capture sequencing at the BCM-HGSC Clinical Laboratory. A new PGx capture reagent (PGx-seq) was designed, constructed, and validated to CAP-CLIA standards for clinical testing. This reagent targeted a combination of complete coding sequences for 77 pharmacogenes and variants present on both the Affymetrix DMET Plus (Affymetrix/Thermo Fisher Scientific) and

Table 1 Drug–gene pair alerts implemented in the Mayo Clinic EHR by year of implementation

Drug	Gene(s)	Year implemented
Abacavir	<i>HLA-B*57:01</i>	2013
Azathioprine	<i>TPMT</i> and <i>NUDT15</i> ^a	2013
Carbamazepine	<i>HLA-B*15:02</i> and <i>HLA-A*31:01</i> ^b	2013
Codeine	<i>CYP2D6</i>	2013
Mercaptopurine	<i>TPMT</i> and <i>NUDT15</i> ^a	2013
Tamoxifen	<i>CYP2D6</i>	2013
Thioguanine	<i>TPMT</i> and <i>NUDT15</i> ^a	2013
Tramadol	<i>CYP2D6</i>	2013
Allopurinol	<i>HLA-B*58:01</i>	2014
Clopidogrel	<i>CYP2C19</i>	2014
Simvastatin	<i>SLC01B1</i>	2014
Warfarin	<i>CYP2C9</i> and <i>VKORC1</i>	2014
Citalopram	<i>CYP2C19</i>	2015
Escitalopram	<i>CYP2C19</i>	2015
Fluvoxamine	<i>CYP2D6</i>	2015
Fluoxetine	<i>CYP2D6</i>	2015
Paroxetine	<i>CYP2D6</i>	2015
Venlafaxine	<i>CYP2D6</i>	2015
Tacrolimus	<i>CYP3A5</i>	2016
Capecitabine	<i>DPYD</i>	2017
Fluorouracil	<i>DPYD</i>	2017

A subset of these alerts were designed to fire in a reactive fashion, ie, recommending PGx testing in response to all initial prescriptions, which are as follows: *TPMT* and *NUDT15* for thiopurines (mercaptopurine, azathioprine, and thioguanine), *HLA-B*57:01* for abacavir, *HLA-B*15:02* and *HLA-A*31:01* for carbamazepine in patients of Asian descent, *HLA-B*58:01* for allopurinol in patients of Asian or African descent, and *CYP2D6* for tamoxifen. This was done to avoid physician alert fatigue that might have occurred if all of the alerts had been reactive. All other alerts currently fire only for patients who already have PGx information in the EHR. Between March 2015 and December 2018, these alerts fired a total of 6620 times. No comparable data are available after December 2018 because of Mayo Clinic's implementation of a new EHR.

EHR, electronic health record; PGx, pharmacogenomics.

^a*NUDT15* added in 2018 and assayed by genotyping.

^b*HLA-A*31:01* added in 2018.

Illumina VeraCode ADME (Illumina) array genotyping platforms not already addressed by the capture, together with supplementary known PGx and fingerprinting SNVs, as well as regional capture of the *CYP2D6* locus that incorporated both of its nearby pseudogenes. In the development of both gene targets and software analysis, a previously characterized cohort of 512 samples was used to validate performance. Those analyses suggested that tag SNVs designed to identify the 4 HLA region allele-types of interest underperformed for 1 allele-type and therefore, Omixon HLA Explore software (Omixon Biocomputing Ltd) was tested and adopted for these loci. For *CYP2D6*, a software solution designed to identify structural and copy number variants was developed by the Mayo Clinic Personalized Genomics Laboratory (PGL) and implemented for these samples. The resulting average sample sequencing depth was greater than 490. See [Supplemental Methods](#) for further details.

Drug–gene pair alerts and clinical decision support

The Mayo Clinic Pharmacogenomics Task Force selected the drug–gene pair alert rules on the basis of peer-reviewed published guidelines from CPIC, the Dutch Pharmacogenetic Working Group, the Pharmacogenetics Knowledgebase, and the FDA as well as advice from intramural clinical specialists. This Task Force also developed the clinical decision support tools required to translate PGx assay results into EHR alerts.

Information technology

The BCM-HGSC and the Mayo Clinic PGL collaborated to identify and 'force call' (override variant caller software to return a locus-specific genotype regardless of conflict with the human reference) 310 potential variant sites defining currently known actionable alleles and developed translation lookup tables specifying drug response–related predicted phenotypes for all reportable genes except *CYP2D6*. For this gene, software developed in the Mayo Clinic PGL, CNVAR, was used to determine final *CYP2D6* predicted phenotypes or, in rare cases, to refer samples for further testing and/or manual review. Software at Baylor was used to filter the Omixon software output to identify relevant HLA allele-types. Further scripts and modifications of existing data pipelines specific to the project were implemented at both institutions. See [Supplemental Methods](#) for further detail.

Results

Introduction

The Mayo-Baylor RIGHT 10K Study was designed to test the long-term hypothesis that ready access at the point-of-care to prescribing recommendations on the basis of a patient's genetic composition would help to optimize that individual's prescription drug therapy both short and long-term. We also sought to assess the rate of occurrence of rare variants within the PGx genes of participants and the added value of using DNA sequencing, rather than genotyping, for clinical testing. We anticipated that increases in drug efficacy and reduction in the rate of adverse events would result in better patient outcomes and enhanced health care economics as we accumulate cohort outcomes data moving forward. The clinicians caring for the 10,077 participants in the study, predominately primary care physicians, had not ordered PGx testing, and therefore, educational programs had to be designed for all health care team members as well as processes for the return of PGx results to both the health care team and to participating subjects.

Table 2 Lists of 77 pharmacogenes that were sequenced for the Mayo-Baylor RIGHT 10K Study

<i>ABCB1</i>	<i>CYP2B6</i>	<i>DPYD</i>	<i>GSTP1</i>	<i>KCNH2</i>	<i>RYR2</i>	<i>SULT1A1</i>
<i>ABCC4</i>	<i>CYP2C8</i>	<i>DRD2</i>	<i>HLA-A (*31:01)</i>	<i>KIF6</i>	<i>SCN1A</i>	<i>TP53</i>
<i>ABCG2</i>	<i>CYP2C9</i>	<i>DRD3</i>	<i>HLA-B (*15:02, *57:01, *58:01)</i>	<i>LDLR</i>	<i>SCN5A</i>	<i>TPMT</i>
<i>ADRB2</i>	<i>CYP2C19</i>	<i>DRD4</i>	<i>HMGR</i>	<i>LEP</i>	<i>SLC19A1</i>	<i>TYMS</i>
<i>ANKK1</i>	<i>CYP2D6</i>	<i>EGFR</i>	<i>HNF1A</i>	<i>LEPR</i>	<i>SLC22A1</i>	<i>UGT1A1</i>
<i>CES1</i>	<i>CYP2E1</i>	<i>F5</i>	<i>HNF4A</i>	<i>MTHFR</i>	<i>SLC22A2</i>	<i>UGT1A3-10 exon1^a</i>
<i>CFTR</i>	<i>CYP2J2</i>	<i>FAAH</i>	<i>HTR2A</i>	<i>NAT2</i>	<i>SLC6A4</i>	<i>UGT2B15</i>
<i>COMT</i>	<i>CYP3A4</i>	<i>G6PD</i>	<i>HTR2C</i>	<i>OPRM1</i>	<i>SLC01B1</i>	<i>UGT2B7</i>
<i>CYP1A2</i>	<i>CYP3A5</i>	<i>GGCX</i>	<i>IFNL3 (IL28B)</i>	<i>PON1</i>	<i>SLC02B1</i>	<i>VEGFA</i>
<i>CYP2A6</i>	<i>CYP4F2</i>	<i>GRIK4</i>	<i>IGFBP7</i>	<i>RYR1</i>	<i>SOD2</i>	<i>VKORC1</i>

The boldfaced genes symbols are those for which predicted drug metabolism–drug response phenotype data were deposited in the Mayo Clinic EHR for RIGHT 10K subjects.
EHR, electronic health record.
^aPlease note that multiple *UGT1* splice isoforms have been included and that results for *CYP1A2*, *CYP3A4*, and *UGT1A1* were deposited to the EHR but are not yet part of drug–gene pair alerts at the Mayo Clinic.

Study participant PGx DNA variants

Targeted DNA sequencing for the 10,077 participants in the study, as anticipated, identified a large number of currently clinically actionable PGx variants as well as currently unclassified rare variants in the genomes of every patient (Table 4)—for all 77 genes and for the 13 genes for which alerts fired in the Mayo Clinic EHR during the study. The targeted genomic regions of all but 55 of the 10,077 participants included a clinically actionable variant in at least 1 of the 13 pharmacogenes included in the 21 drug–gene pair alerts (Table 1), whereas 79% of the participants had clinically actionable variants in 3 or more of those 13 genes, as depicted graphically in Figure 1. Therefore, all but 0.6% of the participants, depending on the drugs prescribed by their clinician, would potentially have benefited from PGx information for just these 13 pharmacogenes.

Sequencing vs genotyping

We chose a targeted DNA sequence–based assay for this project to ensure that we tested all target genes comprehensively. The alternative DNA genotyping arrays currently available are, of necessity, designed to only detect variants that have been previously identified. Consequently, available arrays generally represent relatively more common variation and, conversely, fail to represent less common genomic variants, which could—in aggregate—have significant clinical relevance.¹⁶

As a proxy for a comparison with the collection of variants available on arrays, we filtered our DNA sequence results to remove common variants already categorized by CPIC as clinically actionable (Table 4). After filtering, on average, each participant carried 127 additional SNVs and insertions or deletions variants for the 13 genes listed in Table 1. Computer analysis (eg, Combined Annotation Dependent Depletion [CADD] and Sorting Intolerant From Tolerant [SIFT]) scores^{17,18} identified an average of 7.3 and 8.0 CADD and SIFT variants, respectively, and 3.3 variants

when intersected in each participant as probably deleterious, suggesting a potential clinical impact. A recent report of functional testing by deep mutational scanning in a separate cohort, combined with functional validation of the results, found that 19 of 109 *CYP2C9* and 36 of 121 *CYP2C19* variants that had been identified by sequencing the genomes of large populations displayed severely damaging phenotypes with protein expression that was <25% of that present for wild-type alleles.¹⁹ *CYP2C9* and *CYP2C19* are pharmacogenes that play important roles in variable clinical response to drugs that include warfarin, clopidogrel, and a number of psychiatric drugs. In total, 6 of the subjects included in this study carried functionally severely damaging variants in *CYP2C9* other than those that are usually genotyped, whereas the genome of 1 subject carried 2 such variants. The genomes of 25 of our participants included 1 functionally severely damaging variant in their *CYP2C19* gene beyond those that are usually genotyped, whereas 1 subject carried 2 such variants. All of these cases would have been missed if only standard genotyping methods had been applied. Variants and alleles with unknown function were evaluated using a modification of American College of Medical Genetics and Genomics variant interpretation criteria. Predicted phenotypes for variants of uncertain significance were expressed as a range (Supplemental Methods).²⁰

Application to current therapy

As a first step toward implementation, clinicians caring for patients who were already prescribed medications influenced by variants in genes included in the Mayo Clinic drug–gene pair alerts were informed whenever these initial results suggested that a patient’s drug therapy could potentially be improved by dose adjustment or alternative therapy. If Mayo Clinic pharmacists concluded that the PGx test results indicated either a semiurgent (ie, the drug had the potential to cause serious harm) or a clinically actionable (ie, the drug had the potential to cause an adverse reaction or

Table 3 Characteristics of the RIGHT 10K participants

Characteristic	n (%) N = 10,077
Sex	
Female	6146 (61.0)
Male	3931 (39.0)
Age on January 1, 2016, y	
18-24	58 (0.6)
25-34	647 (6.4)
35-44	824 (8.2)
45-54	1299 (12.9)
55-64	2067 (20.5)
65-74	3215 (31.9)
75+	1967 (19.5)
Race	
White	9475 (94.0)
Non-White	523 (5.2)
Black	50
Asian	91
AIAN	16
NHPI	0
Other and mixed	366
Unknown	79 (0.8)
Ethnicity	
Non-Hispanic	9959 (98.8)
Hispanic	112 (1.1)
Unknown	6 (0.1)
Self-reported education at time of Biobank Consent (2009-2017)	
High school graduate or GED or less	1261 (12.5)
Some college or associates degree (including community college)	2935 (29.1)
Four-year college graduate (Bachelor's degree)	1991 (19.8)
Graduate or professional school	3845 (38.2)
Unknown	45 (0.4)

AIAN, American Indian or Alaska Native; GED, General Educational Development; NHPI, Native Hawaiian or Pacific Islander.

significantly altered efficacy) need to inform the prescriber, e-consults were sent to the primary care provider. Semi-urgent e-consults were sent for 61 patients. The drugs involved were clopidogrel for 41 of the 61 patients (67%), citalopram for 9 of the 61 patients (15%), escitalopram for 7 of the 61 patients (11%), tramadol for 2 of the 61 patients (3%), fluorouracil for 1 of the 61 patients (2%), and allopurinol for 1 of the 61 patients (2%). Providers for those patients accepted 54% of the pharmacists' semiurgent e-consult recommendations. Viewed more globally, a total of 2782 clinically actionable e-consults were sent out to providers on the basis of the RIGHT 10K sequencing data—a figure that begins to provide insight into the potential benefit if PGx information had been available at the time that medications for those patients had initially been prescribed. Obviously, most of these patients had been on their current therapy regimen for some time, and therefore, their drug therapy might have already been altered in response to either the occurrence of an adverse reaction or

lack of efficacy. In addition, the Mayo Clinic has begun collecting evidence of improvement in outcomes traced to the application of the RIGHT 10K results to participant clinical care. Among the several examples in psychiatric patients, 1 participant, found to be a CYP2C19 ultrarapid metabolizer, was switched from an ineffective combination of escitalopram supplemented with bupropion to bupropion monotherapy and is now reported to be in full remission from major depressive disorder. In another example, a participant on combination therapy was found to be a CYP2D6 poor to intermediate metabolizer, resulting in the recommendation that tramadol be replaced or eliminated, resulting in the alleviation of associated dizziness.

Pharmacists and PGx implementation

We found that a team-based approach entailing the involvement of PGx-trained pharmacists, information technology (IT) support for the development of decision support rules and alerts, and effective PGx education programs were all required for the success of this implementation effort. Specifically, the development of PGx test reports that were easily understood by clinicians was essential, along with ensuring that clinicians had access to those reports before they got displayed in patient portals. The Mayo Clinic's Department of Pharmacy played a key role in many of these processes, but initial expertise in PGx among pharmacists was highly variable. Therefore, a train-the-trainer model²¹ was applied to ensure that most pharmacists across the Mayo Clinic had been trained in PGx, with early adopters serving as trainers for their colleagues. The Department also established an electronic consultation and recommendation process (the e-consults referred to earlier) to provide patient-specific PGx guidance to providers. Those efforts resulted in a total of 392 of Mayo's 452 Minnesota licensed pharmacists being trained in PGx, the fact that the Mayo Rochester Pharmacy now includes 3 full-time-PGx specialists, the establishment of an annual Pharmacogenomics Workshop that rotates among the 3 major Mayo Clinic campuses in Minnesota, Florida, and Arizona, a post-graduate year 2 residency training program in Pharmacogenomics for Doctor of Pharmacy graduates, and the launch of an online PGx Certificate Program.

PGx education for medical staff

Previous studies have reported that clinicians often report that lack of education is a major factor limiting their ability to use PGx clinically.²²⁻²⁵ To help address this challenge, multidisciplinary PGx educational content was developed for both practitioners²⁶ and pharmacists as outlined earlier. Furthermore, critical components of this content were incorporated into AskMayoExpert, an institutional online knowledge resource that provides Mayo clinicians with point-of-care information on a wide variety of clinical topics. A direct link to the appropriate AskMayoExpert PGx topic was integrated into each EHR drug-gene pair alert

Table 4 The total and average number of SNVs/indels in the sequenced samples (*N* = 10,077)

	All Calls		Deleterious Calls ^a : CADD/SIFT ^b /Intersection	
	Total Counts	Novel Counts	Total Counts	Novel Counts
SNVs				
Number of SNVs	10,205,546	9,997,316	462,915/360,310/190,311	426,384/346,108/176,148
SNVs/sample	1012.8	992.1	45.9/35.8/18.9	42.3/34.4/17.5
Number of SNVs	1,388,855	1,219,760	93,875/92,352/44,614	73,987/80,835/33,136
SNVs/sample	137.8	121.0	9.3/9.2/4.4	7.3/8.0/3.3
Indels				
Number of indels	620,215	576,068	11,749/0/0	1697/0/0
Indels/sample	61.6	57.2	1.2/0/0	0.2/0/0
Number of indels	69,787	56,346	5509/0/0	0/0/0
Indels/sample	6.9	5.6	0.6/0/0	0/0/0

CADD, Combined Annotation Dependent Depletion; CPIC, Clinical Pharmacogenetic Implementation Consortium; Indel, insertion or deletion; SIFT, Sorting Intolerant From Tolerant; SNV, single nucleotide variation.

^aNovel counts are total SNV/Indel variant counts excluding those included in the 133 CPIC actionable variants included in the Mayo drug–gene pair alerts along with stop gain, stop loss, and frameshift variants. For this analysis, deleterious has been defined as having CADD score > 20¹⁷ and/or SIFT score < 0.05.¹⁸

^bSIFT output is limited to frameshift/nonframeshift for indels.

together with information on both alternative medications and reference to Mayo Clinic experts who could provide assistance. Finally, case-based education for pharmacists, nurses, and other providers was also developed.

RIGHT 10K Study and PGx research

The RIGHT 10K Study also provided a broad foundation for PGx discovery. The availability of DNA sequence information for 77 pharmacogenes joined with clinical data in the EHR created an unusual opportunity for PGx research. The sequence data were made available to Mayo Clinic investigators on the basis of the submission of a short research protocol that underwent Institutional Review Board and scientific peer review.

We have approved 30 protocols that address PGx across a broad spectrum of drug therapies (Supplemental Table 1). An unforeseen bonus of this approach to access has been the fact that the investigators leading those 30 studies have often become both experts in and advocates for PGx within their individual clinical departments and divisions—a development that has assisted with the clinical acceptance and use of PGx at the Mayo Clinic.

PGx 10K participant survey

A survey designed to query knowledge of and attitudes toward PGx was sent to half of the RIGHT 10K Study participants, and 4624 (92.8%) of the invited participants returned

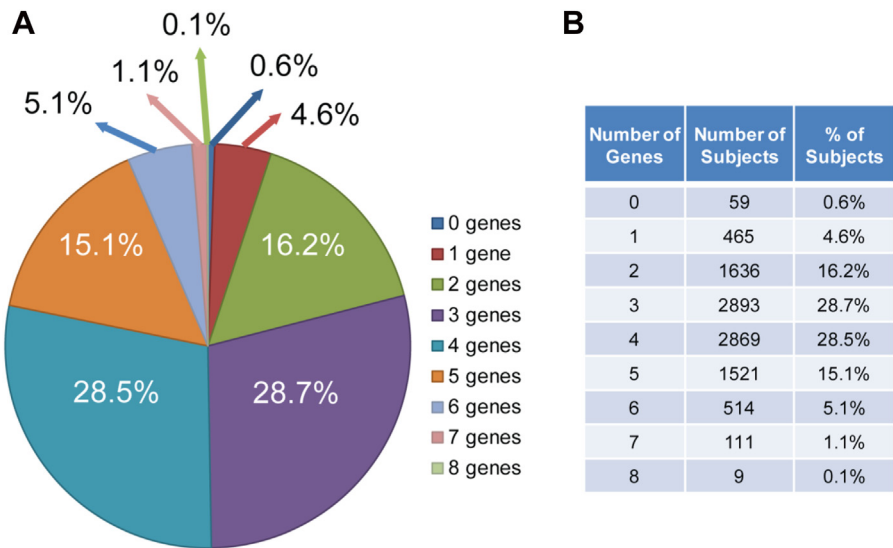


Figure 1 Percentage of study subjects harboring clinically actionable PGx variants. The figure shows the number of genes that contained clinically actionable genomic variants for the 13 genes included in the drug–gene pair alerts listed in Table 1 that were observed in each of the 10,077 RIGHT 10K Study subjects and the percentage of study subjects included in each group. A. The pie chart shows these data graphically, whereas the table in (B.) lists the information upon which the pie chart is based.

the survey. The survey was sent to participants after they had been consented but before they had received their PGx results. Respondents felt that PGx results would help them avoid exposure to medications that might be harmful (Quite Valuable to Extremely Valuable, 94.6%), but relatively few (<18%) expected that their prescription medications or dosages would have to be changed on the basis of the PGx results. In addition, respondents reported low levels of concern regarding potential disruption of their ongoing care and 76% had no or few concerns about the ability of their physician to integrate those results into their care. A follow-up survey is planned after all participants have had an opportunity to discuss the PGx results with their care givers.

Discussion

PGx has long represented one of the most compelling avenues toward bringing DNA-based individualized medicine to clinical care.¹⁻³ Variability in response to medication has long been observed and expected among both providers and patients, and genetic variability underlying this phenomenon is common. Although a small number of mainly academic medical centers have adopted limited PGx testing protocols and momentum is slowing building within a number of provider networks, broad implementation remains slow for several reasons. These include lack of overall knowledge of the topic and therefore, acceptance among medical providers at all levels; challenges in translating test results to dosing recommendations in patients' EHRs while not interrupting the clinical workflow; and in the United States, in particular, a reluctance by both private insurance and government entities to reimburse the relatively minor cost involved in testing.

The Mayo-Baylor RIGHT 10K Study represents a systematic effort to integrate preemptive DNA sequence-based PGx panel testing into clinical workflows across a large medical center incorporating a large cohort of patients. This study both builds on previous work and addresses challenges not generally taken on by others. As suggested by previous analyses of both the 1000 Genomes Project²⁷ and, more recently, the UK Biobank²⁸ and anticipated in this study, we found that nearly all of the 10,077 study participants could potentially have benefited from preemptive PGx data and its attendant interpretation deposited in the EHR—depending on the drugs that their clinician might prescribe. Of importance, we chose to apply targeted DNA sequencing rather than genotyping to allow us to capture less common genomic variants that could by themselves, or in combination, have significant clinical relevance and did so at a cost that barely exceeded the cost of genotyping. We found that the average patient harbored at least 3 current clinically actionable variants, and a conservatively estimated 3 more variants deemed probably deleterious for only the 13 genes included in our study. The utility of the sequence data was further confirmed by the observation that 55 of 230 variants that we observed in the sequence data for *CYP2C9* and *CYP2C19* were recently classified as functionally

significant,¹⁹ although they are unlikely to be assayed using currently available genotyping arrays. While the remaining variants are currently classified as variants of uncertain significance, ongoing functional testing is likely to provide reclassification for some of those variants in the future. Clinical testing by sequencing, rather than via genotyping arrays, ensures that as a variant is reclassified, individuals can be informed of those results without the need for repeat testing with new reagents. We acknowledge a geographically driven bias in our cohort as reflected in the Northern European inheritance present for the vast majority of our samples (94%). As a result, we would anticipate that our data for uncharacterized variant frequency represents a lower boundary when these tools are applied to more diverse populations, as outlined by others.²⁸

Our study developed both reagents and data analysis software tools that allowed the successful assay and reporting of predicted phenotypes across 2 important but highly polymorphic and difficult assay targets, *CYP2D6* and the human HLA region. The former is known to be involved in the metabolism or processing of up to 25% of all drugs currently marketed and the latter is known to be involved in several of the most serious adverse event episodes observed to date. There is little doubt that these loci will continue to play major roles in PGx going forward.

The RIGHT 10K Study also served to highlight a series of challenges associated with the clinical implementation of PGx. For example, we revealed the need to identify health care team interpreters, a role played in this study by Mayo Clinic pharmacists, to act as a conduit between the data, physicians, and patients. In addition, there was a critical need for IT support to build and implement the data pipelines that enable the identification of multiple DNA variant types and the translation of diplotypes to alleles as well as clinical decision support software that integrates smoothly with EHR packages. We also learned where needs existed and developed solutions within Mayo's educational infrastructure. Approaches to address these challenges will differ depending on the local environment of individual medical institutions or provider networks, but having professional staff who can play the interpretive, evaluative, and educational role taken on by the Mayo Clinic pharmacists, such as physicians assistants, nurse practitioners, or genetic counselors in other health care institutional settings, plus the availability of clinical decision support tools, will be required to deliver PGx information to clinical staff quickly, clearly, and without requiring that they be familiar with genomic science or the underlying data.

In summary, the Mayo-Baylor RIGHT 10K Study strongly suggests that preemptive sequence-based PGx panel implementation can be useful clinically—especially if delivered at the point-of-care when drugs are being prescribed—and that it would apply to almost every patient. These results may also be helpful to other medical centers as they consider how or whether they wish to implement preemptive sequence-based PGx panels. This study also serves as an important stepping-stone in the development of the infrastructure necessary to fully use the coming incorporation of genome

sequencing as opposed to targeted sequencing in helping to guide clinical care. We should point out that the FDA has voiced some concerns with regard to PGx, particularly direct to consumer PGx testing and the possible extension of the application of test results beyond supporting clinical evidence.^{16,29} All testing described in this article was conducted in a CAP-CLIA environment with clinician supervision of every aspect of the study. Furthermore, all test interpretations rested on validated consensus-based guidelines.^{6,8-10} It should also be emphasized that PGx will continue to evolve. For example, the future will almost certainly include the application of machine learning-based predictive algorithms that use both clinical and genomic information joined with other types of data that will extend well beyond genotypes for the small number of genes included in the drug-gene pair alerts listed in Table 1.³⁰ Finally, although PGx has not yet been broadly adopted in the clinic, it clearly offers the promise of ultimately becoming a standard component of clinical practice that will help the health care team optimize pharmacotherapy for all patients.

Data Availability

As outlined by Bielinski et al,^{15,31} the RIGHT cohort is a resource for pharmacogenomic research. As stated earlier, a RIGHT Data Access Committee has been created to review data requests for use of RIGHT data. External access to the data is facilitated by the Mayo Clinic Biobank (<https://www.mayo.edu/research/centers-programs/mayo-clinic-biobank/overview>). All potentially damaging variants observed in this study are presented with annotation in Supplemental Table 2. The software developed in this study primarily represents output/input wrappers or filtering scripts and is described in Supplemental Methods. The privately developed CNVAR software (submitted for patent) was conceived and refined on the basis of the genomic targets specified by the PGx capture reagent (PGx-seq) and would need extensive adjustments for other captures. However, those interested in using CNVAR may contact the authors to determine whether the software could be applied to their data set. Omixon HLA Explore is commercially available, whereas the remaining underlying software is available at <https://www.hgsc.bcm.edu/software>.

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Ethics Declaration

All participants in this study were recruited from the Mayo Clinic Biobank and informed consent was obtained under Mayo Clinic Institutional Review Board approval. Participants agreed to the use of their stored Biobank samples for clinical pharmacogenomic testing, deposit of pharmacogenomic results into their electronic health record for clinical use, and use of de-identified pharmacogenomic data for research. For more information on both the Biobank (<https://www.mayo.edu/research/centers-programs/mayo-clinic-biobank/about/governance-oversight>) and the RIGHT cohort, please see Bielinski et al.¹⁵

Conflict of Interest

Liewei Wang, John Logan Black III, and Richard M. Weinshilboum are cofounders of and stockholders in OneOme, LLC, which was used only to return results to the study participants. Additionally, John Logan Black III and Mayo Clinic Ventures have applied for a patent on the CNVAR software cited in this study as well as the methodology upon which the software is based. All other authors declare no conflicts of interest.

Additional Information

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References

- Weinshilboum RM, Wang L. Pharmacogenomics: precision medicine and drug response. *Mayo Clin Proc.* 2017;92(11):1711–1722. <http://doi.org/10.1016/j.mayocp.2017.09.001>.
- Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. *N Engl J Med.* 2011;364(12):1144–1153. <http://doi.org/10.1056/NEJMr1010600>.
- Roden DM, Van Driest SL, Wells QS, Mosley JD, Denny JC, Peterson JF. Opportunities and challenges in cardiovascular pharmacogenomics: from discovery to implementation. *Circ Res.* 2018;122(9):1176–1190. <http://doi.org/10.1161/CIRCRESAHA.117.310965>.
- Marrero RJ, Cicali EJ, Arwood MJ, et al. How to transition from single-gene pharmacogenetic testing to preemptive panel-based testing: a tutorial. *Clin Pharmacol Ther.* 2020;108(3):557–565. <http://doi.org/10.1002/cpt.1912>.
- van der Wouden CH, Cambon-Thomsen A, Cecchin E, et al. Implementing pharmacogenomics in Europe: design and implementation strategy of the Ubiquitous Pharmacogenomics Consortium. *Clin Pharmacol Ther.* 2017;101(3):341–358. Published correction appears in *Clin Pharmacol Ther.* 2017;102(1):152. <https://doi.org/10.1002/cpt.602>.
- Barbarino JM, Whirl-Carrillo M, Altman RB, Klein TE. PharmGKB: a worldwide resource for pharmacogenomic information. *Wiley Interdiscip Rev Syst Biol Med.* 2018;10(4):e1417. <http://doi.org/10.1002/wsbm.1417>.
- Gaedigk A, Ingelman-Sundberg M, Miller NA, et al. The Pharmacogene variation (PharmVar) consortium: incorporation of the human cytochrome P450 (CYP) allele nomenclature database. *Clin Pharmacol Ther.* 2018;103(3):399–401. <http://doi.org/10.1002/cpt.910>.
- Relling MV, Klein TE, Gammal RS, Whirl-Carrillo M, Hoffman JM, Caudle KE. The clinical pharmacogenetics implementation consortium: 10 years later. *Clin Pharmacol Ther.* 2020;107(1):171–175. <http://doi.org/10.1002/cpt.1651>.
- Swen JJ, Nijenhuis M, van Rhenen M, et al. Pharmacogenetic information in clinical guidelines: the European perspective. *Clin Pharmacol Ther.* 2018;103(5):795–801. <http://doi.org/10.1002/cpt.1049>.
- Table of pharmacogenomic biomarkers in drug labeling. US Food and Drug Administration. Updated August 18, 2020. <https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling>. Accessed January 29, 2020.
- Lupski JR, Belmont JW, Boerwinkle E, Gibbs RA. Clan genomics and the complex architecture of human disease. *Cell.* 2011;147(1):32–43. <http://doi.org/10.1016/j.cell.2011.09.008>.
- O'Donnell PH, Wadhwa N, Danahey K, et al. Pharmacogenomics-based point-of-care clinical decision support significantly alters drug prescribing. *Clin Pharmacol Ther.* 2017;102(5):859–869. <http://doi.org/10.1002/cpt.709>.
- Hicks JK, Stowe D, Willner MA, et al. Implementation of clinical pharmacogenomics within a large health system: from electronic health record decision support to consultation services. *Pharmacotherapy.* 2016;36(8):940–948. <http://doi.org/10.1002/phar.1786>.
- Caraballo PJ, Bielinski SJ, St Sauver JL, Weinshilboum RM. Electronic medical record-integrated pharmacogenomics and related clinical decision support concepts. *Clin Pharmacol Ther.* 2017;102(2):254–264. <http://doi.org/10.1002/cpt.707>.
- Bielinski SJ, St Sauver JL, Olson JE, et al. Cohort profile: the right drug, right dose, right time: using genomic data to individualize treatment protocol (RIGHT protocol). *Int J Epidemiol.* 2020;49(1):23–24k. <http://doi.org/10.1093/ije/dyz123>.
- Clinical Pharmacogenetics Implementation Consortium. FDA and pharmacogenomics. Clinical Pharmacogenetics Implementation Consortium. August 2, 2019. <https://cpicpgx.org/wp-content/uploads/2019/08/fda-and-pgen-2019.pdf>. Accessed April 27, 2020.
- Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet.* 2014;46(3):310–315. <http://doi.org/10.1038/ng.2892>.
- Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc.* 2009;4(7):1073–1081. <http://doi.org/10.1038/nprot.2009.86>.
- Zhang L, Sarangi V, Moon I, et al. CYP2C9 and CYP2C19: deep mutational scanning and functional characterization of genomic

- missense variants. *Clin Transl Sci*. 2020;13(4):727–742. <http://doi.org/10.1111/cts.12758>.
20. Lopes JL, Harris K, Karow MB, et al. Targeted genotyping in clinical pharmacogenomics: what is missing? *J Mol Diagn*. 2022;15:S1525–1578(22)00006-X. <https://doi.org/10.1016/j.jmoldx.2021.11.008>.
 21. Formea CM, Nicholson WT, Vitek CR, et al. Implementation of a pharmacogenomics education program for pharmacists. *Am J Health Syst Pharm*. 2018;75(23):1939–1946. <http://doi.org/10.2146/ajhp170771>.
 22. Stanek EJ, Sanders CL, Taber KA, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. *Clin Pharmacol Ther*. 2012;91(3):450–458. <http://doi.org/10.1038/clpt.2011.306>.
 23. St Sauver JL, Bielinski SJ, Olson JE, et al. Integrating pharmacogenomics into clinical practice: promise vs reality. *Am J Med*. 2016;129(10):1093–1099.e1. <http://doi.org/10.1016/j.amjmed.2016.04.009>.
 24. Johansen Taber KA, Dickinson BD. Pharmacogenomic knowledge gaps and educational resource needs among physicians in selected specialties. *Pharmacogenomics Pers Med*. 2014;7:145–162. <http://doi.org/10.2147/PGPM.S63715>.
 25. Haga SB, Burke W, Ginsburg GS, Mills R, Agans R. Primary care physicians' knowledge of and experience with pharmacogenetic testing. *Clin Genet*. 2012;82(4):388–394. <http://doi.org/10.1111/j.1399-0004.2012.01908.x>.
 26. Giri J, Curry TB, Formea CM, Nicholson WT, Rohrer Vitek CR. Education and knowledge in pharmacogenomics: still a challenge? *Clin Pharmacol Ther*. 2018;103(5):752–755. <http://doi.org/10.1002/cpt.1019>.
 27. Wright GEB, Carleton B, Hayden MR, Ross CJD. The global spectrum of protein-coding pharmacogenomic diversity. *Pharmacogenomics J*. 2018;18(1):187–195. <http://doi.org/10.1038/tpj.2016.77>.
 28. McInnes G, Lavertu A, Sangkuhl K, Klein TE, Whirl-Carrillo M, Altman RB. Pharmacogenetics at scale: an analysis of the UK Biobank. *Clin Pharmacol Ther*. 2021;109(6):1528–1537. <http://doi.org/10.1002/cpt.2122>.
 29. US Food and Drug Administration. Evaluation of automatic class III designation for The 23andMe Personal Genome Service (PGS) Pharmacogenomic reports. US Food and Drug Administration. https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN180028.pdf. Accessed April 27, 2020.
 30. Athreya AP, Neavin D, Carrillo-Roa T, et al. Pharmacogenomics-driven prediction of antidepressant treatment outcomes: a machine-learning approach with multi-trial replication. *Clin Pharmacol Ther*. 2019;106(4):855–865. <http://doi.org/10.1002/cpt.1482>.
 31. Bielinski SJ, Olson JE, Pathak J, et al. Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. *Mayo Clin Proc*. 2014;89(1):25–33. <http://doi.org/10.1016/j.mayocp.2013.10.021>.