



# Multi-site investigation of strategies for the clinical implementation of *CYP2D6* genotyping to guide drug prescribing

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**Purpose:** A number of institutions have clinically implemented *CYP2D6* genotyping to guide drug prescribing. We compared implementation strategies of early adopters of *CYP2D6* testing, barriers faced by both early adopters and institutions in the process of implementing *CYP2D6* testing, and approaches taken to overcome these barriers.

**Methods:** We surveyed eight early adopters of *CYP2D6* genotyping and eight institutions in the process of adoption. Data were collected on testing approaches, return of results procedures, applications of genotype results, challenges faced, and lessons learned.

**Results:** Among early adopters, *CYP2D6* testing was most commonly ordered to assist with opioid and antidepressant prescribing. Key differences among programs included test ordering and genotyping approaches, result reporting, and clinical decision support. However, all sites tested for copy-number variation and nine common variants,

and reported results in the medical record. Most sites provided automatic consultation and had designated personnel to assist with genotype-informed therapy recommendations. Primary challenges were related to stakeholder support, *CYP2D6* gene complexity, phenotype assignment, and sustainability.

**Conclusion:** There are specific challenges unique to *CYP2D6* testing given the complexity of the gene and its relevance to multiple medications. Consensus lessons learned may guide those interested in pursuing similar clinical pharmacogenetic programs.

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## INTRODUCTION

The cytochrome P450 2D6 (*CYP2D6*) enzyme metabolizes approximately 25% of prescription drugs and nearly 40% of drugs frequently cited in adverse drug reaction studies.<sup>1</sup> The *CYP2D6* enzyme is the primary metabolic enzyme for select opioids, antidepressants, antiemetics, and tamoxifen. The *CYP2D6* gene is highly polymorphic, which can have important consequences for drug safety and effectiveness.

The *CYP2D6* gene has over 100 allelic variants and subvariants, which introduces a high degree of complexity for gene assays and interpretation.<sup>2–4</sup> Approximately 5–10% of individuals inherit two nonfunctional *CYP2D6* alleles (e.g., \*3, \*4, \*5) and are poor metabolizers (PMs) with no enzyme

activity.<sup>3</sup> Two to 11 percent are intermediate metabolizers (IMs) with a combination of nonfunctional and decreased function (e.g., \*41, \*17) alleles and significant reductions in enzyme activity. An additional 1–2% are ultrarapid metabolizers (UMs) with multiple *CYP2D6* gene copies (e.g., \*1/\*1×2) and increased enzyme activity.

The consequences of *CYP2D6* variation on drug response vary depending on whether the enzyme biotransforms the parent drug into a more active or less active metabolite. The prodrugs codeine, tramadol, and tamoxifen are biotransformed via *CYP2D6* into metabolites with greater pharmacologic activity than their parent compounds. Compared with normal metabolizers (NMs), PMs and IMs have lower

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concentrations of the more potent metabolites and may fail to receive therapeutic benefit from these medications.<sup>5–10</sup> On the other hand, UMs produce higher concentrations of the more potent metabolites of codeine and tramadol compared with NMs,<sup>11,12</sup> which increases risk for serious adverse events including respiratory depression and death secondary to toxic concentrations of more potent metabolites.<sup>13,14</sup>

The implications of *CYP2D6* polymorphisms are different when *CYP2D6* biotransforms drugs to less active metabolites, as with some selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, ondansetron, and tropisetron. Poor metabolizers treated with paroxetine, fluvoxamine, and tricyclic antidepressants are at increased risk for adverse drug effects secondary to higher plasma concentrations of the active parent drugs, whereas UMs are at risk for subtherapeutic concentrations of the parent drug and therapeutic failure.<sup>15,16</sup> While there is insufficient evidence on the consequences of reduced metabolism for ondansetron and tropisetron, reduced antiemetic effects have been observed in UMs.<sup>17–19</sup>

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are available for each of the drugs discussed above.<sup>3,15–17,20</sup> Many institutions within the National Institutes of Health (NIH)-funded Implementing GeNomics In pracTice (IGNITE) Network have clinically implemented, or are in the process of implementing, *CYP2D6* genotyping to assist with drug prescribing.<sup>21</sup> We previously described experiences and challenges with clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy.<sup>22</sup> Given *CYP2D6* gene complexity and relevance for multiple medications, it may present unique implementation challenges. The purpose of this paper is to compare goals and strategies for operationalizing *CYP2D6* genotype-guided therapy among early adopters and summarize challenges faced by both early adopters and those in the process of adoption and approaches to overcome key implementation barriers.

## MATERIALS AND METHODS

Institutions within the IGNITE Network Pharmacogenetics Working Group, a collaboration of pharmacogenetic researchers and implementers who share data and real-world experiences to advance genomic medicine, were invited to participate. All participating institutions had implemented *CYP2D6* testing into practice or were in the process of implementation.

An existing data collection tool was adapted to capture experiences of sites implementing *CYP2D6* genotyping.<sup>22</sup> Data elements included the testing landscape, stakeholder involvement, testing application, genotyping approaches, return of results procedures, clinical decision support (CDS), education strategies, challenges faced, and lessons learned. A second tool was designed to collect data on the testing landscape, planned test applications, and initial challenges from sites in the process of establishing *CYP2D6* testing. Data elements were selected and refined through

discussions at in-person group meetings and teleconferences from September 2017 to December 2017 for the initial tool and January 2018 to May 2018 for the second tool. Challenges faced across sites and recommendations for overcoming challenges were aggregated to a consensus list through teleconference discussions. This research was approved as exempt by the University of Florida Institutional Review Board.

## RESULTS

### Early adopters of *CYP2D6* testing

#### *Institutional landscape and CYP2D6 test implementation planning*

As of July 2018, eight institutions in the IGNITE Network had implemented *CYP2D6* genotyping and contributed information on implementation strategies (Table 1). Two institutions (Cincinnati Children's Hospital Medical Center [CCHMC] and Indiana University School of Medicine [IU]) launched *CYP2D6* testing in conjunction with testing for multiple other genes. All others had previously implemented testing for other genes—most commonly for *CYP2C19* to guide antiplatelet therapy after coronary intervention and *TPMT* to guide thiopurine dosing. Four of the programs were solely clinical implementations, while four included research components. At seven institutions, a formal precision medicine team, usually including a pharmacist, health informatics expert(s), and physician stakeholders, led the design and initiation of *CYP2D6* testing and provided program oversight (Fig. 1a, Table S1). An individual physician champion specializing in psychiatry led the initiative at the University of Alabama at Birmingham (UAB).

#### *Clinical applications of CYP2D6 testing and genotyped populations*

Most institutions reported multiple indications for which *CYP2D6* genotyping was ordered (Fig. 1b, Table S1), with antidepressant and opioid prescribing being the most common. Other indications included prescribing of antiemetic and antipsychotic agents. Three sites reported limited instances of *CYP2D6* testing to assist with tamoxifen prescribing.

Most institutions used both reactive (e.g., test ordered at time of drug prescribing) and preemptive (e.g., test ordered to assist with future prescribing) genotyping models (Table S1). At IU, the *CYP2D6* test is part of a multigene panel ordered for patients prescribed any drug with CPIC Level A evidence.<sup>23</sup> In this regard, if the prescription triggering the genotype order was for a *CYP2D6* substrate drug (e.g., opiate, SSRI), *CYP2D6* genotyping would be reactive. Otherwise, *CYP2D6* testing would be done preemptively as part of the panel to inform future prescribing of *CYP2D6* substrates. Similar models were in place at Vanderbilt University Medical Center (VUMC) and Sanford Health. Other preemptive models included testing of patients with depressive symptoms to assist with initial prescribing of antidepressants or antipsychotics, testing patients preoperatively to assist with

**Table 1** Landscape of early adopters of *CYP2D6* testing and implementation design  
Previous gene–drug pairs implemented into practice

Institution name	Institution type	Previous gene–drug pairs implemented into practice	<i>CYP2D6</i> testing Year of launch	Model
Cincinnati Children's Hospital Medical Center Indiana University	Nonprofit academic	<i>CYP2C19</i> -select SSRIs, TCAs; <i>CYP2C9</i> -warfarin; and <i>TPMT</i> -thiopurines <sup>a</sup>	2004	Clinical
Sanford Health	Academic	<i>CYP2C19</i> -clopidogrel, proton pump inhibitors, SSRIs, voriconazole; <i>TPMT</i> -thiopurines; <i>IFNL3</i> -peg-interferon; <i>SLCO1B1</i> -simvastatin; <i>CYP2C9</i> / <i>VKORC1</i> / <i>CYP4F2</i> -warfarin; <i>G6PD</i> -rasburicase; <i>CYP3A4</i> / <i>CYP3A5</i> -tacrolimus; <i>CYP2C9</i> -phenytoin; <i>CYP2D6</i> -codeine, SSRIs, atomoxetine, tramadol; <i>CYP2B6</i> -efavirenz; <i>ITPA</i> -thiopurines; <i>DPYD</i> -fluoropyrimidines <sup>a</sup>	2014	Clinical and research
University of Florida Health	Integrated health system; not-for-profit Academic	<i>CYP2C19</i> -clopidogrel; <i>TPMT</i> -thiopurines; <i>SLCO1B1</i> -simvastatin; <i>CYP2C9</i> / <i>VKORC1</i> -warfarin	2014	Clinical
Mission Health	Community health system	<i>CYP2C19</i> -clopidogrel; <i>TPMT</i> -thiopurines; <i>IFNL3</i> -peg-interferon	2015	Clinical and research
Mount Sinai Hospital University of Alabama, Birmingham	Academic	<i>HLA-B*15:02</i> -carbamazepine; <i>TPMT</i> -thiopurines	2015	Clinical and research
Vanderbilt University Medical Center	Academic	<i>CYP2C19</i> -clopidogrel, escitalopram, citalopram, sertraline; <i>SLCO1B1</i> -simvastatin; <i>CYP2C9</i> / <i>VKORC1</i> -warfarin	2016	research
		<i>CYP2C19</i> -clopidogrel	2016	Clinical
		<i>CYP2C19</i> -clopidogrel; <i>TPMT</i> -thiopurines; <i>SLCO1B1</i> -simvastatin; <i>CYP2C9</i> / <i>VKORC1</i> -warfarin; <i>CYP3A5</i> -tacrolimus	2017	Clinical

*CYP* cytochrome P450, *DPYD* dihydropyrimidine dehydrogenase, *G6PD* glucose-6-phosphate dehydrogenase, *HLA-B* human leukocyte antigen subtype B, *IFNL3* interferon lambda 3, *ITPA* inosine triphosphate pyrophosphatase, *SLCO1B1* solute carrier organic anion transporter family member 1B1, SSRIs selective serotonin receptor inhibitors, TCAs tricyclic antidepressants, *TPMT* thiopurine methyltransferase, *VKORC1* vitamin K oxidoreductase complex 1.

<sup>a</sup>*CYP2D6* testing implemented at the same time as testing for other gene–drug pairs.

opioid prescribing, and testing for primary care patients as part of a pilot pharmacogenetic implementation project. One site had a reactive only testing model where genotyping was primarily reserved for patients with depression not responding to current therapy.

### Genetic testing

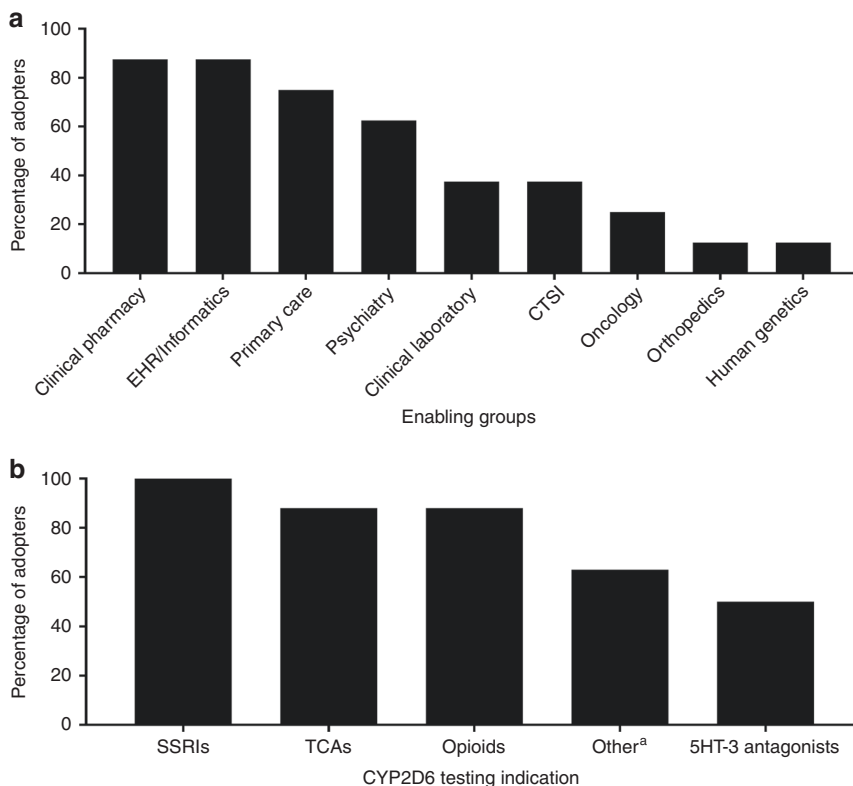
The process for *CYP2D6* test ordering varied among programs (Table S2). Prescribers electively placed genotype orders at 7 of 8 sites. Three of these sites also ordered clinical genotyping for participants in pharmacogenetic studies. At one site, *CYP2D6* genotyping was preselected on the order set for patients admitted to a psychiatric unit as part of routine care.

Six sites performed testing onsite in a College of American Pathologists (CAP)/CLIA-certified laboratory (Table S2). Deciding factors in choosing in-house testing (versus outsourcing) included having existing expertise and infrastructure for clinical genotyping, desire to have the ability to alter variants tested as evidence evolves, and in the case of very early adopters, the limited availability of commercial testing when the program began. While genotyping platforms varied across these sites, all tested and reported allele-defining variants for \*2, \*3, \*4, \*6, \*9, \*10, \*17, and \*41, at minimum, in addition to gene deletion (\*5) and copy-number variation (CNV) (Fig. 2). Four institutions genotyped *CYP2D6* as part of a multigene panel. Factors considered in genotyping platform selection were workflow; turnaround time; ability to batch samples, detect full gene deletion and duplication, and customize variants tested; capability for multiplexed targeted genotyping; and FDA clearance. Four sites had validated assays for blood and either buccal cell or saliva samples. Genotype test turnaround time ranged from 2 to 14 business days across sites.

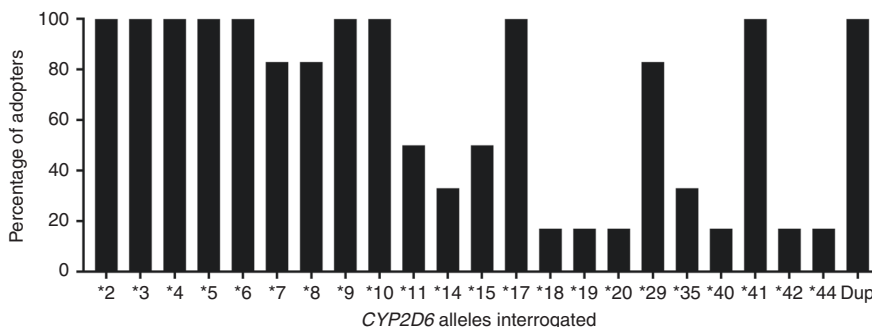
Two sites relied solely on commercial or reference laboratories for genotyping. Two sites with in-house genotyping capabilities also reported use of commercial laboratories in select cases, such as when patients preferred noninvasive sample collection and in-house genotyping was validated for blood samples only or when patient payment assistance, available through some commercial laboratories, was desired. Factors influencing the choice of outside laboratory included which genes were tested besides *CYP2D6*, cost of testing, characteristics of patient assistance programs, and provider knowledge/awareness of a specific laboratory.

### Phenotype assignment

All but one site reported *CYP2D6* phenotype assignment based on activity scores as described in the current CPIC guidelines;<sup>3</sup> IU classified patients with one no-function and one normal function allele (e.g., \*1/\*4) as NM for codeine, per CPIC guidelines, and as IM for tramadol, per Dutch Pharmacogenetic Working Group guidelines.<sup>24</sup> Three sites reported that either the laboratory report or patient-specific clinical consult note mentioned use of *CYP2D6* inhibitors that can cause phenoconversion (i.e., change the phenotype from that predicted based on genotype alone).



**Fig. 1 Stakeholder involvement and CYP2D6 genotyping applications.** (a) Groups enabling CYP2D6 genotype implementation at eight early adopters of testing. EHR electronic health records, CTSI Clinical Translational Science Institute. (b) Target drugs for CYP2D6 genotyping among eight early adopters. SSRI selective serotonin reuptake inhibitor, TCA tricyclic antidepressant. <sup>a</sup>Aripiprazole, haloperidol, olanzapine, perphenazine, risperidone, thioridazine, venlafaxine, atomoxetine.



**Fig. 2 CYP2D6 variations tested across sites.** Dup duplications.

*Communication of results, approach to therapy modification, and education strategies*

All institutions reported CYP2D6 test results in the EHR, usually within the “laboratory results” section (Table S3). Six sites reported both CYP2D6 genotype and predicted phenotype (metabolizer status) in the laboratory report, and two sites (CCHMC and IU) additionally provided genotype-specific drug therapy recommendations. All but one institution had a designated service or pharmacist available to provide genotype-informed drug therapy recommendations, and four institutions provided an automatic consultation via

personal communication or an electronic consult note. Five of eight sites provided downstream alerting or electronic CDS triggered with future drug orders within the EHR, most commonly with codeine, tramadol, and antidepressants. A sixth site was in the process of building electronic CDS.

Five programs provided patients with their test results via a patient web portal. Most programs provided education to patients about CYP2D6 testing through disseminated brochures, pamphlets, or other literature, or in-person education. Authors reported that providers were most engaged when education was delivered through focused discussions with

providers who prescribe the target drugs, particularly when directly related to a patient case, and in-services to specialty groups.

### Institutions in the process of implementing *CYP2D6* testing into practice

Eight institutions were in the process of *CYP2D6* implementation (Table S4). All but one had previously implemented testing of other genes, with *CYP2C19* being most common. Precision medicine “teams” or “steering committees” were the drivers of these efforts at most sites. Four institutions were in the process of engaging stakeholders and leadership support. Development of informatics-related support and resources and selection or validation of the genotyping platform were also commonly identified as a current step in the implementation process. Nearly all locations were weighing considerations related to panel (multigene) versus single-gene testing and whether to conduct *CYP2D6* testing internally versus through a reference laboratory. All but two institutions were planning to implement *CYP2D6* testing as part of clinical practice (as opposed to a research protocol). Varying therapeutic areas were identified for implementation, although pain management and psychiatry were specifically noted by 6 and 5 institutions, respectively. Institutions anticipated deploying *CYP2D6* testing in settings ranging from targeted populations and specific clinical care locations to a larger, institution-wide general patient population.

### Implementation challenges and lessons learned

Table 2 summarizes challenges reported and lessons learned across sites. A major challenge was the inability to determine which allele was duplicated or multiplied for heterozygous genotypes with CNV, which often led to the inability to unambiguously assign phenotype. Further challenges were variable phenotype assignment based on the *CYP2D6* substrate, and the potential for phenoconversion with concomitant *CYP2D6* inhibitor use. An additional challenge reported by sites in the process of adopting testing was related to potential risk management issues in the event that appropriate action was not taken in response to genotype results. Sites reported that providers were especially concerned given the multiple drug substrates for *CYP2D6* whose response may be impacted by genotype. This concern was not shared by sites that had already adopted testing, though they reported it was discussed prior to implementation.

Choosing genotyping methodology that detects CNV was felt to be critical to identify UMs (due to gene duplication) and some IMs (due to gene deletion). Recognizing that most genotype platforms at present cannot detect which allele is duplicated/multiplied, sites agreed that a process must be in place for assigning phenotype for heterozygous genotypes with CNV to allow for appropriate reporting and downstream CDS.<sup>25,26</sup> Most sites used a ranged phenotype (e.g., NM to UM) when this occurred. Also ranked as important was having multidisciplinary stakeholder involvement and in particular, a physician champion, to facilitate implementation

and additional stakeholder buy-in. It is in the authors’ consensus opinion, that while not required for implementation, in an ideal future state where feasible to do so, the following would also be in place to support the provision of *CYP2D6* genotype-guided therapies: (1) noninvasive methods for DNA sample collection, especially for pediatric patients; (2) assay methods capable of assessing which allele was duplicated or multiplied; (3) rapid or preemptive testing to minimize or eliminate delays in prescribing decisions; (4) *CYP2D6* result (genotype and phenotype) reporting in an easily accessible location in the EHR, preferably one for lifetime results, and as discrete data to enable automated CDS; (5) automated CDS that accounts for phenoconversion secondary to use of *CYP2D6* inhibitors; and (6) a mechanism for patients and providers to access genotype results throughout the patient’s life.

### DISCUSSION

In surveying early adopters of *CYP2D6* genotyping to guide prescribing decisions, we found multiple approaches to implementation, even within the same institution, with sites reporting use of both reactive and preemptive genotyping models, single and multigene testing, and clinical and research-based deployment, much like in our previous report of implementation of *CYP2C19*-guided antiplatelet therapy.<sup>22</sup> Other similarities between implementing *CYP2D6*-guided therapies and *CYP2C19*-guided antiplatelet therapy<sup>22</sup> included the role of a physician champion working alongside clinicians who ordered and applied test results clinically and use of a multidisciplinary team approach, including pharmacists and health informatics experts, to lead implementation. While *CYP2D6* testing was most commonly ordered to assist with antidepressant and opioid prescribing, most institutions applied genotype results to multiple therapies. In addition, most sites had electronic CDS tools in place or under development and designated personnel to assist with interpretation and translation of genotype results to inform prescribing decisions. Provider education and building evidence to support the utility and cost-effectiveness of testing were recognized as keys to driving greater stakeholder engagement.

There were also notable differences between *CYP2D6* testing and *CYP2C19*-guided antiplatelet therapy.<sup>22</sup> Whereas *CYP2C19*-guided antiplatelet therapy was most often the first pharmacogenetic implementation, *CYP2D6* genotyping was typically a subsequent deployment or only implemented as part of a larger, more comprehensive pharmacogenetics program. This may be reflective of the relative complexity of the *CYP2D6* genotype and resultant challenges related to genotype procedures and phenotype assignment. In contrast to *CYP2C19* where all institutions deployed testing on site, half of the early adopters of *CYP2D6* testing leveraged external reference labs as primary or supporting *CYP2D6* testing facilities. For *CYP2C19*-guided antiplatelet therapy, institutional efforts were focused on a single use case and engaged the interventional cardiology practitioners. This



**Table 2** Primary implementation challenges and lessons learned

Challenges	Lessons learned
<b>Obtaining provider/stakeholder buy-in</b>	
<ul style="list-style-type: none"> <li>Limited provider exposure to pharmacogenetics and awareness about genotyping availability</li> <li>Limited data on clinical utility of <i>CYP2D6</i> genotype-guided drug therapy</li> </ul>	<ul style="list-style-type: none"> <li>Having broad, multidisciplinary program buy-in, including a physician champion, facilitates implementation</li> <li>Important to educate providers about testing availability and applications to prescribing decisions and to engage physicians when building CDS language</li> </ul>
<b>Sample collection and <i>CYP2D6</i> genotyping</b>	
<ul style="list-style-type: none"> <li>Multiple single-nucleotide variants, gene deletion, duplication, and multiplication define alleles</li> <li>Difficult to quantitate duplication/multiplication or determine which allele is duplicated/multiplied in heterozygotes</li> </ul>	<ul style="list-style-type: none"> <li>Noninvasive sample collection method facilitates testing for children and when no phlebotomy services are available on site</li> <li>Saliva and buccal cell samples can give inconsistent copy-number results</li> <li><i>CYP2D6</i> genotype expertise important for establishing genotyping procedures and interpreting results</li> <li>Platform must be able to detect gene deletion and copy-number variation, and a process should be in place for indeterminate genotypes due to copy-number variation</li> </ul>
<b>Genotype reporting and phenotype assignment</b>	
<ul style="list-style-type: none"> <li>Large number of possible <i>CYP2D6</i> diplotypes complicates automation of EHR processes</li> <li>Phenotype assignment may vary depending on drug substrate<sup>a</sup></li> <li>Moderate to strong <i>CYP2D6</i> inhibitors can cause phenoconversion</li> <li>EHR changes may interfere with functioning of electronic CDS</li> </ul>	<ul style="list-style-type: none"> <li>Genotypes should be reported in a consistent location in the EHR</li> <li>Entering genotype results as discrete data enables genotype-specific electronic CDS</li> <li>Designated personnel and/or electronic CDS are important to assist with integrating genotype results into prescribing decisions</li> <li>Need CDS system that assigns phenotype based on drug substrate and accounts for phenoconversion</li> <li>Quality control procedures are important for ensuring electronic CDS maintained with EHR updates</li> </ul>
<b>Sustainability</b>	
<ul style="list-style-type: none"> <li>Building a reimbursement model</li> <li>Updates to genotype reports and automated CDS needed as evidence evolves to support genotype-guided prescribing for additional medications</li> </ul>	<ul style="list-style-type: none"> <li>Clinical outcomes and cost-effectiveness data may support reimbursement and additional stakeholder buy-in</li> <li>Personnel need to stay abreast of scientific developments in the field and update reports and decision support as needed</li> </ul>
<b>Personnel issues<sup>b</sup></b>	
<ul style="list-style-type: none"> <li>Having sufficient personnel to direct and support implementation</li> </ul>	<ul style="list-style-type: none"> <li>Create partnerships with pharmacists or other clinicians on clinical teams through a decentralized model</li> </ul>
<b>Risk management issues<sup>b</sup></b>	
<ul style="list-style-type: none"> <li>Concern if there is an actionable variant and no one acts on it</li> </ul>	<ul style="list-style-type: none"> <li>While risk management issues may be part of the discussion prior to implementation, they were no longer voiced as a concern postimplementation</li> </ul>

CDS clinical decision support, EHR electronic health record.

<sup>a</sup>Combination of one normal function allele plus one no-function allele may be assigned the intermediate metabolizer phenotype for tamoxifen, but the normal metabolizer phenotype for codeine, tricyclic antidepressants, and select selective serotonin reuptake inhibitors).<sup>14,15,19</sup>

<sup>b</sup>Challenges specific to institutions in the process of implementing.

allowed for highly tailored workflows and targeted educational efforts. In our experiences, *CYP2D6* implementation efforts, in contrast, required engaging practitioners across multiple practice areas (e.g., psychiatry, primary care, surgery, and oncology) given the multiple drug substrates for the *CYP2D6* enzyme (e.g., antidepressants, opioids, antiemetics, tamoxifen). This may require a broader strategy and more extensive educational effort to rally the practice groups in acceptance and adoption of *CYP2D6* genotype-guided medication therapy. In addition, unlike *CYP2C19* testing for

antiplatelet guidance where patients are undergoing an invasive procedure and collection of a blood sample for genotyping was not an issue, having a noninvasive sample collection method for *CYP2D6* testing was deemed important as it is commonly done in an outpatient setting where phlebotomy may not be available or for children who may be especially averse to blood collection.

There were several common challenges with *CYP2D6*-guided therapy. Some were technical in nature and related to *CYP2D6* gene complexity, with variation including

single-nucleotide polymorphisms, deletions and multiple copies of the entire gene, and fusions with downstream pseudogenes.<sup>4</sup> As the field moves more toward genome sequencing, these unique characteristics of *CYP2D6* make extracting the accurate information from short-read genome sequencing difficult and require special informatics approaches to accurately call the alleles.<sup>27,28</sup> Thus, sites agreed that local *CYP2D6* expertise was an important asset to implementation, and in the absence of such, sites may prefer to utilize a commercial laboratory for genotyping.

Despite gene complexity and independent assay development, there was remarkable similarity across sites in the variants tested. No site was performing comprehensive analysis of all known *CYP2D6* variants, and each site tested for copy-number variation and assays enabling the assignment of nine common alleles. While having a list of “must-test alleles” would be helpful to guide assay development, in the absence of that, the list of variants tested across sites may be useful for other institutions considering *CYP2D6* testing.

A second layer of technical challenges surround reporting test results in EHRs and use of results in CDS. Many systems do not have mature EHR systems in place for storing, reporting, and using genetic results. Historically, many genetic testing results have been reported in EHRs in text-based reports or scanned documents. Building the technical capability for genetic results to be stored as discrete data enables downstream applications like genotype-specific electronic CDS but requires an initial investment and ongoing maintenance. In addition, accounting for use of *CYP2D6* inhibitors is important for refining *CYP2D6* phenotype given evidence of altered enzyme activity, disposition of *CYP2D6* substrates, and drug response with *CYP2D6* inhibitors.<sup>29–32</sup> Strong inhibitors (e.g., paroxetine) can convert NMs, based on genotype results, to PMs, whereas moderate inhibitors (e.g., duloxetine) can convert NMs, based on genotype, to IMs.<sup>3,32</sup> More sophisticated decision support may be necessary to account for this phenoconversion with concomitant use of *CYP2D6* inhibitors.

Challenges that were specific to the early implementation phase included the unknown ramifications of failure to act on genotype results, especially because *CYP2D6* genotype has implications for multiple therapies, and having sufficient personnel in place to facilitate implementation. Interestingly, early test adopters stated that potential risk management issues were discussed prior to implementation but are no longer perceived as a barrier, indicating that potential risk ramifications around pharmacogenetic testing are a common perceived obstacle, but may not be a practical reality at this time. Indeed, there are limited examples of a legal action involving the use or lack of use of pharmacogenetic information in clinical practice.<sup>33</sup> Regarding personnel, early adopters were able to overcome this obstacle by engaging across departments, teams, and services to build multi-disciplinary teams. Of note, the effort of those teams is ongoing, as *CYP2D6* testing and pharmacogenetic CDS requires maintenance in the face of laboratory and EHR

changes, and continual assessment of new developments in all aspects from variant detection to prescribing advice.

Strengths of this research are the inclusion of multiple institutions and different applications of genotype results, increasing the generalizability of challenges faced and lessons learned. A potential limitation is that all institutions were from a common research network and approaches to implementation may be similar for this reason. In addition, we do not provide data on specific recommendations provided or implementation success metrics because our intent was to survey the landscape of *CYP2D6* testing across multiple sites. Future studies may focus on individual applications of *CYP2D6* testing. While we provide information on the platforms used for genetic testing, it was beyond the scope of the paper to provide details on genotyping methodology in each laboratory. Finally, we do not address the cost of implementation or genetic testing. The cost of analytical validation can be significant with a new laboratory test (approximately \$30,000 in reagents alone based on personal observations [V.M.P.]), and increases further if the laboratory has to invest in new equipment. The cost of genetic testing for institutions and patients or payers is influenced by multiple factors, including technology used for the assay, turnaround time, number of samples, and state-specific rules and regulations. With evolving technology and policies, genotyping costs are also variable over time.

In summary, despite of the complexity of the *CYP2D6* genotype and associated challenges with genotype interpretation and phenotype assignment, multiple institutions have prioritized implementation of *CYP2D6* genotyping to inform drug prescribing. To our knowledge, this is the first description of strategies for *CYP2D6* testing to guide drug prescribing across multiple sites along with challenges faced and important lessons learned. Implementation resources from our sites, including supporting literature, CDS language, and education materials are available through the IGNITE website (<https://ignite-genomics.org/>). Our experiences and lessons learned may be valuable for other institutions seeking to implement *CYP2D6* testing.

#### SUPPLEMENTARY INFORMATION

The online version of this article (<https://doi.org/10.1038/s41436-019-0484-3>) contains supplementary material, which is available to authorized users.

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## DISCLOSURE

N.A.L. serves as a consultant for Admera Health. V.M.P. is affiliated with the Indiana University School of Medicine Pharmacogenomics Laboratory, which is a fee-for-service clinical laboratory. J.K.H. receives clinical trial support from OneOme and serves as a consultant for Quest Diagnostics. R.A.G. is employed by OneOme, a for-profit genotyping laboratory. L.H.C. has received research funding from Mallinckrodt Pharmaceuticals. The other authors declare no conflicts of interest.

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