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ARTICLE

Multisite evaluation of institutional processes and implementation determinants for pharmacogenetic testing to guide antidepressant therapy

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Abstract

There is growing interest in utilizing pharmacogenetic (PGx) testing to guide antidepressant use, but there is lack of clarity on how to implement testing into clinical practice. We administered two surveys at 17 sites that had implemented or were in the process of implementing PGx testing for antidepressants. Survey 1 collected data on the process and logistics of testing. Survey 2 asked sites to rank the importance of Consolidated Framework for Implementation Research (CFIR) constructs using best-worst scaling choice experiments. Of the 17 sites, 13 had implemented testing and four were in the planning stage. Thirteen offered testing in the outpatient setting, and nine in both outpatient/inpatient settings. PGx tests were mainly ordered by psychiatry (92%) and primary care (69%) providers. *CYP2C19* and *CYP2D6* were the most commonly tested genes. The justification for antidepressants selected for PGx guidance was based on Clinical Pharmacogenetics Implementation Consortium guidelines (94%) and US Food and Drug Administration (FDA; 75.6%) guidance. Both institutional (53%) and commercial laboratories (53%) were used for testing. Sites varied on the methods for returning results to providers and patients. Sites were consistent in ranking CFIR constructs and identified patient needs/resources, leadership engagement, intervention knowledge/beliefs, evidence strength and quality, and the identification of champions as most important for implementation. Sites deployed similar implementation strategies and measured similar outcomes. The process of implementing PGx testing to guide antidepressant therapy varied across sites, but key drivers for successful implementation were similar and may help guide other institutions interested in providing PGx-guided pharmacotherapy for antidepressant management.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Many centers are beginning to utilize pharmacogenetic (PGx) testing to guide antidepressant therapy but this is not yet part of routine clinical practice. Implementation science, with its focus on systematically assessing implementation barriers and strategies, can enhance the integration of PGx into clinical care.

WHAT QUESTION DID THIS STUDY ADDRESS?

We evaluated the approaches taken by early adopters to operationalize clinical PGx testing for antidepressant management and assessed what factors were perceived to be important to the implementation.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The process of providing PGx testing, such as where the testing was performed (i.e., in-house vs. commercial laboratory) and how results were returned to patients and providers, varied across sites. However, there were several common key factors that determined successful PGx implementation, such as the use of Clinical Pharmacogenetic Implementation Consortium guidelines, leadership engagement, identification of clinical champions, and deployment of educational strategies for clinical providers.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Experiences gained by early adopters of PGx implementation may help guide other institutions interested in providing PGx-guided pharmacotherapy for antidepressant medications.

INTRODUCTION

Antidepressants are commonly prescribed medications used by ~ 13% of the population.[1] Although originally developed and approved for the treatment of major depressive disorder (MDD), many antidepressants are also used to treat other conditions, such as anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder. Approximately one in five people in the United States meets diagnostic criteria for a depressive or anxiety disorder at some point in their lifetime, both of which are commonly treated with antidepressants.[2] Identifying effective treatment(s) for a given patient can be difficult as clinicians are challenged to select antidepressants based on a number of factors.[3] Less than half of patients with depression achieve some response to a first antidepressant, only a third experience remission, and a third do not have adequate improvement or tolerability to two or more trials of an antidepressant.[4] Each trial involving a new antidepressant medication or dose in a given patient requires 4–8 weeks to evaluate effectiveness. This can result in extended trial-and-error odysseys and adverse effect experiences across a period of months to years, while a patient's depression remains inadequately treated.

Common genetic variation may explain 42% of individual differences in antidepressant response,[5] highlighting the potential opportunities for using pharmacogenetic (PGx) information as part of clinical care for some psychiatric conditions. Genetic variability in the *CYP2D6* and *CYP2C19* drug metabolizing enzymes impacts dose-adjusted exposure to a number of commonly used antidepressants.[6] Minimal doses and exposures of antidepressant medications are required for clinical efficacy and dose relationships with side effects and tolerability are well-established.[7] Large cohort studies suggest that poor and ultrarapid metabolizer status is associated with treatment discontinuation, side effects, or lack of efficacy to some antidepressants.[8] Prospective PGx test guidance may improve symptom remission in patients with MDD requiring antidepressant therapies.[9]

Although many psychiatrists and primary care providers agree that PGx testing will become part of standard care when prescribing psychotropics,[10] established processes of how best to incorporate this technology into clinical workflows are lacking. To aid the translation of PGx results for implementation into clinical practice, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was established to create peer-reviewed, evidence-based guidelines.[11] The CPIC has published guidelines for how to use existing PGx information for greater than 50 medications, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).[12,13] Furthermore, the US Food and Drug Administration (FDA) recognizes PGx associations with antidepressants that may be clinically relevant.[14] However, there are cautionary recommendations or position statements on clinical use of PGx testing from society guidelines focused on mental health.[15,16]

Evidence-based practices can take 15–20 years to be incorporated into routine clinical care.[17] Assessing and quantifying barriers to implementation within and external to a healthcare organization are essential for promoting the efficient adoption of novel interventions. Implementation science is an emerging field that can evaluate strategies to enhance the integration of genomic medicine interventions as applied to mental health clinical practice.[18]

The Implementing Genomics in Practice (IGNITE) network is a multidisciplinary collaboration focused on the development, implementation, and dissemination of methods that incorporate genomic medicine into clinical care.[19] Previous work by the network identified factors based on the Consolidated Framework for Implementation Research (CFIR) that were vital to the adoption of genomic medicine interventions across six clinical sites,[20,21] although these were not necessarily specific to PGx. The growing availability of PGx tests to guide prescribers of mental health medications along with previously described challenges with clinical application presents a need to identify successful approaches to implementation for antidepressants. To understand factors important for the implementation of PGx testing to guide antidepressant prescribing, we surveyed 17 institutions of the IGNITE PGx Working Group. We conducted two surveys to understand (1) how sites were operationalizing PGx testing within their center and (2) the relative importance of implementation characteristics at institutions with planned or established programs to guide antidepressant use with PGx.

METHODS

Funded and affiliate members of the IGNITE Network that had either implemented or were planning to implement clinical laboratory testing (e.g., performed in a College of American Pathologists [CAP] accredited/Clinical Laboratory Improvement Amendment [CLIA] certified laboratory) to guide antidepressant prescribing were invited to participate in the surveys. Two electronic surveys (Supplementary Material) were developed to assess and describe institutional and practice environment characteristics and workflows for delivering PGx results and factors important for the implementation of PGx testing to guide antidepressant therapy. Survey 1 was developed by the IGNITE PGx Working Group to capture 34 measures regarding the process of implementing PGx

for guiding antidepressant therapies. Data collection was completed at each site by IGNITE institutional representatives using a Research Electronic Data Capture (REDCap) database hosted at the University of Florida.[22] The data collection tool was piloted for feasibility and clarity prior to dissemination to participating sites. To reconcile completed survey irregularities, study investigators followed up with individual communications. Some questions allowed a free-text response, which were subsequently recoded as an additional response or grouped into similar survey choices. Survey 1 was administered and completed between June 1, 2020, and October 1, 2020.

Survey 2 was distributed to those sites that completed survey 1 with the goal of identifying: (1) which factors were most important when implementing PGx for antidepressants, (2) which implementation outcomes, as defined by Proctor et al.,[18] were observed or planned to be evaluated, and (3) the implementation strategies that were perceived to be most effective during active or planned implementation. Survey 2 was informed by the CFIR because (1) it is the framework that was used in prior IGNITE work[20,21]; and (2) it is broadly applied in clinical implementation research and provides a stakeholder engaged framework.[23] The CFIR is composed of 37 constructs organized into five major domains that may influence implementation of an intervention. The domains are (1) Outer Setting (e.g., economic or political context), (2) Inner Setting (e.g., institutional climate or readiness for change), (3) Characteristics of Individuals (e.g., knowledge or beliefs about the intervention, individual stage of change), (4) Intervention Characteristics (e.g., evidence strength, quality, and cost), and (5) Process of Implementation (e.g., planning the interventions and engaging opinion leaders). To evaluate the importance of implementation factors, participants were asked to rank all constructs of the CFIR[24] across its five domains using best-worst scaling (BWS) choice experiments: Outer Setting (4 constructs evaluated in 3 choice tasks), Inner Setting (14 constructs evaluated in 9 tasks), Intervention Characteristics (9 constructs evaluated in 6 tasks), Characteristics of Individuals (5 constructs evaluated in 3 tasks), and Process (8 constructs evaluated in 5 tasks). Choices included additional constructs from the Genomic Medicine Integrative Research Framework[25] not specified in CFIR but may be pertinent to PGx testing. The BWS method has been used to determine preferences for a wide range of health care applications.[26] BWS is a low-burden method for quantitatively prioritizing a large number of observed factors that offers advantages to traditional rating or ranking techniques. Rather than only choosing the best alternative, respondents in BWS select the best (highest ranking) and worst (lowest ranking) items in a series of tasks, which provides ratio scales of importance. BWS circumvents common limitations with techniques that require individuals to rank alternatives, such as Likert-style rating scales. Specifically, this method addresses concerns that respondents do not use the ratings the same way across responses as well as the challenge of evaluating multiple items that have similar importance. Survey 2 was administered and completed between September 15, 2020, and December 15, 2020.

This research was approved as exempt by the University of Florida Institutional Review Board.

Analysis

Descriptive statistics were characterized for all sites and then stratified by sites with established implementation programs and those in the planning stages. Exploratory comparisons between implemented and planning sites were conducted using the χ^2 or Fisher's exact tests for categorical data and independent *t*-tests for continuous data. Both the BWS data collection and the quantitative analysis to estimate individual preferences for each construct were conducted using Lighthouse Studio (version 9.9.2; Sawtooth Software). We used multinomial logistic regression to estimate the probabilities of respondents choosing particular alternatives. Probability scores were then transformed into probability scaled scores (i.e., relative importance scores), which allowed for comparisons across attributes. The importance score summarizes how much impact the attribute had upon choice, given the range of constructs under evaluation. Importance scores are calculated as percentages of the range of constructs (that sum to 100% for each domain). Additionally, we applied a Bayesian approach using a Monte Carlo Markov chain to compare and update respondents' estimates on the basis of the distribution of preferences from other respondents. Utility estimates of each construct were averaged after 10,000 random draws.

RESULTS

Survey 1

Institutional characteristics and programmatic drivers

Representatives of 17 sites responded and indicated that they had implemented ($n = 13$) or were in the planning phases ($n = 4$) of implementing PGx to guide antidepressant utilization. Detailed institutional characteristics are included in Table S1. All respondents completed both surveys. These were largely academic ($n = 12$) institutions

implementing or planning implementation in the context of clinical care. Among sites that had already implemented, 13 (100%) were testing in the outpatient setting and nine (69%) were also testing in the inpatient setting.

Most respondents indicated that programmatic initiatives for PGx-guided antidepressant implementation were initially championed by a dedicated precision medicine or PGx service (71%) and that this group was also leading current activities at most institutions (88%; Figure 1). Although fewer respondents indicated PGx leadership roles from psychiatry service lines, they were noted as essential collaborators by most (94%). Collaborating clinical or academic units spanned a range of groups within institutions (e.g., informatics, laboratory medicine, nursing, pharmacy, primary care, and psychiatry). PGx tests were predominantly ordered by psychiatry (92% of respondents) and primary care (69%; Figure 1).

Tables 1 and S2 provide additional details about testing and workflow considerations. Most (88%) respondents indicated that they did not require specific diagnoses or utilization of prior antidepressants for a test to be ordered. All institutions with established implementation programs utilized multigene PGx testing approaches, with five sites also offering single gene test orders. Most institutions included *CYP2C19* and *CYP2D6* genotypes as a core genetic basis for antidepressant guidance with five of the 13 implementing sites also offering testing for other drug metabolism or pharmacodynamic genes. Most respondents indicated PGx guidance was used for tailoring SSRIs and TCAs (Figure 3). The justification for antidepressants selected for PGx guidance was largely based on CPIC (94%) and FDA (75.6%) guidance with other groups referencing the Dutch Pharmacogenetics Working Group (DPWG; 23.5%) or internal evidence review (17.6%; Figure S1).

Testing and operational workflow

Figure 2 provides an overview of PGx testing workflow. Most institutions (82%) indicated that prescribers were responsible for identifying patients for testing, whereas 53% noted options for patient self-referral, and 35% indicated that pharmacy referrals were also available. Both institutional (in-house) and commercial laboratories were used for testing.

Return of results

The majority (76%) of respondents indicated that results were (or will be) returned to providers via the electronic health record (EHR), whereas 47% utilized prescriber-specific portals associated with commercial tests (Figure 2, Table S2). Most (82%) respondents indicated that prescribers communicated results to patients, whereas less than 30% of institutions reported that results

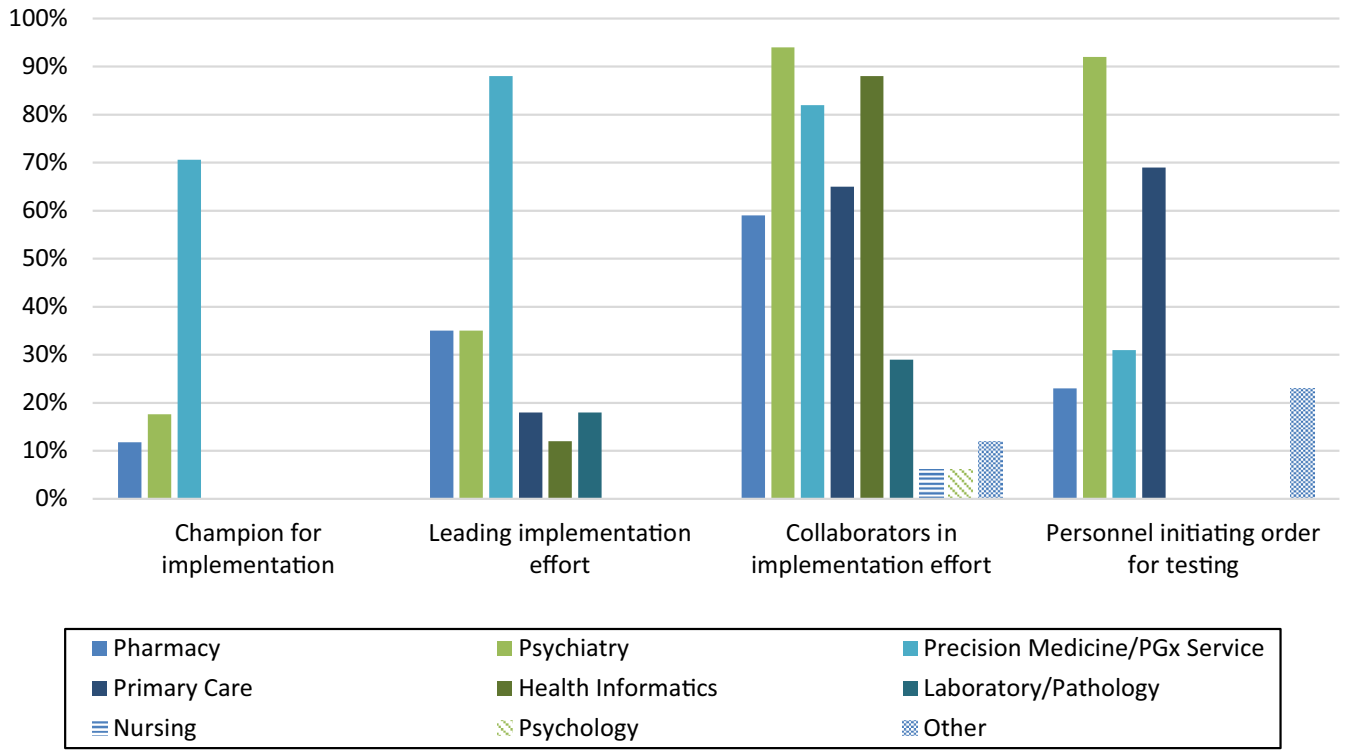

FIGURE 1 Personnel involved in antidepressant pharmacogenetic testing

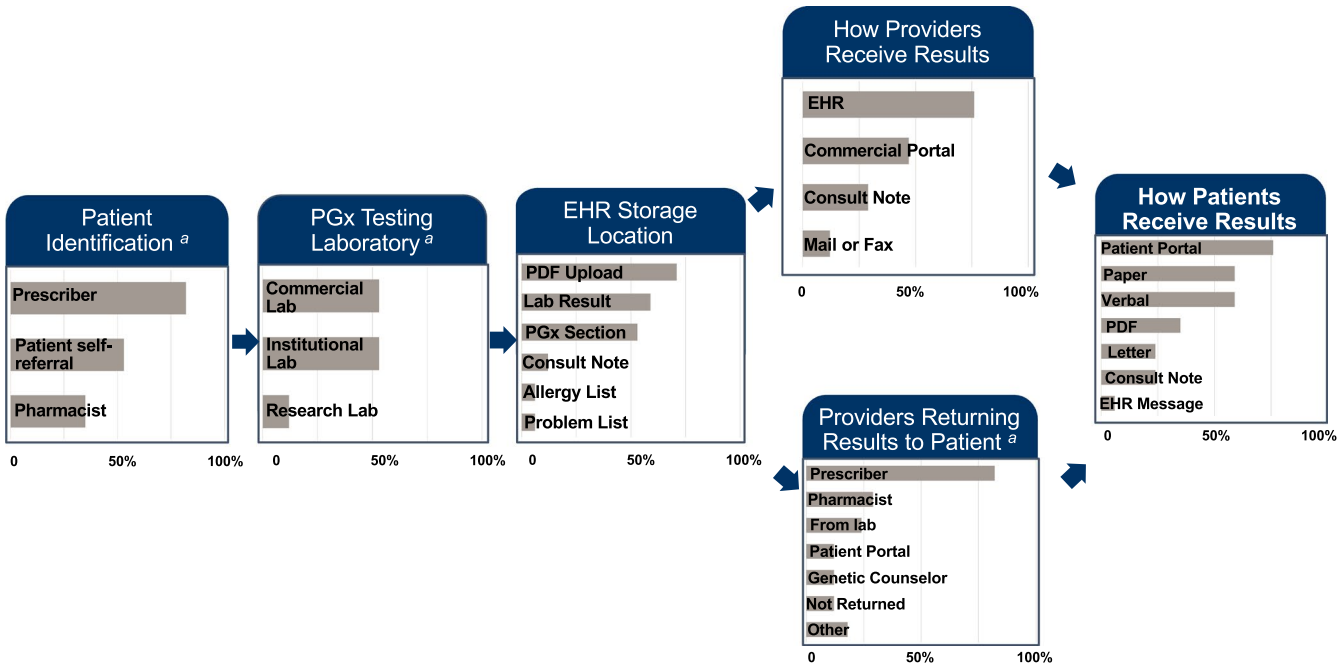

FIGURE 2 Pharmacogenetic testing and return of results workflow. The most common methods for PGx testing and return of results from 17 sites implementing or planning to implement PGx testing for tailoring antidepressant therapy are provided. EHR, electronic health record; PDF, portable document format; PGx, pharmacogenetic. [a]The most common methods are displayed in the figure; additional options can be found in Table S2

were communicated by pharmacists, genetic counselors, or through laboratory reports.

Of the sites that had already implemented, prescribing decisions were further supported using expert consultation (77%), portable document format (PDF) reports (69%), and electronic clinical decision support (CDS; 62%; Table 1). Most institutions indicated that they uploaded the genotype results as discrete variables (e.g., with star [*] allele nomenclature) into the EHR (65%).

Survey 2

Implementation characteristics

Using BWS, respondents from each institution ranked CFIR constructs important to the uptake of PGx testing to guide antidepressant prescribing. Figure 4 shows the ranking of the top three constructs within each domain across all sites. The top constructs for each domain identified as most important for PGx implementation were: patient needs/resources (domain: Outer Setting), leadership engagement (domain: Inner Setting), clinician knowledge and beliefs about the intervention (domain: Characteristics of Individuals), strength and quality of the evidence supporting PGx testing (domain: Intervention Characteristics) and the identification of champions to support PGx testing (domain: Process). A complete ranking of all constructs within each domain can be found in Table S3 with further stratification by sites that had already implemented PGx testing for antidepressants and those that were in the planning phases. The top ranked constructs between sites that had already implemented PGx testing and those in the planning phase were largely consistent with a few exceptions. Compatibility (domain: Inner Setting) or fit of antidepressant PGx testing with individual values or institutional workflow, was ranked second among those in the planning phase, whereas it ranked sixth among those that had implemented. Formally appointed internal implementation leaders (domain: Process) was ranked as the third most important construct among sites that had implemented, whereas it ranked fifth among those in the planning phase. Sites were also consistent in those constructs that were least important for implementing PGx testing, which included cosmopolitanism (domain: Outer Setting) or the degree to which the organization is connected to other institutions; organization incentives and awards (domain: Inner Setting); individual identification with the organization (domain: Characteristics of Individuals); design quality and packaging of the PGx intervention (domain: Intervention Characteristics); and identifying external change agents (domain: Process).

Sites were also asked about what outcomes they were collecting to assess implementation success. Table 2 reports the most common outcomes measured. Most sites were measuring implementation outcomes, including

TABLE 1 Pharmacogenetic testing and operational workflow for guiding antidepressant therapy

Process	Total ($n = 17$) *N* (%)	Stage of implementation: Implemented total ($n = 13$) *N* (%)	Stage of implementation: Planning Total ($n = 4$) *N* (%)
Prior antidepressant treatment required			
No	15 (88)	12 (92)	3 (75)
Age of patients eligible for PGx testing			
<18 years	1 (6)	0 (0)	1 (25)
≥18 years	4 (24)	4 (31)	0 (0)
No age restriction	12 (71)	9 (69)	3 (75)
Type of PGx test[a]			
Single gene	7 (41)	5 (39)	2 (50)
Multigene	16 (94)	13 (100)	3 (75)
Method used for genotyping			
Genotyping	17 (100)	13 (100)	4 (100)
Sequencing	3 (18)	3 (23)	0 (0)
Testing payment method			
Patient/self-pay	12 (71)	8 (62)	4 (100)
Insurance/third party billed	11 (65)	10 (77)	1 (25)
Research funded	7 (41)	5 (39)	2 (50)
Other	3 (18)	3 (23)	0 (0)
Genes used to guide antidepressant therapy			
CYP2C19	16 (100)[b]	13 (100)	3 (100)[c]
CYP2D6	15 (94)[b]	12 (92)	3 (100)[c]
Other	5 (39)[b]	5 (39)	0 (0)
Established institutional workflow for ordering and return of results			
Yes	12 (71)	10 (77)	2 (50)
Results reported as discrete data			
Yes	11 (65)	9 (69)	2 (50)
Clinical decision support available for prescribing decisions			
Consultation	12 (71)	10 (77)	2 (50)
PDF report	11 (65)	9 (69)	2 (50)
Electronic CDS	9 (53)	8 (62)	1 (25)
None	1 (6)	0 (0)	1 (25)
Other	1 (6)	1 (8)	0 (0)
Results used to guide other therapies in addition to antidepressants			
Yes	10 (59)	9 (69)	1 (25)

Abbreviations: CDS, clinical decision support; PGx, pharmacogenetic; PDF, portable document format.

[a]Sites could select more than one option.

[b]Out of 16 sites.

[c]Out of 3 sites.

acceptability, adoption, and costs of the PGx intervention. Sites that had already implemented testing were more likely to measure patient and service outcomes compared with sites in the planning phase. In addition, sites indicated that they deployed a multifaceted implementation strategy to enhance uptake of PGx testing, with the most common strategies being identifying barriers for implementation, developing educational materials for providers, and facilitating the relay of PGx test results to providers within the EHR (Table S4). All but one site

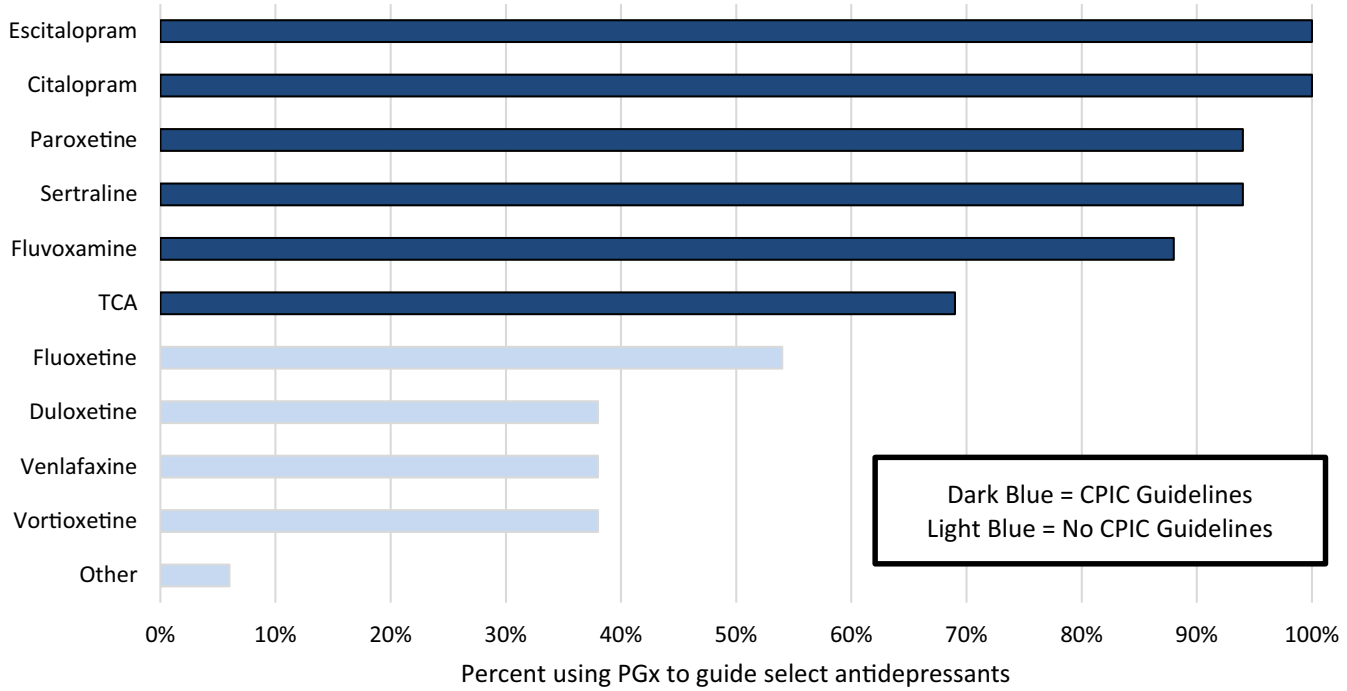

FIGURE 3 Antidepressants considered for pharmacogenetic guidance. More than one response was allowed. Only 16 of 17 sites responded. Providers may have access to the PGx report and use it to tailor additional psychotropic medications. CPIC, Clinical Pharmacogenetics Implementation Consortium; PGx, pharmacogenetic, TCA, tricyclic antidepressants

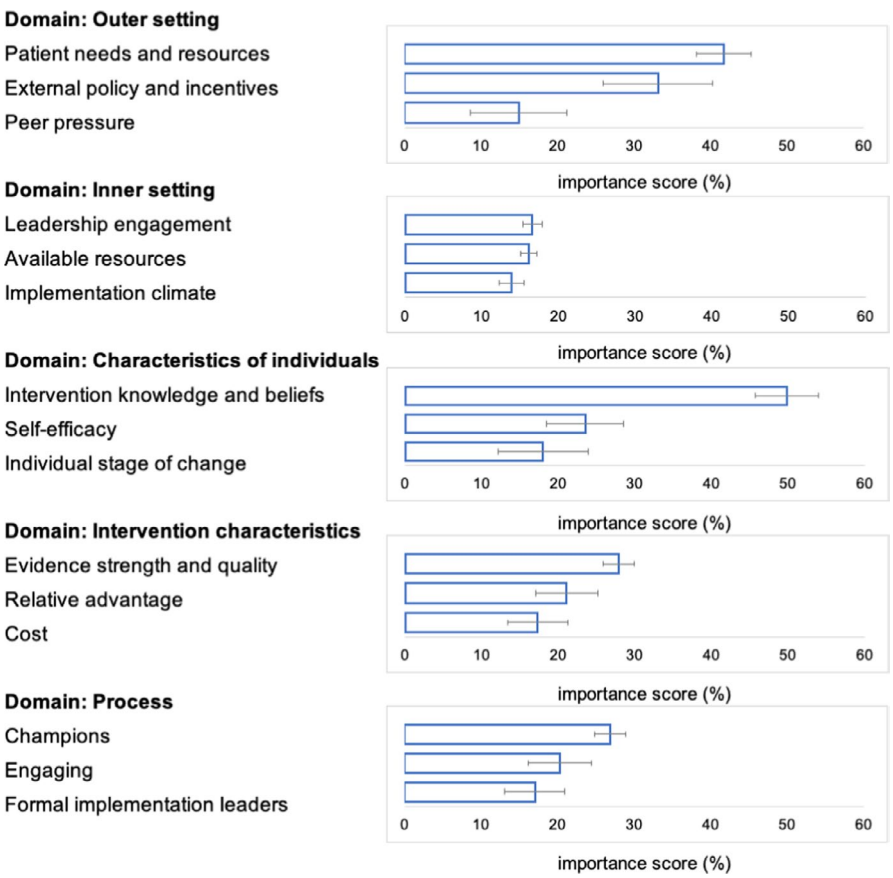

FIGURE 4 The top three constructs within each domain from the Consolidated Framework for Implementation Research (CFIR) rated as most important for implementation of pharmacogenetic testing to guide antidepressant treatment with importance scores and 95% confidence intervals

TABLE 2 Outcomes assessed or planned to be assessed during implementation of pharmacogenetic testing for antidepressants

Outcomes	All ($n = 17$) *N* (%)	Stage of implementation: Implemented ($n = 13$) *N* (%)	Stage of implementation: Planning ($n = 4$) *N* (%)
Implementation outcomes			
Acceptability	14 (82)	11 (85)	3 (75)
Adoption	13 (76)	10 (77)	3 (75)
Costs	13 (76)	10 (77)	3 (75)
Feasibility	13 (76)	11 (85)	2 (50)
Penetration	12 (71)	11 (95)	1 (25)
Appropriateness	10 (59)	8 (62)	2 (50)
Fidelity	10 (59)	8 (62)	2 (50)
Sustainability	9 (53)	7 (54)	2 (50)
Service outcomes			
Effectiveness	14 (82)	13 (100)	1 (25)
Safety	13 (76)	12 (92)	1 (25)
Timeliness	12 (71)	10 (77)	2 (50)
Patient-centeredness	10 (59)	9 (69)	1 (25)
Efficiency	6 (35)	4 (31)	2 (50)
Equity	6 (35)	6 (46)	0 (0)
Patient outcomes			
Symptomatology	12 (71)	11 (85)	1 (25)
Satisfaction	9 (53)	8 (62)	1 (25)
Function (QOL)	6 (35)	5 (38)	1 (25)
Impact on health and social policy	3 (18)	3 (23)	0 (0)

Outcomes from Proctor et al.[20]

Abbreviation: QOL, quality of life.

(94%) indicated that they received internal institutional-level funding to support implementation (Table S5). Sites that had already implemented were more likely to have additional sources of funding, including external funding, such as the National Institutes of Health (NIH) grants and philanthropic sources (Table S5). Four sites ($n = 3$ implemented and $n = 1$ planning) indicated that clinical revenue was also a current or planned source of support.

DISCUSSION

Our study assessed testing processes and operational workflow considerations from institutions that are part of the IGNITE Network PGx Working Group and are implementing or planning to implement PGx guidance for antidepressant therapy. We also asked sites to rank the relative importance of constructs from the CFIR. We found notable similarities across sites in testing process and CFIR rankings. Most sites reported their implementation being led by a multidisciplinary PGx service, providing recommendations according to CPIC guidelines, and communicating recommendations through electronic CDS. The primary constructs within the CFIR that were identified as most important included patient needs and resources (domain: Outer Setting), leadership engagement (domain: Inner Setting), intervention knowledge and beliefs (domain: Characteristics of Individuals), evidence strength and quality (domain: Intervention Characteristics), and the identification of champions (domain: Process). The results from our study provide important information for institutions seeking to advance precision medicine approaches for mental health.

Other centers implementing PGx testing for the management of antidepressants have described similar processes. Common themes highlighted across those institutions as well as those examined herein include leadership by a multidisciplinary team, extensive efforts to integrate results into the EHR, and use of electronic CDS.[27–29] In developing CDS for prescribers, PGx

management recommendations in these centers are largely based on CPIC or DPWG guidelines, which is similar to our findings.

Prior studies that have evaluated the clinical or economic impact of PGx testing in psychiatry clinics have primarily examined commercial tests that provide results to prescribers through provider-specific portals established by the testing lab outside the EHR.[30,31] Although this approach informs mental health care with PGx data at a specific point in therapy, it presents challenges for how best to store results, make them available to other providers, determine relevance to medications beyond those used for mental health indications, and assure accessibility for future treatment decisions. Many commercially available PGx tests provide information for multiple genes beyond those included in guidelines and FDA labeling and results that are formatted differently across laboratories. Some of these include combinatorial tests that use proprietary algorithms to provide pharmacotherapy recommendations and may include genes with weaker levels of evidence. Despite some of the positive outcomes reported with the use of commercial testing that report results directly to providers,[30–32] there are no gold standard approaches for how best to implement or organize this process. Due to this situation and concerns about differences across commercial tests, mental health professional organizations have issued cautionary statements suggesting that PGx testing is either not recommended or not ready for widespread use.[15] Institution and implementation characteristics identified herein bridge this gap and identify considerations and strategies for other organizations considering application of evidence-based PGx information to guide antidepressant use. Although this may provide some optimism, a reality is that the institutions responding to our surveys have developed programmatic efforts with defined leadership and interprofessional collaboration that took time and capital to create.

In survey 2, we asked sites to rank constructs within the CFIR that were most (and least) important for implementation of PGx testing for antidepressants. The sites were consistent in the selection of factors from the CFIR deemed most important for implementation. The constructs of evidence strength and quality (domain: Intervention Characteristics) and provider knowledge and beliefs (domain: Characteristics of Individuals) were among the top constructs identified as important for implementation. As shown by this study, rankings of these constructs reinforce the results of previous surveys of psychiatrists and primary care providers in which providers expressed concern about the evidence supporting PGx testing and its clinical utility as well as provider lack of comfort in interpreting PGx test results to guide drug therapy decisions.[33,34] Much of the evidence supporting genotype-guided antidepressant therapy consists of pharmacokinetic data, with differences in serum drug concentrations observed across genotype groups, rather than evidence of improved remission rates with genotype-guided therapy from prospective trials.[6] While we await the results of large randomized controlled trials showing the clinical utility of PGx guided approaches,[34,35] sites that have implemented PGx testing for antidepressants are concurrently collecting effectiveness and safety outcomes needed to grow the evidence base, which may be needed to support broader clinician and payer uptake and acceptance of PGx testing. All sites surveyed in the present study were focused on collecting data regarding implementation outcomes, such as acceptability, adoption, and costs of PGx testing.

Successful implementation is inherently collaborative and complex, involving multiple stakeholders across institutional hierarchies.[17] The CFIR constructs of leadership engagement, available resources, and implementation climate were also ranked highly among sites both that have implemented and were in the planning phases of implementation. PGx implementation can be resource intensive and involves buy-in from multiple stakeholders, such as precision medicine leadership, laboratory medicine, provider groups, pharmacists, and information services. As such, 16 of the 17 sites surveyed indicated that they received some degree of internal funding to support this initiative. Genomic medicine and PGx face the additional burden of the costs or reimbursement for genetic tests. However, US payer coverage for PGx tests is improving and now includes Medicare patients through new Molecular Diagnostic Services (MolDx) local coverage determinations (LCDs).[36] The LCD includes gene-drug pairs that are clinically actionable as defined by the CPIC or the FDA and includes *CYP2C19*/*CYP2D6* for antidepressant prescribing.

These results expand findings from previous implementation science work conducted by the IGNITE network, which identified system-level barriers for genomic medicine implementation more broadly.[20,37] Prior research from IGNITE identified three common challenges to genomic medicine implementation, including integration of genomics in the EHR, improving clinician knowledge and beliefs about genomic medicine, and engaging patients to become active participants in genomic medicine studies, for example, by giving feedback on specific implementation activities.[20] These themes are reinforced in our study where sites implementing PGx testing ranked constructs related to knowledge and beliefs about the intervention and patient needs and resources as critical to implementation success. Previous IGNITE research also ranked CFIR constructs important to genomic medicine implementation and created standardized measurement

instruments for those identified as high priority.[21] There was some overlap in the rankings of these constructs in our study, including knowledge and beliefs about the intervention and self-efficacy (domain: Characteristics of Individuals); implementation climate and readiness for implementation (domain: Inner Setting); relative advantage and cost (domain: Intervention Characteristics); and engaging (domain: Process). Additional constructs that were highly ranked in our study unique to PGx implementation were leadership engagement and available resources (domain: Inner Setting) and the identification of champions (domain: Process). The rankings of the outer and inner setting constructs are aligned with the notion that successful implementation (and sustainability) is predicated upon increasing the fit of the PGx testing program with its inner and outer settings (e.g., institutional support and available resources).

The IGNITE PGx working group has also previously published implementation barriers and offered strategies for implementation of *CYP2C19* for selection of antiplatelet medications[38] and *CYP2D6* for prescribing opioid medications.[39] These previous papers highlight the importance of establishing multidisciplinary teams, identifying a physician champion, educating providers, creating electronic CDS to facilitate PGx testing, and collection of clinical outcomes data to support the utility of PGx testing. In the current study, sites reiterated the importance of these themes and are using similar strategies to facilitate PGx testing for antidepressants, such as developing educational materials for physicians and pharmacists, identifying and training physician champions, relaying PGx results with CDS within the EHR, and creating a centralized PGx consult service.

The results of our study should be interpreted in the context of their limitations. Respondents of the surveys were sites participating in the IGNITE network; therefore, some findings from our study may not be representative to the broader community. For example, most sites indicated support by a dedicated precision medicine or PGx service to oversee their implementation, which may not be readily accessible at all centers. However, processes for implementing PGx testing and factors important for implementation from these early adopter sites may be beneficial to centers seeking to newly implement PGx testing. The unfunded affiliate sites that constituted most of the respondents herein, are expected to be representative of many institutions in the active or planning stages of implementation. Formalized PGx implementation processes to guide antidepressant use are relatively new, and the overall number of respondents, particularly those in the planning phase was small. We did not collect the specific genotypes that were used for phenotype translation because of the large number of genotypes included on many commonly used test panels. Our approach was not suitable to quantify organizational capacity for incorporating a PGx program. This is an important characteristic connected to sustainability to assess in future studies. Implementation is a constantly evolving process, and most sites are observing early- to mid-stage implementation outcomes (e.g., acceptability), whereas only a minority of sites are observing later-stage outcomes (e.g., sustainability). As implementation progresses across sites, these later-stage outcomes will be important to evaluate. Similar to other stakeholder engagement approaches, the primary limitation of BWS is its focus on stated preferences, or respondents' perceptions of what multilevel factors are most and least likely to influence implementation. These responses may not be reflective of actual practice, and there may be other important factors influencing implementation that were not observed in this study.

In summary, the process of implementing PGx testing to guide antidepressant use in sites from the IGNITE PGx working group is varied with respect to test ordering process and the process for returning results to the providers and patients. However, sites were consistent with respect to dedicated PGx program leadership of a multidisciplinary implementation team and efforts to integrate results into the EHR. Furthermore, the genes and medications used to guide antidepressant therapy were largely informed by CPIC guidelines. Additionally, sites identified similar CFIR constructs that were important to drive their implementation, used strategies to address implementation barriers, and collected similar implementation and effectiveness outcomes to measure the success of their implementations.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

S.T., R.G.S., A.L.E., D.M.S., E.R., K.V.B., N.A.L., C.L.A., J.B., A.L.B., A.C., B.Q.D., P.E.E., C.M.F., J.K.H., P.M., D.W.O., A.L.P., N.P., C.B.R., A.S., S.M.S., K.M.W., K.W., T.C.S., S.L.V., L.H.C., and J.R.B. wrote the manuscript. S.T., R.G.S., L.H.C., and J.R.B. designed the research. S.T., R.G.S., A.L.E., D.M.S., E.R., K.V.B., N.A.L., C.L.A., J.B., A.L.B., A.C., B.Q.D., P.E.E., C.M.F., J.K.H., P.M., D.W.O., A.L.P., N.P., C.B.R., A.S., S.M.S., K.M.W., K.W., T.C.S., S.L.V., L.H.C., and J.R.B. performed the research. S.T., R.G.S., A.L.E., L.H.C., and J.R.B. analyzed the data.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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