Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Pharmacogenomics

Early adoption of pharmacogenetic testing for veterans prescribed psychotropic medications

Leland E Hull*[1,2], Catherine Chanfreau-Coffinier[3], Sony Tuteja[4,5], Dan Berlowitz[2], Lisa S Lehmann[1,8], David W Oslin[4,5], Jeffrey M Pyne[6], Scott L DuVall[3,7] & Julie A Lynch[2,3]

[1]VA Boston Healthcare System, Boston, MA 02130, USA
[2]Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA 01730, USA
[3]VA Informatics and Computing Infrastructure, VA Salt Lake City Health Care System, Salt Lake City, UT 84148, USA
[4]Corporal Michael J Crescenz VA Medical Center, Philadelphia, PA 19104, USA
[5]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[6]Central Arkansas Veterans Healthcare System, Little Rock, AR 72205, USA
[7]University of Utah School of Medicine, Salt Lake City, UT 84132, USA
[8]Harvard Medical School, Boston, MA 02115, USA
*Author for correspondence: leland.hull@va.gov

Aim: Describe the characteristics of providers ordering, patients receiving, and clinical impact of a psychotropic pharmacogenetic test on veteran care. **Patients & methods:** Observational cohort study linking veterans' laboratory results to electronic health record data. Changes in psychotropic medication prescribing were measured as a function of test results. **Results:** A total of 38 providers tested 181 veterans between 10/6/2014 and 2/1/2018. Prescriptions for medications with severe gene–drug interactions decreased; however, 11 such medications were used after testing. For 43 patients, documentation of the results was missing. **Conclusion:** Most prescribing decisions were congruent with test results, but in a nontrivial number of cases, prescribers appeared not to act on the results. Poor result documentation impeded the potential of results to inform clinical care.

First draft submitted: 26 April 2019; Accepted for publication: 10 June 2019; Published online: 8 August 2019

Keywords: pharmacogenetic testing • psychotropic medications • veterans

Healthcare providers order pharmacogenetic (PGx) tests to assess for genetic differences that may impact drug metabolism, efficacy and patient risk for adverse drug events [1]. Several commercial PGx tests are available to guide prescribing of psychotropic medications [2]. Many of these are combinatorial PGx panels that test for several gene–drug interactions and use proprietary algorithms to sort drugs into categories based on the likelihood of a gene–drug interaction. The GeneSight® Psychotropic Panel (Assurex Health, OH, USA) is one such PGx test [3,4]. This psychotropic PGx panel has become increasingly available to US providers following a 2014 positive Medicare coverage determination for use when treating patients with refractory depression [5]. According to the company website, over 1,000,000 people have undergone testing [6]. The Department of Veterans Affairs (VA) has also made this test available for use in the VA since 2014 [7]. While robust efforts are underway to understand if using this PGx test can improve outcomes for patients with depression [8], little is known about the veterans who previously underwent testing and how use of this panel has influenced their clinical care.

Despite growing use of commercial PGx testing by VA and non-VA providers, it is unclear how providers use these tests, especially in the absence of clinical practice guidelines. Therefore, we performed a retrospective observational study using national data to describe the patients and providers using the psychotropic PGx panel in VA. We also sought to better understand how the test results were being used to inform prescribing decisions. Finally, we explored unexpected provider actions to identify potential barriers to test use.

Future Medicine

Patients & methods

We obtained permission to conduct this research from the Bedford, MA, Little Rock, AR and Salt Lake City, UT (USA) VA institutional review boards and research and development committees which authorized waivers of informed consent and the Health Insurance Portability and Accountability Act.

The psychotropic PGx panel

The psychotropic PGx panel is a combinatorial PGx test that assesses for interactions between up to 12 genes and 55 drugs [3,4]. Most of the genes affect drug metabolism, altering serum drug concentrations and, in turn, the likelihood of drug response and/or side effects. A few of the genes on the panel indicate predisposition to adverse drug reactions as well. The medications include antidepressants, anxiolytics, antipsychotics and mood stabilizers. The test uses a proprietary algorithm to categorize medications into color 'bins' based on any gene/drug interactions detected: green bin (use as directed), yellow bin (moderate gene–drug interaction) or red bin (significant gene–drug interaction).

During our study period, veterans were administered four different versions of the panel (Supplementary Table 1); later versions added more genes and drugs. The earliest version of the panel (Version 1.8.0.0) analyzed six genes for potential interactions with 32 medications, including both antidepressants and antipsychotics. Later versions (Versions 3.0.0.1 and 3.0.0.2) included drugs from two additional classes of medications: anxiolytics and mood stabilizers. In total, a maximum of 12 genes and 55 psychotropic medications were included on the latest version of the panel used in our cohort.

When a PGx test was ordered, a buccal swab was collected from the patient and the sample was sent out to the laboratory. Laboratory test results were returned to ordering providers as a paper report that included the genetic variants identified and potential gene–drug interactions, sorted by bin color with footnotes to guide interpretation.

Study population

We conducted a retrospective observational study using secondary data analysis. We identified patients receiving PGx testing using two different methods. First, the laboratory directly reported test results to VA national clinical leadership for veterans who underwent testing. Second, we queried the VA's Corporate Data Warehouse (CDW), where all laboratory test results are aggregated, to ensure we had not missed additional veterans with test orders. Administrative VA pharmacy data revealed that between 6/15/14 (when the test was first made available in VA) and 2/1/2018, inclusive, 2,138,718 unique patients had ≥1 incident prescription for any of the 55 drugs on the psychotropic panel. These new prescriptions were issued by 85,489 unique providers. However, only 221 veterans underwent psychotropic PGx testing during this period, with the first test ordered on 10/6/2014; 40 veterans were excluded from analyses due to insufficient data (Supplementary Figure 1). Our final study population included 181 veterans treated by 38 different providers.

Data sources

The primary sources of data were the VA's electronic health record (EHR), called the Veterans Information Systems and Technology Architecture (VistA) [9], the VA CDW and patient-level laboratory test data obtained from the test laboratory, Assurex Health. We developed a chart abstraction tool (Supplementary Table 2) to collect data from VistA using the Computerized Patient Record System interface including patient age at test order date, sex (male/female), race/ethnicity (White non-Hispanic vs other), whether the patient was a current smoker at the time of testing (yes vs no/not documented), history of alcohol or drug abuse (yes vs no/not documented) and mental health diagnoses present (depression, post-traumatic stress disorder, anxiety and/or panic disorder and schizophrenia and/or bipolar disorder). Chart abstractors also collected data as to whether patients' test results had been documented in the EHR (yes vs no/not documented). Test results were considered documented if there was either evidence in the medical chart that the clinician had discussed the test results with the patient or if the test results could be found scanned into the EHR. The chart abstraction was performed between 5/24/2017 and 3/27/2018.

Chart abstractors also gathered data about prescriptions for any of the 55 psychotropic medications included on the most recent version of the panel. They indicated which of the 55 medications were prescribed immediately prior to testing, and which were prescribed after testing. Chart abstraction data were linked to data supplied by the test laboratory, including the panel version the patient received, the medications tested for gene–drug interactions and the bin color assignment of each medication (green, yellow or red). Because earlier panel versions did not include

all 55 medications, if a patient was prescribed a psychotropic medication not included on that panel version, the bin color was listed as 'missing'. The company also supplied data included in the footnotes of the report that would that would be associated with each of the gene–drug interactions detected.

Laboratory data also included the name of the ordering clinician and VA facility where the test was ordered. These data were linked to data from the CDW to better characterize the providers ordering these tests, including their ages, genders, positions and practice locations.

Data analyses

First, we described the characteristics of the patients and providers who ordered tests. Next, we explored provider prescribing actions following PGx testing as a function of the bin color assigned to each medication. Providers' prescribing actions for each medication following PGx testing were categorized into three different outcomes: medication started, medication stopped or medication continued. We performed a 4×3 contingency table analysis, comparing bin color of the medication (green, yellow, red or missing) with the potential outcomes (whether the medication was started, stopped, or continued). We performed a χ^2 test to determine whether the distribution of outcomes was different across bin colors for the contingency table and compared the expected bin numbers with the actual bin numbers to characterize the directionality of the relationships. The unit of analysis was individual prescriptions. All quantitative analyses were performed using Stata version 15.1 (StataCorp LLC, College Station, TX, USA).

Exploring unexpected provider actions

We explored unexpected provider actions to gain additional insight into provider responses to test results. We defined an unexpected action as either the continuation of or initiation of a red bin medication following PGx testing. We performed in-depth chart review of the clinician notes for these patients and summarized our findings.

Results

The 181 veterans included in our cohort are characterized in Table 1 . The average age at specimen collection was 46 years. Patients were on a mean of 1.96 psychotropic medications prior to testing. Most patients (84%) were male and White, non-Hispanic (73%). The most prevalent mental illnesses in our population were depression and post-traumatic stress disorder (68%, respectively), although 12% had a diagnosis of either bipolar disorder or schizophrenia. In 24% of cases (43/181), we did not find evidence that the test results had either been discussed with the patient or scanned into the EHR.

We characterized the VA providers ordering these tests (Table 2). The mean age of providers was 53 years, and a slight majority (51%) was male. Most practiced in the mental health setting and were physicians, although 13% were nonphysician providers, such as advanced practice nurses and physician assistants. Most providers ordered the test a single time (66% of providers); five providers practicing at two VA Medical Centers (VAMCs) ordered more than ten tests.

In Figure 1, we detail medication prescribing as a function of bin color. A minority of patients (14/181) had not been prescribed any of the 55 medications listed on the panel at the time of testing. Among these 14 patients, seven were started on new medications following testing; the new medications that were started were overwhelmingly green (6/8). Out of the 167 veterans who were on at least one psychotropic prior to testing, 121 had at least one medication started or stopped following testing; 21 red bin medications were stopped and 93 green bin medications were started.

For the entire cohort, there was a net increase (started minus stopped) in green medications (+45 prescriptions) and net decrease in yellow and red medications (-24 and -18 prescriptions, respectively) comparing pretest prescribing to posttest prescribing (p-value < 0.001; Table 3). The total number of medications prescribed remained similar before and after testing (net increase of four medications prescribed). Prescriptions for the antidepressant desvenlafaxine increased more than any other medication after testing (+14 prescriptions); this medication was in the green bin 100% of the time (Supplementary Table 3). Prescriptions for trazodone (-6), citalopram (-5) and sertraline (-5) decreased the most following testing (these medications were not always in the green bin).

Although red bin medications are not absolutely contraindicated, eight prescriptions for red medications were continued after testing and three new red medications were started. We performed in-depth chart review to try to understand the factors driving these results (Table 4). Of the 11 red medications prescribed after testing, eight were a continuation of prior therapy. Despite footnotes suggesting gene/drug interaction(s) could alter expected serum

Table 1. Characteristics of the cohort (N = 181).

Characteristic	Mean	Standard error
Age at specimen collection	46.47	1.05
Number of panel-tested psychotropic medications prescribed prior to PGx testing†	1.96	1.20
	Frequency	**Column %**
Age group		
<50	109	60%
50-60	38	21%
>60	34	19%
Number of panel-tested psychotropic medications prescribed prior to PGx testing†		
0	14	8%
1	62	34%
≥2	105	58%
Gender		
Male	152	84%
Female	29	16%
Race/ethnicity		
White, non-Hispanic	133	73%
Other	48	27%
History of alcohol or drug abuse		
Yes	79	44%
No	102	56%
Current smoker		
Yes	52	29%
No/not documented	129	71%
Mental health diagnoses		
Depression	123	68%
PTSD	123	68%
Anxiety/panic disorder	82	45%
Schizophrenia or bipolar disorder	22	12%
Panel Version Used		
Psychotropic V3.1 or greater	64	35%
Other	117	65%
Results documented in chart		
Yes	138	76%
No/not documented	43	24%

†Limited assessment to the 55 medications included on the PGx panel.
PGx: Pharmacogenetic; PTSD: Post-traumatic stress disorder.

levels of the drug, seven out of eight medications were continued without any dose adjustments. We could not find evidence that the results had been scanned into the EHR for five out of the eight red medications continued, suggesting that the providers may not have had access to the results.

Three new red medications were started after testing (Table 4). Mirtazapine and duloxetine were started for gastrointestinal issues and pain, respectively; both were prescribed by the same provider who had ordered PGx testing. In the mirtazapine case, it was unclear whether the provider received or reviewed the PGx test results. For duloxetine, the provider had originally reviewed the PGx results, but prescribed the medication during a subsequent encounter; it was not apparent that the provider referenced the PGx results when prescribing duloxetine. Venlafaxine was a red medication started by the provider who ordered the PGx test because the results did not include any green bin medication options that were on the VA's preferred medication formulary. The provider decided to try a red bin medication first, and if the patient did not have a good response, request special approval for a nonformulary medication.

Table 2. Characteristics of ordering providers (N = 38)[†].

Characteristic	Mean	Standard Error
Age (years)[‡]	52.9	1.85
	Frequency	**Column %**
Gender[‡]		
Female	18	51%
Male	17	49%
Specialty		
Mental health[§]	34	89%
Other/undetermined	4	11%
Provider type[‡]		
Physician	32	86%
Nonphysician provider[¶]	5	14%
# of panels ordered		
1	25	66%
2–10	8	21%
>10	5	13%

[†]143/181 tests (77%) were ordered at two VA Medical Centers where these providers practiced.
[‡]Missing results: age: 4; gender: 3; provider type: 1.
[§]Providers were considered as mental health providers if they either were listed as psychiatrist or if their service section included either mental or behavioral health.
[¶]Nonphysician providers include advanced practice nurses and physician assistants.

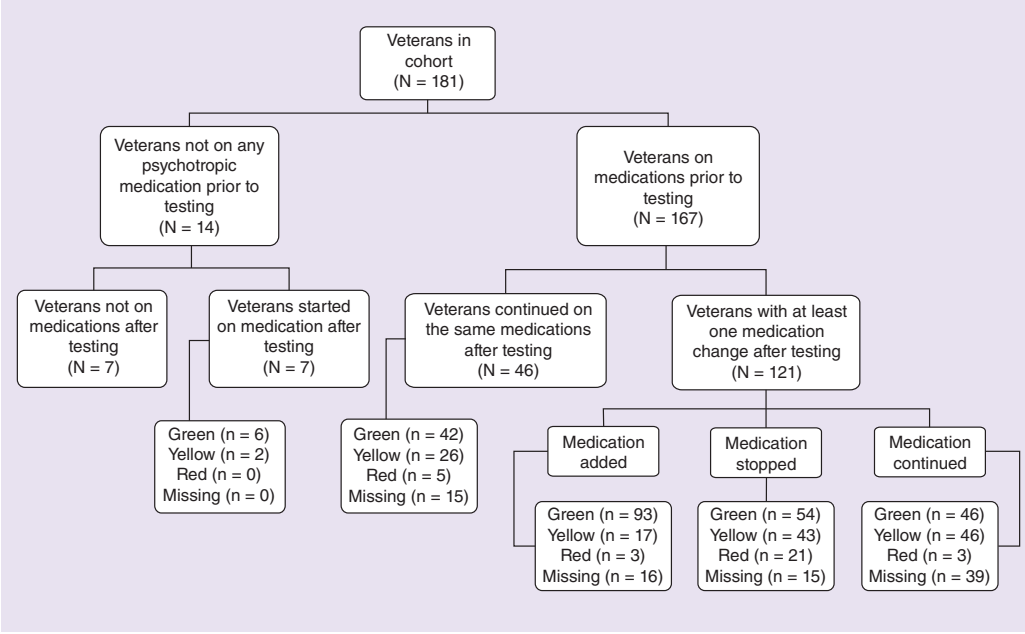

Figure 1. Provider prescribing actions by medication bin color.
N = number of patients; n = number of prescriptions.

Table 3. Prescriptions that were stopped, started, or continued as a function of bin color.

Colour	Medication changes by bin color; actual number of prescriptions (expected number of prescriptions)			
	Started	**Stopped**	**Continued**	**Net Change**
Green	99 (67.1)	54 (65.1)	88 (108.7)	+45
Yellow	19 (37.3)	43 (36.2)	72 (60.5)	-24
Red	3 (8.9)	21 (8.7)	8 (14.4)	-18
Missing	16 (23.7)	15 (23.0)	54 (38.4)	+1
Totals	137	133	222	+4

Pearson's χ^2 = 69.54, degrees of freedom = 6, p-value <0.0001.

Table 4. Classification of unexpected provider prescribing actions.

Medication (pre-test dose)	Results documented?†	Summary of documented provider actions	Footnotes associated with medication
Red medications continued after pharmacogenetic testing			
Fluoxetine (80 mg PO daily)	No	The reason for red medication continuation was not documented. The provider initially continued fluoxetine at same dose following testing, but later decreased fluoxetine to 60 mg daily due to the addition of a second antidepressant, mirtazapine 7.5 mg PO nightly, to regimen.	High serum level; increased side effect risk
Amitriptyline (25 PO mg nightly)	No	The provider documented use of genetic testing in the chart, stating: "*We had investigated genetic testing… his liver metabolism higher functioning than most. But still h/o poor reactions to many medications.*" Per chart abstraction the patient was a smoker, but this is not mentioned in the note. The chart did not show evidence that the genetic test results were discussed with the patient or used to inform specific medication choices. The test results were not found scanned into the electronic health record. The red medication was continued at the same dosage after testing.	Low serum level; low serum level in smokers
Mirtazapine (15 mg PO nightly)	No	The reason for red medication continuation was not documented. The provider continued the medication at the same dose after testing. Per chart abstraction, the patient was a smoker.	Low serum level; low serum level in smokers
Mirtazapine (15 mg PO nightly)	No	The reason for red medication continuation was not documented. The provider continued the medication at the same dose after testing. Per chart abstraction, the patient was not a smoker.	Low serum level; low serum level in smokers
Bupropion (150 mg PO twice daily)	No	The reason for red medication continuation was not documented. The provider continued the medication at the same dose after testing.	High serum level; increased side effect risk
Mirtazapine (22.5 mg PO nightly)	Yes	The reason for red medication continuation was not documented. The provider continued the medication at the same dose after testing.	High serum level; increased side effect risk
Bupropion (300 mg PO daily)	Yes	Bupropion (red bin) medication was initially stopped and duloxetine (green bin) was started. *"Patient was seen for… follow-up evaluation of GENESIGHT gene-testing protocol. PHQ-9 and HAM-D done as well."* However, the patient immediately returned to prior therapy. *"While taking low-dose bupropion and* [duloxetine] *developed sweaty palms, decreased appetite, increased irritability and depression… He was only 24 hours on* [duloxetine]*… after which he stopped taking* [duloxetine] *and restarted* [bupropion]*… bupropion doesn't gave him side effects. His wish is to remain on these medications. He is reluctant to another trial as part of the Genesight testing."*	High serum level; increased side effect risk
Bupropion (150 mg PO twice daily)	Yes	The patient was maintained on bupropion at same dosage. *"Reviewed results of pharmacogenomic testing. Discussed… med hx, hx of side effects, agreed to discontinue Citalopram* [yellow bin]*, start Venlafaxine* [green bin] *and continue both Bupropion* [red bin] *and Aripiprazole* [yellow bin]*."* A specific rationale for continuing the red medication was not given.	High serum level; increased side effect risk
New red medications started after pharmacogenetic testing			
Mirtazapine	No	The patient had been previously tapered off the medication due to sedation. Provider ordered PGx testing to guide use of fluoxetine, but did not document the test results in the chart. 1.5 months after the test was ordered, provider writes: "*Called by GI MD- …wanted to return to using mirtazapine for his GI Issues."* The provider never mentions PGx test results in the record and orders mirtazapine 7.5 mg PO nightly and decreases the fluoxetine dose.	High serum level; increased side effect risk
Duloxetine	Yes	It is noted by the provider: *"Called pt and discussed results of pharmacogenomic testing.…* [it] *suggested serum levels may be too low with Duloxetine…particularly in smokers."* Per chart abstraction and the provider's notes, the patient was not a smoker. On a separate visit to the same provider: *"She reports it occurred to her that her pain is playing a larger part in her depression…* [Discussed] *Duloxetine for depression, anxiety and pain…"* The patient was started on titration to target dose 30 mg PO daily. Provider did not reference the PGx results that they had documented 6.5 months earlier.	Low serum level; low serum level in smokers
Venlafaxine	Yes	The provider who ordered the PGx test started the patient on a red bin medication because green medications were unavailable. "*Writer went over the results of his pharmacogenomic testing with him, which were sent for scanning into his chart… The only antidepressants in the "use as directed" category were* [desvenlafaxine], [levomilnacipran]*, and* [vilazodone]*, which… are either non-formulary or unavailable at the VA. Patient was agreeable to trying venlafaxine and if it does not work… will* [request approval] *for* [desvenlafaxine]." Dose 75 mg PO daily.	High serum level; increased side effect risk

†Results were considered documented if there was either evidence in the chart that the provider had discussed the test results with the patient or that the test results had been scanned into the electronic health record.
PGx: Pharmacogenetic(s); PO: By mouth.

Discussion

To our knowledge, this is the first study detailing how providers in a national healthcare system ordered and used a commercial psychotropic PGx panel in routine clinical practice. We found that providers often used test results to drive their prescribing towards greater numbers of green bin medications for patients with diverse mental illnesses. However, there were notable exceptions to this trend, and in a nontrivial number of cases, prescribers appeared not to act on the results of the PGx testing. Understanding why could provide insights into how providers perceive the utility of these tests and the barriers they face when accessing and interpreting the results.

After PGx testing, providers shifted towards prescribing more green bin medications and away from prescribing yellow and red bin medications. Desvenlafaxine was the individual medication with the greatest increase in prescriptions; no veterans were prescribed the drug before testing, and 14 were after testing. The high preponderance of desvenlafaxine for the green bin likely reflects that it is not affected by variation in the *CYP2D6* gene [10]; the increase in desvenlafaxine prescriptions, therefore, may be driven by a misperception that not having a drug–gene interaction is equivalent to suggesting that a medication is the 'right' drug for a patient, without considering other important factors. Medications such as sertraline and citalopram, which are affected by variation in the highly polymorphic *CYP2C19,* had a net decrease in prescriptions [11,12]. Future investigation should explore the extent to which panel results reflect known metabolic pathways, as well as the downstream effects of shifting to more green medications, such as treatment response and cost-effectiveness.

It was unclear whether providers considered other factors that could affect drug metabolism in their clinical decision making, such as the patient's smoking status or alcohol use [13]. We did not find evidence in the chart that the providers referenced the patient's smoking status explicitly in their decision making when we explored unexpected red bin medication prescribing. Additionally, most of our patients were co-prescribed multiple psychotropic medications at baseline; these co-prescriptions could result in a different metabolic phenotype than that which would be expected based on the genotype alone (i.e., phenoconversion) [14,15]. In the future, we hope to better understand if and how providers might incorporate other factors affecting anticipated drug response into their decision-making.

Exploring unexpected prescriptions revealed several potential barriers to using PGx test results, including obtaining the results and recalling them to inform future prescribing. For 5/8 of the red medications that were continued after PGx testing, we could not find clear evidence that the results had been discussed with the patient or scanned into the EHR. In these cases, the medications were maintained at the same dosage pre- and post-testing. This finding raises the concern that clinicians did not necessarily have the results of the testing they ordered on hand during decision making.

Additionally, three patients were started on new red medications after PGx testing had been completed. In one of these cases, the same provider who had previously documented that duloxetine had a severe gene–drug interaction prescribed this medication on a subsequent visit. The provider did not document a reference to the previously completed PGx test results when prescribing this medication. This finding raises concern that, while the provider may have initially reviewed the PGx results, they may not have recalled the results when they were relevant to later prescribing decisions.

These findings speak to the importance of developing systems to integrate PGx test results into the EHR as discrete data. Although the challenges of integrating reference laboratory test results into EHRs have been well-documented [16], doing so would help to facilitate recall of pertinent test results at the point-of-prescribing [17,18]. Our findings highlight the urgency to develop better systems both for electronic integration of reference laboratory results and clinical decision support to facilitate appropriate use of PGx test results longitudinally.

There are several limitations of this study, many of which are rooted in a naturalistic evaluation of PGx test use. First, given that there are not clear guidelines for test ordering in the VA, we were unable to formally compare the veterans who underwent testing and their providers' characteristics with the broader veteran population. Additionally, the generalizability of our findings may be limited since five providers dominated test ordering for our cohort. Nonetheless, we were surprised to find that providers ordered the test for patients with a broad range of mental illnesses, including bipolar disorder and/or schizophrenia, since these patients have traditionally been excluded from studies of the PGx panel [19–21], and future investigation could evaluate how providers' selected patients for PGx testing. We also found that there was insufficient longitudinal administrative data and chart documentation to evaluate patient outcomes. Fortunately, there are several prospective investigations through which we are learning about the clinical utility of this test for the treatment of depression [8,22]. Our study only

focused on the 55 medications included on the psychotropic panel. We did not evaluate for changes in drug dosing except in select cases, and it is possible that the patients in the cohort received prescriptions from sources other than VA Pharmacy services. Finally, it is possible that veterans received alternative PGx tests to guide prescribing of their psychotropic medications; we hope to explore broader use of PGx testing for veteran care in the future.

Conclusion

Our findings highlight that providers within a national healthcare system ordered psychotropic PGx tests for a broad range of patients and generally used the data to inform their clinical decision making when the results were available, although there were notable exceptions. Designing systems to facilitate return and recall of PGx test results will be necessary to optimize the potential benefit of these test panels.

Summary points

Methods

- It is unclear how providers are using commercially available pharmacogenetic (PGx) tests to guide psychotropic medication prescribing outside of controlled settings.
- The objective of this retrospective analysis was to describe early uptake of a psychotropic PGx panel within the Department of Veterans Affairs (VA), including the patients and providers using the test, and the resulting clinical actions.

Results

- Between 10/6/2014 and 2/1/2018, 181 veterans underwent psychotropic PGx testing. The majority (68%) had a diagnosis of depression and 12% had a diagnosis of schizophrenia or bipolar disorder. Provider actions trended towards starting green bin medications and stopping red bin medications, although there were exceptions. For 24% of patients (N = 43), documentation was missing that results had been discussed or scanned into the electronic health record.

Conclusion

- These results indicate that, among early adopters of a commercially available PGx test, most prescribing decisions were congruent with the test results. However, a non-trivial number of providers failed to act on the test results. Further work could investigate why provider's chose to order the test, especially when they failed to act on results. Poor result documentation may have lessened the potential for test results to inform clinical care.

Financial & competing interest disclosure

LE Hull is supported by the Department of Veterans Affairs Office of Academic Affiliations Advanced Fellowship Program in Health Services Research, the Center for Healthcare Organization and Implementation Research (CHOIR), VA Boston Healthcare System. Authors SL DuVall, JA Lynch, DW Oslin and JM Pyne received funding support from a VA Office of Research and Development award to DW Oslin (SDR 16-348; ClinicalTrials. gov ID: NCT03170362). This work was supported using resources and facilities at the VA Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-457. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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

Disclaimer

The views expressed in this article are those of the author(s) and do not necessarily represent the views of the Department of Veterans Affairs.

References

1. Relling MV, Evans WE. Pharmacogenomics in the clinic. *Nature* 526(7573), 343–350 (2015).
2. Fabbri C, Zohar J, Serretti A. Pharmacogenetic tests to guide drug treatment in depression: comparison of the available testing kits and clinical trials. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 86, 36–44 (2018).
3. Altar CA, Carhart JM, Allen JD, Hall-Flavin DK, Dechairo BM, Winner JG. Clinical validity: combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. *Pharmacogenomics J.* 15(5), 443–451 (2015).

4. Jablonski MR, King N, Wang Y *et al.* Analytical validation of a psychiatric pharmacogenomic test. *Per. Med.* 15(3), 189–197 (2018).
5. Assurex Health Inc. Medicare for the first time to cover combinatorial genetic testing to guide individualized selection of depression medications. https://genesight.com/medicare-for-the-first-time-to-cover-combinatorial-genetic-testing-to-guide-individualized-selection-of-depression-medications-2/
6. Assurex Health Inc (2019). https://genesight.com
7. Assurex Health Inc. U.S. Department of Veterans Affairs Awards GeneSight® Federal Supply Schedule Contract. https://genesight.com/u-s-department-of-veterans-affairs-awards-genesight-federal-supply-schedule-contract-2/
8. VA Office of Research and Development. PRIME Care (PRecision Medicine In MEntal Health Care). https://clinicaltrials.gov/ct2/show/study/NCT03170362
9. Maynard C, Chapko MK. Data resources in the department of veterans affairs. *Diabetes Care* 27(Suppl. 2), B22–26 (2004).
10. Preskorn SH, Nichols AI, Paul J, Patroneva AL, Helzner EC, Guico-Pabia CJ. Effect of desvenlafaxine on the cytochrome P450 2D6 enzyme system. *J. Psychiatr. Pract.* 14(6), 368–378 (2008).
11. Hicks JK, Bishop JR, Sangkuhl K *et al.* Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of selective serotonin reuptake inhibitors. *Clin. Pharmacol. Ther.* 98(2), 127–134 (2015).
12. Fabbri C, Minarini A, Niitsu T, Serretti A. Understanding the pharmacogenetics of selective serotonin reuptake inhibitors. *Expert Opin. Drug Metab. Toxicol.* 10(8), 1093–1118 (2014).
13. Kroon LA. Drug interactions with smoking. *Am. J. Health Syst. Pharm.* 64(18), 1917–1921 (2007).
14. Shah RR, Smith RL. Addressing phenoconversion: the Achilles' heel of personalized medicine. *Br. J. Clin. Pharmacol.* 79(2), 222–240 (2015).
15. Shah RR, Smith RL. Inflammation-induced phenoconversion of polymorphic drug metabolizing enzymes: hypothesis with implications for personalized medicine. *Drug Metab. Dispos.* 43(3), 400–410 (2015).
16. Kratz A. Electronic reporting of all reference laboratory results: an important step toward a truly all-encompassing, integrated health record. *Health Informatics J.* 22(3), 496–504 (2016).
17. Weitzel KW, Cavallari LH, Lesko LJ. Preemptive panel-based pharmacogenetic testing: the time is now. *Pharm. Res.* 34(8), 1551–1555 (2017).
18. Dias MM, Sorich MJ, Rowland A, Wiese MD, McKinnon RA. The routine clinical use of pharmacogenetic tests: what it will require? *Pharm. Res.* 34(8), 1544–1550 (2017).
19. Hall-Flavin DK, Winner JG, Allen JD *et al.* Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. *Pharmacogenet. Genomics* 23(10), 535–548 (2013).
20. Winner JG, Carhart JM, Altar CA, Allen JD, Dechairo BM. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discov. Med.* 16(89), 219–227 (2013).
21. Hall-Flavin DK, Winner JG, Allen JD *et al.* Using a pharmacogenomic algorithm to guide the treatment of depression. *Transl. Psychiatry* 2, e172 (2012).
22. Greden JF, Parikh SV, Rothschild AJ *et al.* Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. *J. Psychiatr. Res.* 111, 59–67 (2019).