QUERI

Evidence Brief: The Comparative Effectiveness, Harms, and Cost-effectiveness of Pharmacogenomics-guided Antidepressant Treatment versus Usual Care for Major Depressive Disorder

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces "rapid response evidence briefs" at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program. Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Antidepressants are a mainstay of treatment for Major Depressive Disorder (MDD). To guide the choice of antidepressants, clinicians have typically taken a "trial and error" approach, informed by various clinical factors thought to be associated with variable treatment response. But rates of remission are low and variable, with approximately 11-30% of patients remitting, even after one year of antidepressant treatment. As a result, there is intense interest in identifying additional factors that could help clinicians optimize the effectiveness of available treatments. Genetic variation has long been explored as another potential contributor to individual differences in antidepressant treatment outcome. Whether using genetic information can help predict how an individual might respond to a particular antidepressant – referred to as 'pharmacogenomics' – is of great interest for further advancing precision medicine efforts.

Because many patients may have several trials of antidepressants before they find one that they can tolerate, pharmacogenomic data might ultimately shorten the time to identify the optimal treatment. Specifically, the clinical rationale behind using pharmacogenomic data to inform antidepressant therapy is that a patient's unique genetic profile may help predict whether a patient will tolerate or respond to a drug, or help tailor the dose that may have the best potential effectiveness and tolerability. For example, some individuals are CYP2C19 ultra-rapid metabolizers, which means they are predicted to have lower concentrations of certain drugs, limiting expected efficacy at the usual starting dose. Other individuals are CYP2C19 poor metabolizers and are predicted to have higher concentrations of certain drugs, which may lead to greater intolerability. Key to determining the clinical utility of using pharmacogenomic data to guide antidepressant therapy versus usual care is demonstration of improvements across numerous outcomes including remission, response, quality of life, functional capacity, and tolerability; reduced time to these outcomes; and reducing associated treatment switches. An important question is what the optimum clinical scenarios are for adding pharmacogenomics to usual care, depending on patients' prior experience with antidepressants, demographics, psychiatric and medical comorbidities, depression characteristics, concomitant medication, or other health or lifestyle behaviors.

While there is a plausible clinical rationale for expecting benefits from pharmacogenomics-guided treatment, the actual impact has not been well-established. Three pharmacogenomics-guided treatment strategies have been evaluated in published studies that

Background

In January, 2015, the White House identified Veterans Affairs (VA) as a participating agency in the Precision Medicine Initiative. To inform this initiative, the VA Office of Research and Development (ORD) is developing a clinical study that builds on the Million Veteran Program (MVP) by implementing precision medicine in mental health (PMH). The PMH committee focused on depression because of its high prevalence, a need for better treatment strategies, and a growing use of genetic testing for decision making. As funding for this study is arranged for FY17, ORD is convening a planning committee meeting for April 2016 to discuss study development. To inform their meeting, ORD commissioned the Evidence-based Synthesis Program Coordinating Center (ESP CC) to conduct an evidence brief on the clinical utility of pharmacogenomics-guided treatment for major depressive disorder.

Methods

To identify studies, we searched MEDLINE®, the Cochrane Central Registry of Controlled Trials, and PsychINFO through March 2016, and other sources. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for our full methods.

compare pharmacogenomics-guided care to usual care (Executive Summary Table). There is some doubt that the studies' findings are valid, because there is a single, small, short-term study of each strategy, and these studies have numerous minor methodological limitations.

Of the 3 pharmacogenomics-guided treatment strategies, CNSDose has the most favorable preliminary findings. One additional patient had a remission by 12 weeks for every 3 genotyped (95% CI, 1.7-3.5), and the effect on intolerability was also favorable. ABCB1 genotyping also improved chance of remission, but less so – there was one additional remission at 5 weeks for every 3 to 20 patients genotyped. This difference could be due to the short duration of the study. Effects of GeneSight were not statistically significant and left unclear whether the chance of remission was substantially better or worse than usual care.

There are numerous gaps in the evidence. First, from a VA perspective, it is important to consider the characteristics of the patients and providers evaluated in these studies. Most patients in these studies were females in their forties who lacked comorbidities, such as PTSD, that are common among Veterans who have depression. Some had refractory depression. Others were being treated as inpatients while participating in the Munich Antidepressant Response Signature (MARS) project, which included use of weekly plasma monitoring. Even if a pharmacogenomics-guided strategy worked in the specific populations tested, it might have different results in Veterans Affairs (VA). Second, no studies have demonstrated that pharmacogenomics result in increased use of genetically-congruent medication and shorten time to identifying optimal treatment by improving multiple key outcomes of remission, response, quality of life, functional capacity, and tolerability. New research would be more meaningful if it included a broader population, recorded what medication changes were recommended and how often following the recommendations resulted in remission, and by how much the time to remission was reduced. Third, available research has not yet evaluated to what extent patients' prior experience with antidepressants, demographics, psychiatric and medical comorbidities, depression characteristics, concomitant medication, or other health or lifestyle behaviors impact the utility of pharmacogenetics in MDD treatment. Finally, the cost-effectiveness of pharmacogenomics-guided care versus usual care in Veterans with major depressive disorder is also not clear. This is primarily because there is too much uncertainty about the effectiveness of pharmacogenomics-guided care in Veteran-representative patients whose primary diagnosis is major depressive disorder.

Additional research is needed to establish more clearly the clinical validity of pharmacogenomic testing in the VA population. The potential benefit of testing is influenced by several variables, such as the frequency of key genetic variants in the population; the effectiveness of different antidepressants in relation to these variants; how often VA clinicians' choices and the pharmacogenomics-guided recommendations coincide; and to what extent comorbidities and/or health or lifestyle behaviors limit or direct the options for treatment. Some of the preliminary studies of pharmacogenomics-guided treatment evaluated highly refractory patients who had failed several courses of antidepressants, but provide little information about how, why, or when they failed. Was it because of specific side effects? How often was treatment failure observed? Were the recommended antidepressants ones that are often first or second line in VA? Initial actions for ORD may be (1) to conduct an updated evidence review to better examine the association between key genetic variants and antidepressant effectiveness and (2) to undertake new primary research to evaluate the potential association between genes and variants and antidepressant medication benefits and harms. In designing a study that compares usual care to

pharmacogenomics-guided treatment, VA ORD should consider the following important factors: (1) selection of genetic variants, (2) format of pharmacogenomics results delivery, (3) education, (4) ethical, legal, and social considerations, and (5) accounting for key patient characteristics and improving outcome assessment methods.

Executive Summary Table: Summary of Best Evidence that Compares Pharmacogenomics-guided Antidepressant Treatment versus Usual Care

Pharmacogenomic test: (Characteristics of best evidence)	Benefits	Comment
CNSDose (polygene panel of ABCB1, ABCC1, CYP2C19, CYP2D6, UGT1A1, not yet commercially available): 1 fair-quality, 12-week RCT[1] of N=148	Increases remission (HAM-D ≤ 7; 72% vs 28%; RR 2.52, 95% CI 1.71 to 3.73; NNG=3, 95% CI, 1.7-3.5) moderate SOE) and reduces the proportion of patients taking sick leave (usual care = 15% vs guided = 4%; RR 1.13, 95% CI 1.01 to1.25; low SOE)	Reduces intolerability (having an event where patient needed to reduce the dose or stop their antidepressant: usual care = 15% vs guided = 4%; RR 1.13, 95% CI 1.01 to 1.25; low SOE)
ABCB1 genotyping added to weekly plasma monitoring: 1 fair-quality, 5-week, observational study[2] of N=116	Improved remission (HAM-D < 10): 83.6% vs 62.1%; X^2 (1) = 6.596, P = 0.005) [ESP-calculated RR 1.33 (CI 1.06 to 1.72) and NNG=5; 95% CI 3 to 20]	No evidence about harms
GeneSight (polygene panel of CYP2D6, CYPC19, CYP1A2, SLC6A4, HTR2A): 1 fair-quality, 10-week RCT[3] of N=51	No improvement in remission (HAM-D ≤ 7: 20% vs 8%; RB 2.40, 95% CI 0.51 to 11.21) or response (≥ 50% HAM-D improvement: 36% vs 21%; RB 1.73, 95% CI 0.68 to 4.42 (Low SOE) [4])	No evidence about harms

HAM-D=Hamilton Rating Scale for Depression; SOE=Strength of Evidence; RR=Risk Ratio; RB=Relative Benefit; NNG=number needed to genotype; CI=Confidence Interval; RCT=Randomized Controlled Trial; CYP=Cytochrome p450; SLC6A4=Solute Carrier Family 6 (Neurotransmitter Transporter), Member 4; HTR2A=5-Hydroxytryptamine (Serotonin) Receptor 2A; UG1A1=UPD Glucuronosyltransferase Family 1 Member A1; ABCB1= ATP Binding Cassette Subfamily B Member 1

EVIDENCE BRIEF

PURPOSE

In January, 2015, the White House identified Veterans Affairs (VA) as a participating agency in the Precision Medicine Initiative, an effort to "enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care" that takes into account individual differences in people's genes, environments, and lifestyles.[5] To inform this initiative, the VA Office of Research and Development (ORD) is developing a clinical study to implement precision medicine in mental health (PMH). This study will supplement the Million Veteran Program's (MVP) capabilities to (1) understand the lifestyle, genomics and pharmacogenomics of depression in Veterans, (2) develop individualized approaches to treat depression in Veterans, and (3) develop and implement a responsible and efficient process of returning genetic data to providers and patients to determine how to use genetic findings in the clinical setting.[6] The PMH planning committee identified depression as a relevant focus because of its high prevalence, the continuing need for better treatment strategies, and the growing use of genetic testing for decision making. As funding for this study is arranged for FY17, ORD is convening a planning committee meeting for April 2016 to discuss study development. To inform their meeting, ORD commissioned the Evidence-based Synthesis Program Coordinating Center (ESP CC) to conduct an evidence brief on the comparative effectiveness, harms, and cost-effectiveness of pharmacogenomics-guided antidepressant treatment versus usual care for major depressive disorder.

BACKGROUND

Variability in Antidepressant Treatment of Major Depressive Disorder

Major depressive disorder (MDD) is a common problem and is associated with significant morbidity, mortality, and cost.[7] Based on 2014 National Survey on Drug Use and Health (NSDUH) data, the prevalence of major depression in Americans was 6.6%, which led to severe impairment for 65.5%.[8] In Veterans, the prevalence of MDD is as high as 13.5%.[9] Antidepressants are a mainstay of treatment for MDD, including the second-generation medications citalopram, sertraline, fluoxetine, escitalopram, paroxetine, venlafaxine, duloxetine, bupropion, and mirtazapine. But rates of remission are low and variable, with approximately 11-30% of patients remitting, even after one year of treatment.[10-13] Even in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial, it took more than 50 weeks to obtain a remission rate of 67%.[14] In this study, all participants were initially treated with citalopram, and those who did not achieve remission were offered up to 4 separate additional clinical treatment approaches until remission was obtained. Thus, even in this large, state-of-the-art clinical trial, a large proportion of patients did not achieve remission. This is concerning as treatment that falls short of remission is associated with continued disabling symptoms, higher rates of depression relapse and recurrence, poorer work productivity, more impaired psychosocial functioning, higher levels of health care use, and potentially higher risk for suicide.[10]

To guide the choice of antidepressants, clinicians have typically used clinical factors thought to be associated with variable treatment response, including the character of depressive symptoms

(*eg*, atypical, melancholic, and comorbid anxiety), family history, the possibility of drug-drug interactions, renal and hepatic function, medical and psychiatric comorbidity, nutritional status, nature of prior response to medication, and personal preference. However, few data are available to show that consideration of these factors improve remission rates or reduce adverse events. Therefore, clinicians match patients with specific antidepressants via a prolonged trial-and-error process. This delays clinical improvement and potentially increases the risks and cost of depression treatment. There remains a need for identification of additional strategies to better personalize a pharmacological approach to further improve antidepressant effectiveness. A variety of biomarkers, including pharmacogenomic approaches, have been studied to improve antidepressant prescribing.

Role of Genetic Factors in Antidepressant Treatment Variability

Genetic variation has long been explored as a potential contributor to individual differences in antidepressant treatment outcome. Pharmacogenetics/pharmacogenomics is "the use of genomic information to help predict how an individual might respond to a particular drug, to identify individuals who might experience an adverse reaction to taking a drug, or to assist in selecting the optimal dosage of a drug."[15] Antidepressant pharmacogenomic research has largely focused on genes involved in the pharmacokinetic action of medications. Pharmacokinetics is the study of the time course of medications through the body and involves absorption, presystemic elimination, drug distribution, and elimination. The most widely studied genetic differences in pharmacokinetics involve the cytochrome p450 (CYP) liver enzyme system (*eg*, CYP2D6, CYP2C19). CYP450 variants are believed to alter drug metabolizing enzyme (DME) function and change the normal rate of antidepressant metabolism and resulting plasma drug levels.[16] CYP450 variants that *reduce* enzyme function may cause poor or intermediate metabolism levels, which may lead to higher than expected active drug levels or reduced prodrug levels. CYP450 variants that *increase* enzyme function may cause ultra-rapid metabolism, which may lead to lower than expected active drug levels or increased prodrug levels. ABCB1, which encodes the P-glycoprotein which regulates transport across the blood-brain barrier, has also been studied. Genetic differences in pharmacodynamics, which is the study of the time course and intensity of pharmacological effects of drugs, have been less-extensively studied. Studies of serotonin receptors (*eg*, 5-HTT, 5-HT1A, 5-HTR2A), the serotonin transporter, and dopamine receptor (DAT1) have been studied. Finally, the mediation of inflammatory response to antidepressant drugs (*eg*, interleukin-1β)[17] may impact both pharmacokinetics and pharmacodynamics.

Understanding the extent to which genetic variation is meaningfully associated with individual differences in antidepressant treatment outcomes continues to be a challenge, however. Reviews and meta-analyses of studies that evaluated the potential interaction between antidepressant and genetic variants on remission, response, and harms have emphasized the following key limitations of the evidence base: (1) individual studies failed to control for known clinical and environmental confounders, (2) small sample sizes, and (3) heterogeneity across studies in the direction and magnitude of effect sizes and with regard to patients' clinical characteristics (*eg*, depression type, severity, *etc*), patient health behaviors such as food intake, medication regimen (*eg*, different types and classes, monotherapy versus combination therapy), and outcome measurement methods (*eg*, remission versus response, different end time points, different rating scales, *etc*).[16-24]

Characteristics and Regulation of Antidepressant Pharmacogenomic Testing Resources

Despite the challenges of understanding the association between genetic variation and antidepressant treatment outcomes, many tests for detecting genetic variants are now available for clinical use.[25,26] Antidepressant pharmacogenomic testing resources vary widely in which gene variants or alleles are genotyped, how the testing is performed and regulated, and how they report results. At minimum, the majority of testing resources include some CYP2D6 and CYP2C19 variants.[26] But the testing resources differ in which and how many CYP2D6 and CYP2C19 variants are included and if and how many other genes variants or alleles are genotyped.[25]

Regulation of pharmacogenomic tests differs depending on whether they are developed and performed by a single, central laboratory or sold to multiple labs. Some pharmacogenomic tests are sold as kits – "a group of reagents used in the processing of genetic samples that are packaged together and sold to multiple labs" – and these are regulated by the US Food and Drug Administration (FDA) as Class II devices and subject to the 510(k) marketing clearance process.[15,27] The 510(k) is "a premarket submission made to the FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device."[28] The Roche AmpliChipÒ Test – which genotypes 28 CYP2D6 variants and 3 CYP2C19 variants – is the first and only pharmacogenomic testing platform with 510(k) marketing clearance.[27] The majority of pharmacogenomic tests are Laboratory-Developed Tests (LDTs) that are developed and performed by a single, central laboratory. LDTs have historically not been assessed before being offered for clinical use and have only been regulated by the Centers for Medicare and Medicaid Services (CMS) with regard to whether laboratories' practices for using them are in compliance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA).[15,20,25] However, in 2010, the FDA proposed initiating premarket evaluation of pharmacogenomic LDTs' analytical and clinical validity as well.[29] In October 2014, FDA released for public comment a Draft Regulatory Guidance document and 9-year implementation time-frame.[15,30,31] Main concerns about the FDA LDT oversight proposal include that the anticipated added cost and time involved in compliance with new regulations could potentially impede advances and negatively impact patient care.[32,33]

Format for reporting results also varies widely across pharmacogenomic testing. Sources of variation include (1) whether they are drug-focused or gene-focused,[26] (2) how much detail is provided about therapeutic implications, categorization of interaction, and clinical impact, and (3) whether or not consultation with a professional genetic counselor and/or a pharmacist is available to help treating clinician interpret the results. For example, the interpretive report for the GeneSight test organizes the results by gene-drug interaction category and clinical impact and highlights these features at the top of the report. For gene-drug interaction category, the GeneSight report stratifies *specific* antidepressant and antipsychotic medications into 3 color-coded categories: (1) green "use as directed" bin to indicate little or no gene-drug interaction, (2) yellow "use with caution" bin to indicate moderate gene-drug interaction, and (3) red "use with caution with more frequent monitoring" bin to indicate more severe gene-drug interaction.[3] Footnotes supply the details of the therapeutic implications of the gene-drug interactions for the yellow and red categories and the gene results are in a table at the bottom of the report. In contrast, the Genecept Assay interpretive report organizes the results by gene result and provides much more detailed information about therapeutic implications for each gene result. Gene-drug

interaction is also stratified by 3 categories: (1) a green check mark for "no known gene-drug interaction", (2) a blue lightbulb for "therapeutic options", and (3) an orange caution symbol for "use caution" with related therapies to indicate medications that may require a dose adjustment or have a higher risk of side effects of inefficacy. Compared to the GeneSight report, the Genecept report guidance on clinical impact is more general, referring to classes of antidepressants and antipsychotics, rather than listing specific antidepressants.[34] It is unclear if and how such differences in pharmacogenomic testing results format may affect the accuracy of their interpretation and use.[25]

Guidelines and Labeling for Use of Pharmacogenomics in Antidepressant Treatment

With the increased availability of pharmacogenomic testing, its clinical use is increasing. This has led to development of antidepressant FDA product labeling and clinical practice guidelines from various professional genetic societies on the use of pharmacogenomic testing.[25,27] A 2014 review by Drozda et al provides a detailed analysis of information contained in FDA labeling of antidepressant drugs and consensus guidelines.[25] At the time of the Drozda review, the number of neuropsychiatric medications with FDA labeling listing a CYP450 variant metabolizer status as an important biomarker was 27 for CYP2D6 and 3 for CYP2C19.

Guidance on using *existing* CYP2D6 and/or CYP2C19 genotyping results to inform antidepressant selection and dosing is also provided by a few professional genetic societies (see appendix A in supplemental materials).[25,27,35-38] These guidelines vary in when they were released, the antidepressant medications they address, their development methods, and how they assess the level of evidence and/or classification of recommendations. The most up-to-date genotyping-based dosing guidelines (late 2015 to early 2016) are from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and available on the Pharmacogenomics Knowledge Base (PharmGKB website).[37] CPIC guidelines provide metabolism implications and therapeutic recommendations for various antidepressant drugs and generally classify the recommendations as moderate to strong.

When Should Antidepressant Pharmacogenomic Testing Be Performed?

Despite availability of guidance on how to use *already available* pharmacogenomic testing results, uncertainty remains on *when and for whom* pharmacogenomic testing should be performed. Professional genetic society guidelines vary on whether and how they address when to perform pharmacogenomic testing to inform antidepressant treatment.[25,27,35-40] The earliest guideline, released in 2007 by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group,[38] which was based on an evidence review[16] by the Agency for Healthcare Research and Quality's Duke Evidence-based Practice Center, concludes that CYP2D6 testing for SSRI treatment for depression was not recommended at that time. More recent guidelines have identified some "important indications" for combining genotyping with therapeutic drug monitoring[39] and have suggested "clinicians *consider* FDA drug labeling recommendations about genetic testing for some specific drugs," but with the caveat that evidence remains inconclusive about possible clinical utility of CYP450 in psychiatry.[40] Guidelines specific to the treatment of patients with depressive disorders either do not reference pharmacogenomic testing at all,[41,42] or mention it only briefly as an area for future research.[43-45]

The conservative nature of existing formal guidance about the clinical utility of pharmacogenomic testing is likely due at least in part to the fact that it was developed prior to the emergence of the first of several recent studies that have compared the use of pharmacogenomic data to guide antidepressant treatment selection for depressive disorders to treatment as usual. Although various articles[19,20,26,27,46] have briefly reviewed findings from some of the recent studies, they have not formally critically appraised the complete body of available evidence. The purpose of this report is to conduct an evidence brief on the comparative effectiveness, harms, and cost-effectiveness of pharmacogenomics-guided antidepressant treatment versus usual care for major depressive disorder, to inform an April 2016 ORD planning meeting for development of a clinical study to implement precision medicine in mental health (PMH).

SCOPE

The clinical scenarios evaluated by this evidence brief are the use of pharmacogenomic testing for predicting effectiveness and harms of antidepressant treatment for certain adults with depressive disorders, such as prior to initiation of antidepressants or after failure of one or more courses.[47] Areas of particular relevance for evaluating evidence for this use of genetic tests include Analytic validity, Clinical validity, Clinical utility, and Ethical, legal, and social implications (ACCE Model, National Office of Public Health Genomics).[47,48] Within this evaluation framework, this evidence brief focused on clinical utility and post-pharmacogenomic testing analytic factors. The VA Office of Research and Development (ORD) originally identified 4 key questions and associated Population, Interventions, Comparators, Outcomes, Timing, Setting, and Study design (PICOTSS) characteristics of interest to be addressed by this report. The ESP Coordinating Center investigators then worked with ORD to clarify and refine the key questions and PICOTSS as listed below and illustrated by the analytic framework.

KEY QUESTIONS

1) What is the impact of using pharmacogenomics-guided antidepressant treatment on remission, response, quality of life, and functional capacity in patients with MDD?

2) What is the impact of using pharmacogenomics-guided antidepressant treatment on reducing *time to* remission, response, improved functional capacity or reducing treatment switches in patients with MDD?

3) Are improved outcomes from pharmacogenomics-guided treatment explained by implementation of pharmacogenomically informed intervention changes (*eg*, switching medication, adjusting dose)?

4) How does the use of pharmacogenomics-guided treatment impact risk of harms of antidepressant medications?

5) Does the impact of using pharmacogenomics-guided treatment on the effectiveness and harms of antidepressants differ according to patient characteristics such as demographics, psychiatric and medical comorbidities, depression symptomatology (*eg*, melancholic, atypical, psychotic, catatonic, postpartum, anxiety features), depression severity and duration, history of antidepressant treatment resistance, concomitant medication, polypharmacy, medication side effects, nonadherence, or other health or lifestyle behaviors?

6) What is the cost-effectiveness of using pharmacogenomics to guide treatment of patients with MDD?

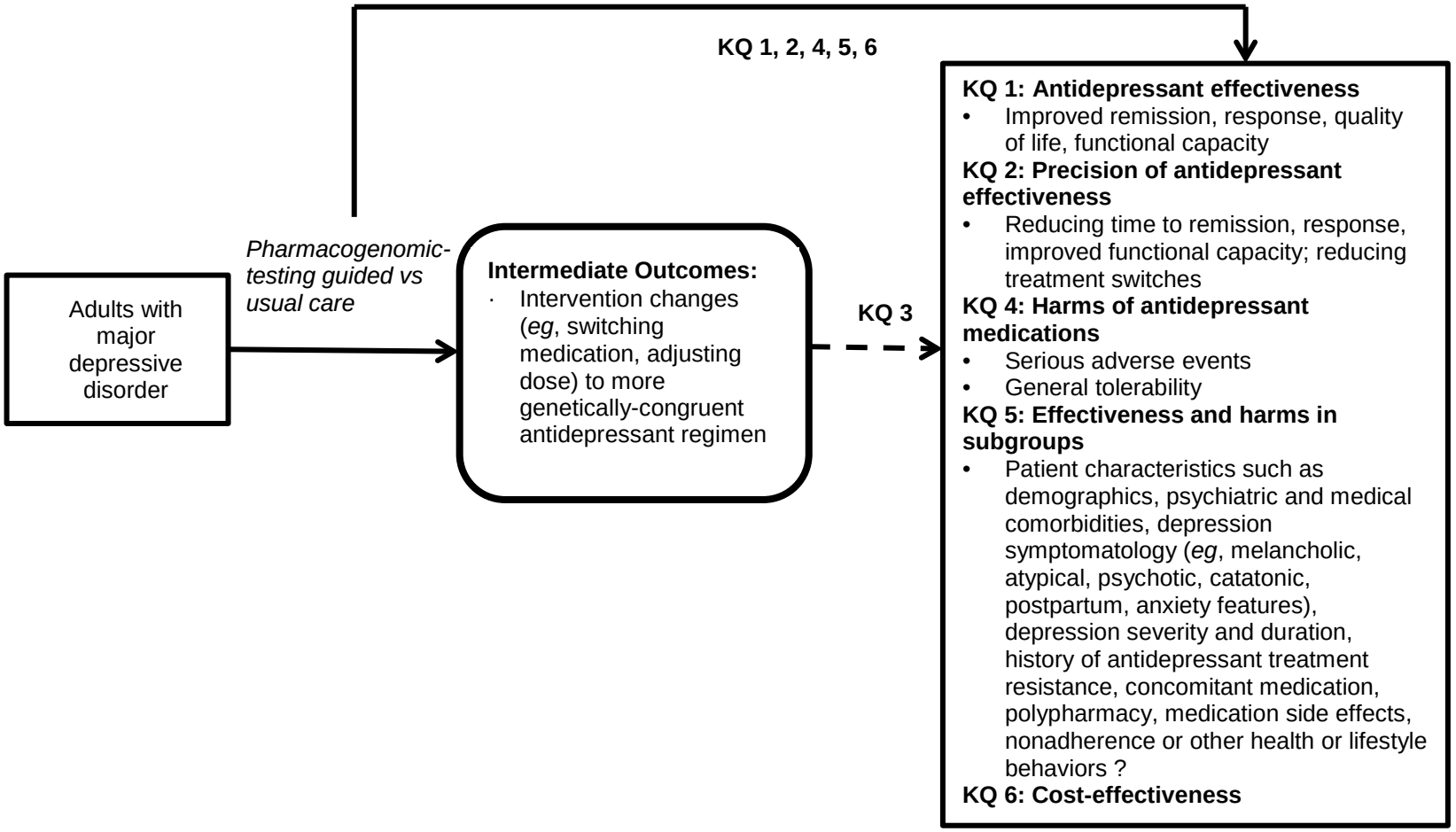
ELIGIBILITY CRITERIA

- ***P****opulation:* Adults with major depressive disorder
- ***I****ntervention*: Any pharmacogenomic testing platform, used alone or in combination with other clinical risk prediction tools
- ***C****omparator*: Usual care, other types of risk prediction tools
- ***O****utcomes:*
  - *Antidepressant effectiveness*: Remission, response, quality of life, functional capacity
  - *Precision of antidepressant effectiveness*: Reducing time to remission, response, improved functional capacity, reducing treatment switches
  - *Harms of antidepressant medication:* Serious adverse events and general tolerability
- ***T****iming:* No restrictions
- ***S****etting*: No restrictions
- ***S****tudy design:* No restrictions

ANALYTIC FRAMEWORK

The analytic framework below (Figure 1) illustrates the Population, Interventions, Comparators, Outcomes, Timing, Setting, and Study design (PICOTSS) of interest that guided this review and their relationship to the key questions. This evidence brief addresses the overarching question of clinical utility, focusing on evidence evaluating the direct link between use of pharmacogenomics-guided treatment and health and clinical outcomes (key questions 1, 2, 4, 5, and 6). To further evaluate clinical utility, key question 3 also examines how adding pharmacogenomic testing affected the reclassification of patients into different prognostic groups based on level of gene-drug interaction (*eg*, little or no, moderate, severe) and their predicted antidepressant drug efficacy and harms[49] and what difference this made on health outcomes.

Figure 1. Analytic Framework



METHODS

An evidence brief differs from a full systematic review in that the scope is narrowly defined and some traditional review methods may be streamlined in order to synthesize evidence within a shortened timeframe. An evidence brief does not outline the full context in which the information is to be used and does not present a comprehensive assessment of knowledge on the topic. Brief or rapid review methodology is still developing and there is not yet consensus on what represents best practice.

To identify articles relevant to the key questions, we searched MEDLINE® and the Cochrane Central Registry of Controlled Trials on March 4, 2016 and PsychINFO on March 8, 2016, using terms for *pharmacogenomics, pharmacogenetics,* and *depression* from 1996 forward (see appendix B in supplemental materials for complete search strategies). We limited the search to published and indexed articles involving human subjects available in the English language. Additional citations were identified from hand-searching reference lists and consultation with content experts. To identify additional unpublished or ongoing studies as well as guidelines on pharmacogenomics for MDD, we searched the following non-bibliographic database sources: government websites, conference proceedings, relevant genetic and psychiatric professional organizations, clinicaltrials.gov, test manufacturer websites, the VA Health Services Research & Development (HSR&D) Research Studies and Implementation Projects database, and Google. Study selection was based on the eligibility criteria described above. Titles and abstracts were reviewed by one investigator. Full-text articles were reviewed by one investigator and checked by another. All disagreements were resolved by consensus.

We used predefined criteria to rate the internal validity of all randomized controlled trials and controlled cohort studies. We rated the internal validity of controlled trials based on criteria established by the Drug Effectiveness Review Project.[50] We rated the internal validity of observational studies based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[51] We abstracted data from all included studies and results for each included outcome. All data abstraction and internal validity ratings were first completed by one reviewer and then checked by another. All disagreements were resolved by consensus.

We graded the strength of the evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[52] This approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Strength of evidence is graded for each key outcome measure and ratings range from high to insufficient, reflecting our confidence that the evidence reflects the true effect. Synthesis was first completed by one reviewer and then checked by another, and we resolved disagreements using consensus.

A draft version of this report was reviewed by technical experts selected to represent relevant specialties including genomics, psychiatry, cost-effectiveness, and systematic review methodology. Their comments and our responses are available in appendix G in the supplemental materials.

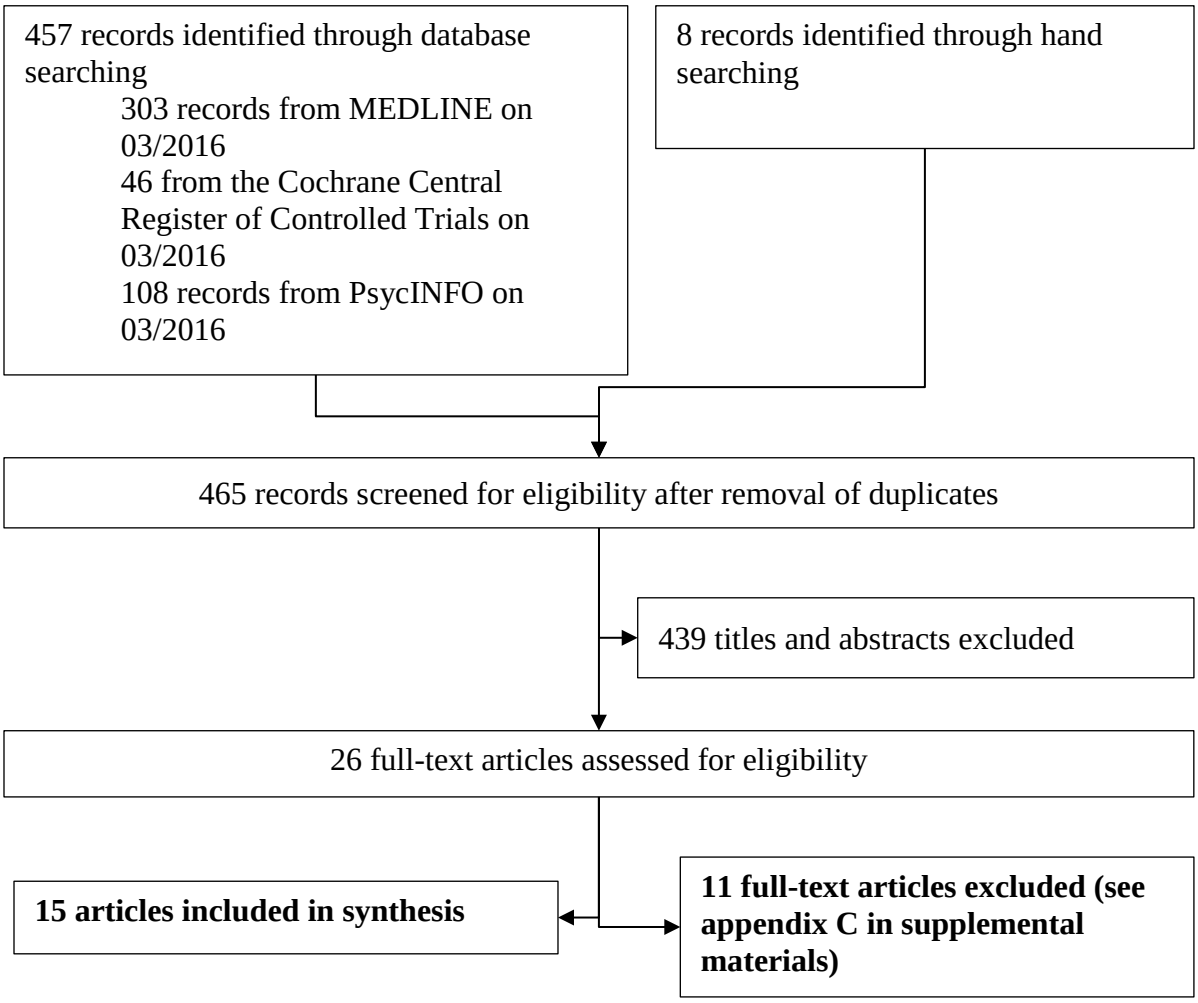
The complete description of our full methods can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42016036358).

RESULTS

LITERATURE FLOW

We screened 465 unique records and included 15 articles in this evidence brief (Figure 2). Among the included studies, 2 were randomized controlled trials, 7 were observational studies, and 6 were modeling studies.

Figure 2: Literature Flowchart



Of the included studies, 7 addressed KQ1 and KQ4,[1-3,53-56] 2 studies addressed KQ3,[3,53] and 8 studies addressed KQ6.[16,57-63] No studies addressed KQ2 or KQ5. All of the included randomized controlled trials and controlled cohort studies were rated as fair quality[2 3,53,54,62,63] except one RCT which was rated as good quality.[1] See appendix D in the supplemental materials for full data abstraction, quality assessment, and strength of evidence details. Additionally, we identified 23 unpublished or ongoing studies (see appendix E in supplemental materials).

Only 3 pharmacogenomics-guided treatment strategies are evaluated in published studies that compare guided and usual care: (1) CNSDose, which is a polygene panel of ABCB1, ABCC1, CYP2C19, CYP2D6, UGT1A1), not yet commercially available; (2) GeneSight, which is a

polygene panel of CYP2D6, CYPC19, CYP1A2, SLC6A4, HTR2A), and (3) ABCB1 genotyping added to weekly plasma monitoring. The strength of the evidence for each is generally low because each is supported by only a single, small, short-term study with some methodological limitations as summarized below and detailed in Appendix D. Although methods used to predict phenotype (*eg*, poor metabolizer) from genotype may vary across laboratories,[36] they were not specified in any of the studies. Studies of polygene panels also did not describe the algorithms they used to combine phenotype information across multiple variants to make drug selection and dosing recommendations or what guidelines they based their recommendations on. The lack of this information limits interpretation of findings and comparison of panels. Study sample characteristics are applicable to a narrow range of patients, including primarily females in their mid-upper forties who were the most refractory to treatment (mean of 4 previous failed medication trials), and lacked common comorbidities such as PTSD, and/or were hospitalized with genotype guiding added to weekly plasma monitoring.

KEY QUESTION 1 AND 4: ANTIDEPRESSANT EFFECTIVENESS AND HARMS

Polygene Panel of CYP2D6, CYPC19, CYP1A2, SLC6A4, HTR2A (GeneSight)

Compared to usual care, GeneSight-guided care has not yet been shown to significantly improve remission or response in a randomized trial.[3,4,46] The only completed double-blind, randomized trial provided low-strength evidence that 10 weeks of GeneSight-guided care does not significantly improve remission rates (HAM-D ≤ 7: 20% vs 8%; RR 2.40, 95% CI 0.51 to 11.21) or response (≥ 50% HAM-D improvement: 36% vs 21%; RR 2.14, 95% CI 0.56 to 7.69).[3] This trial was conducted in the outpatient clinics of Pine Rest Christian Mental Health Services in Grand Rapids, Michigan and involved 51 patients with major depressive disorder, with a mean baseline HAM-D of 21, who had failed a mean of 4 previous psychiatric medication trials. The applicability of these findings to Veterans is unclear, however, as the mean age was 49 years, only 20% of patients were male, and the types of antidepressants medications used were not reported. Another weakness of this study is that it did not report on adverse effects.

Results from 2 previous open-label nonrandomized studies[53,54] were less informative than the findings of the RCT.[3] These studies were also short-term (8 weeks), did not evaluate adverse effects, and included mostly females in their mid-forties with unknown comorbidities, and had more methodological limitations. Although these open-label nonrandomized studies found that GeneSight-guided care significantly improved response, defined as a 50% or greater decreased from baseline in HAM-D17 score (ESP-pooled: 40% vs 23%; RR 1.73, 95% CI 1.09 to 2.73), there is a high likelihood that this was due to increased expectations in the GeneSight-guided group based on their knowledge that their medication selection was being guided by DNA testing and, in the case of the Hall-Flavin 2013 study, fewer previously failed psychiatric medication trials in the guided group (4.7 vs 3.6; P = 0.021).[53] Also, because groups were not matched on psychiatric and medical comorbidities, concomitant medications, medication adherence, and health and lifestyle characteristics, important differences could exist that could have confounded the effects of the GeneSight guiding. When data from the double-blind RCT[3] and these 2 open-label nonrandomized studies[53,54] were combined in a meta-analysis,[4] the improved response with GeneSight-guided care reached statistical significance (RR 1.71; 95% CI 1.17 to 2.49). However, the described specific weaknesses of these open-label, nonrandomized studies also seriously limit the validity of the meta-analysis.

We identified 3 ongoing clinical trials assessing the efficacy of GeneSight-guided management of depressive disorders (NCT02189057, NCT02466477, NCT02109939). All studies are double-blind RCTs that are expected to address some gaps in the existing evidence by increasing precision with larger sample sizes and providing longer follow-up (see appendix E in supplemental materials).[46] The studies are expected to be completed between 2015 and 2018.

Polygene Panel of ABCB1, ABCC1, CYP2C19, CYP2D6, UGT1A1 (CNSDose, Not Commercially Available)

Compared to usual care, 12 weeks of CNSDose-guided antidepressant treatment improves remission (HAM-D $\leq$ 7; 72% vs 28%; RR 2.52, 95% CI 1.71 to 3.73; moderate SOE) and reduces the proportion of patients taking sick leave (usual care = 15% vs guided = 4%; RR 1.13, 95% CI 1.01 to 1.25; low SOE) and intolerability (having an event where patient needed to reduce the dose or stop their antidepressant: usual care = 15% vs guided = 4%; RR 1.13, 95% CI 1.01 to 1.25; low SOE) in patients with baseline HAM-D score of 25 taking various second-generation antidepressants.[1] Supporting evidence comes from one randomized trial of 148 adults with MDD conducted in Australia. The main strength of this study is its high internal validity due to its use of robust methodology. However, the main weakness of this study is its limited applicability to the VA population. This study excluded smokers and patients with other active comorbid psychiatric disorders and ended up with a population of mostly employed females in their early forties. Average number of MDD episodes was 2, with average duration of 8.55 months, but number of previously failed antidepressant trials was not reported, nor was current number of antidepressant medication or other types of concomitant treatment. A replication study of CNSDose has been completed and its findings have been submitted for peer review (author correspondence, Australian and New Zealand Clinical Trials Registry ID # ACTRN12613001135707). Its results are expected to be more applicable to the typical VA MDD population as its eligibility criteria were more inclusive, allowing psychiatric comorbidities such as PTSD and smoking.

ABCB1 Genotyping (Codes for P-glycoprotein, Not Commercially Available)

Compared to usual care treatment, 5 weeks of ABCB1 genotyping-guided antidepressant treatment improves remission (improved remission (HAM-D < 10): 83.6% vs 62.1%; X^2 (1) = 6.596, P = 0.005; ESP calculated-RR 1.33; CI 1.06 to 1.72; low SOE). Response (50% reduction in HAM-D), quality of life, functional status, and side effects and tolerability were not reported. Supporting evidence comes from one observational pilot study of 116 adults with MDD and bipolar disorder conducted in Germany.[2] The study has several weaknesses that limit its applicability to Veterans. First, the HAM-D remission cut-off (< 10) is not considered complete remission according to typical HAM-D scoring methods, so remission may be overestimated in this study. Also, all treatment occurred while patients were hospitalized, and clinicians were given antidepressant plasma levels weekly in addition to the ABCB1 genotyping. It is unclear how antidepressant plasma monitoring impacted care in this study and it has limited applicability to VA care as antidepressant plasma levels are not routinely monitored in the VA. The mean age in the sample (46.59 to 48.53) was somewhat younger than the mean age of US Veterans currently enrolled in care with depression (57.2) and some patients had bipolar disorder, which is a relative contraindication to treatment with antidepressants. The study population was predominantly female, with an average number of depressive episodes of 4.24, duration of current episode of 25 weeks, and 1.3 antidepressant trials during recent admission in the experimental group, compared to 2.43 depressive episodes, 39.2 weeks for the current episode of

depression, and 0.98 antidepressant trials during the recent admission for the comparison group. These were not statistically significantly different.

CYP2D6, CYP2C19, SLC6A4, CACNA1C, DRD2, COMT, MTHFR (Genecept)

There is insufficient evidence to draw conclusions about the comparative benefits and harms of Genecept-guided care versus usual care in patients with depressive disorders. This is because we found no completed studies that evaluated this comparison. In a single-group before-after study of 685 adults with mood and anxiety disorders, 38% achieved remission (Quick Inventory of Depression Symptoms – QIDS-SR < 5) and 39% achieved response (≥ 50% reduction in QIDS-SR score) after 3 months of Genecept-guided care.[55] However, this type of study design – lacking an usual care control group – generally does not provide reliable evidence of the specific effects of an intervention as distinct from what may have naturally occurred over time regardless of the intervention.

We identified one ongoing double-blind randomized controlled trial of 8 weeks of Genecept-guided versus usual care in adults with MDD that expected to assess response, remission, and safety outcomes (NCT02634177). This study is expected to complete in October of 2016 and should provide more relevant and higher-quality evidence with which to evaluate the clinical utility of Genecept.

CYP2D6 AND CYP2C19

There is insufficient evidence to draw conclusions about the clinical utility of CYP2D6 and CYP2C19 genotyping for MDD. The only study we found was a single-group before-after study of less than or equal to 100 adults receiving antipsychotics/antidepressants for unspecified reasons.[56] Twelve weeks after genotypic information was considered in their drug therapy, "several" of the patients reported they were "much improved." But because this study lacks an usual care control group and its data was not presented in a scientifically rigorous manner – lacking detail on patient characteristics, completeness of the data, etcetera – it does not provide clearly relevant or reliable evidence on the clinical utility of CYP2D6 and CYP2C19 genotyping for MDD.

KEY QUESTION 2: PRECISION

We found no studies that evaluated whether using pharmacogenomics-guided treatment reduced time to remission, response, improved functional capacity, or reduced treatment switches in patients with MDD.

KEY QUESTION 3: IMPACT OF MEDICATION CHANGES BASED ON PGX TESTING

In establishing the clinical utility of pharmacogenomics-guided treatment, a first step is to demonstrate an *overall* improvement in the key outcomes of remission, response, and tolerability for guided versus usual care. An essential second step is to also demonstrate that the improvement on those key outcomes is due to a greater incidence in the guided group of actually implementing recommended medication changes to more genetically-suitable regimens. At the time of this report, no pharmacogenomics-guided treatment strategy has met both of these criteria.

Guided care with GeneSight (Polygene panel of CYP2D6, CYPC19, CYP1A2, SLC6A4, HTR2A) is the only strategy with any evidence for the second step of showing that improvements were associated with switches to more genetically-suitable regimens (Table 1).[3,53] However, the clinical meaningfulness of the evidence is unclear because it was measured based on *mean change* in depression symptoms, rather than remission and/or response.[3]

Table 1. Association between Switches to More Genetically Suitable Medication Regimens and Mean Change in HAM-D Scores in Subgroups of Patients on Genetically Discordant Medication Regimens at Baseline

	Double-blind RCT[3] N=13		Open-label observational study[53] N=34	
	Switched to more genetically suitable medication	**% improvement in mean HAM-D scores**	**Switched to more genetically suitable medication**	**Mean change in HAM-D score**
Genesight-guided	100%	33.1%	93.8%	42.5%
Usual care	50%; P=0.02	0.8%; P=0.06	55.6%; P=0.01	16.6%; P=0.01

KEY QUESTION 5: SUBGROUPS

We found no studies that evaluated the impact of using pharmacogenomics-guided treatment on the effectiveness and harms of antidepressants differ according to patient characteristics such as demographics, psychiatric and medical comorbidities, depression symptomatology (*eg*, melancholic, atypical, psychotic, catatonic, postpartum, anxiety features), depression severity and duration, history of antidepressant treatment resistance, concomitant medication, polypharmacy, medication side effects, nonadherence, or other health or lifestyle behaviors.

KEY QUESTION 6: COST-EFFECTIVENESS

The cost-effectiveness of pharmacogenomics-guided care versus usual care in Veterans with major depressive disorder is not clear. This is primarily because there is too much uncertainty about the effectiveness of pharmacogenomics-guided care in Veteran-representative patients whose primary diagnosis is major depressive disorder. The 2 available controlled cohort studies only measured cost savings and not cost-effectiveness, were comprised of populations using antidepressant medication primarily for diagnoses other than depressive disorders (*ie*, anxiety, ADHD, other mood disorder, dementia, personality disorder, 'all other psych'), and did not evaluate the subgroups of patients with depressive disorders (14%-39%).[62,63] One modeling study found GeneSight testing to be cost-effective over a wide range of clinical scenarios,[57] but, as with any modeling study, its reliance on inferences of likely outcomes rather than directly linking interventions to actual observed outcomes is a key limitation.

Cohort Studies

No study has prospectively compared the cost-effectiveness of pharmacogenomics-guided care versus usual care specifically in patients with depressive disorders. We identified one prospective cohort study[63] and one retrospective cohort study[62] that compared actual healthcare costs between pharmacogenomics-guided versus usual care, but their applicability to patients with depressive disorders is likely very limited. This is because they both focused on use of

psychotropic medications for any diagnosis. In the prospective study, only 29% of the neuropsychiatric medication use was for CNS disorders and among that only 14% was for major depression.[63] In the retrospective study, only 29% of patients had depressive disorders.[62] Neither study performed subgroup analyses of cost in the depression subgroups. Other main limitations of both studies are that (1) they lacked measurement of antidepressant medication clinical benefits and harms and (2) there is a high risk of residual confounding as patients were matched only on demographics and the presence of a CNS diagnosis, which does not account for depression severity or subtype. The prospective study had additional limitations of (1) lacking measurement of other outpatient and inpatient healthcare costs and (2) not accounting for comorbidity. In the prospective study, compared to usual care, GeneSight-guided care (CYP2D6, CYPC19, CYP1A2, SLC6A4, HTR2A) reduced *total* medication costs by $1035.60 over one year (P=0.007).[63] But, the majority of savings related to non-CNS medications ($714.24; 69%), with only $321.36 (31%) annual savings for CNS medications. In the retrospective study, Genecept-guided care reduced overall pharmacy and outpatient care-related costs by 9.5% over 4 months, or $562.[62]

Modeling Studies

Table 2 below summarizes the characteristics and findings from 6 modeling studies.[16,57-61] Pharmacogenomic test type varied across studies, including the GeneSight polygene panel (CYP2D6, CYPC19, CYP1A2, SLC6A4, HTR2A),[57] 5-HTTLPR,[58,59] HTR2A,[60] and CYP450 polymorphisms.[16,61] A key limitation of all modeling studies is their reliance on inferences of likely outcomes rather than directly linking interventions to actual observed outcomes. Also, the findings of these studies have questionable relevance to the VA setting, as in some cases the treatment regimens were poorly characterized and the base-case parameters used in the models may have been more favorable than the average characteristics of Veterans with depression.

Five of 6 modeling studies found limited cost-effectiveness, only under certain circumstances. The exception was that, compared to treatment as usual, the GeneSight polygene panel was found to have a high probability (94.5%) of being cost-effective at the Willingness-To-Pay (WTP) threshold of $50,000/Quality-Adjusted Life-Years (QALYs) (Table 2).[57] This finding was robust to variation in input parameters (95% confidence intervals), with 74.7% of 10,000 simulations showing that Genesight-guided care was more effective and more cost-saving than treatment as usual. This study used a Markov state-transition analysis to evaluate QALYs, cumulative direct (*ie*, depression and non-depression drugs, inpatient and outpatient physician treatment, psychotherapy, and other costs) and indirect (*ie*, productivity and absenteeism) costs, and cost per QALY gained. Relative benefit ratio of GeneSight on response rate, catch-up year, and starting age were the top 3 input parameters that had the greatest influence on incremental costs, with ranges that included cost-increasing scenarios. First, for the test effect on response rate, its reliability is important because sensitivity analyses ranked it as having the largest effect on incremental costs. In this analysis, the test effect on response rate was estimated at 1.71 based on 3 clinical studies of GeneSight. However, as discussed above, these studies involved populations that were younger and included more females than in the Veteran population and for which psychiatric and medical comorbidities, concomitant medications, medication adherence, and health and lifestyle characteristics were not well-characterized.[3,53,54] But at least one of the studies[3] excluded individuals with comorbid substance abuse or dependence. Therefore, it is unclear how applicable that 1.71 relative benefit of GeneSight on response is to a VA population. The Probabalistic Sensitivity Analysis of the lower and upper bound of the 95% confidence

interval around the test effect (1.17 to 2.49) includes both increased total cost of $815 to an increased savings of $8543. Because we don't know what the test effect on response rate actually is in Veterans, we can't determine the cost implications within this continuum. Second, this analysis included the time-related parameter of "catch-up year," that assumed that it would take 3 years for the usual care group's response rate to "catch up" to the Genesight-guided group. Sensitivity analyses found that if the usual care group caught up faster, within one year, the use of the GeneSight test to guide care became cost-increasing ($491 higher). Finally, compared to the mean age of getting tested at 44 years of age used in the model, the higher mean age of 57 years in Veterans with depression[9] may be expected to reduce cost-effectiveness. Age had the third-highest impact on the incremental costs. The Probabalistic Sensitivity Analysis of the lower and upper bound of the 95% confidence interval around age (18 to 82 years) includes both increased total cost savings of $3835 to a higher incremental cost of $2500, and we don't know where along that continuum the mean Veteran age of 57 falls. Although each of these cases led to cost-increasing scenarios, Incremental Cost-Effectiveness Ratio (ICER) values were noted to remain below WTP threshold of $50,000/QALYs. However, it was unclear how the combination of lower response benefits, lower catch-up year, and higher age – as potentially characteristic of Veterans – may have affected ICER values. On the other hand, compared to the $2500 cost of the GeneSight test, the likely lower cost of pharmacogenomic testing in the VA – particularly if a process is adapted for returning results to Veterans from their already available Million Veteran Program genetic analysis – may be expected to improve cost-effectiveness. For these reasons, there remains a need for further cost-effectiveness analysis in more representative samples to better determine the true benefits in Veterans with depression.

Table 2. Summary of Cost-effectiveness Findings from Modeling Studies

Author Year Setting	***Hornberger 2015[57] US***	***Olgati 2012[58] Europe[1]***	***Seretti 2011[59] Italy***	***Perlis 2009[60] US***	***Pyne[61] VA***	***AHRQ 2007[16] US***
Test	GeneSight polygene panel	5-HTTLPR	5-HTTLPR	HTR2A	CYP450polymorphisms	CYP450
Population	Patients nonresponsive to ≥ 1 treatment Mean age = 44 years	Modeled on STAR*D: 64% female with mean age of 40.8; 35% Axis I comorbidity	Modeled on STAR*D: 64% female with mean age of 40.8; 35% Axis I comorbidity	41-year old patients in a current episode of MDD (based on STAR*D)	NR	Healthy treatment-naïve adults, no meds, can interact w/ SSRIs
Anti-depressant treatment algorithm	Guided vs usual care No restrictions on antidepressants	Usual citalopram vs 5-HTTLPR genotyping-guided citalopram or bupropion vs 5-HTTLPR genotyping-guided citalopram or citalopram plus bupropion	Usual citalopram or bupropion vs Guided citalopram or bupropion	(1) Test first, then citalopram or bupropion vs (2) Test second after citalopram failure, then sertraline or bupropion, vs (3) No test: citalopram to sertraline, citalopram to bupropion, bupropion to sertraline	Initiate treatment with paroxetine vs Initiate w/ citalopram vs Test CYP2D6 poly-morphisms (fast metabolizers prescribed paroxetine & slow metabolizers prescribed citalopram)	Non-CYP metabolized SSRI w/o testing vs Non-CYP or CYP metabolized SSRI w/ test vs CYP dose metabolized SSRI w/ test vs CYP metabolized SSRI w/o test
Treatment Effects	Response and suicide[2]	Remission; QALW	Remission, tolerability[3]	Response, no side effects	NR	Response and quality-adjusted survival
Costs included in analysis (pharmacy, direct, indirect)	Drugs, testing ($2500) inpatient and outpatient treatment, psychotherapy; productivity and absenteeism	Drug acquisition and delivery, outpatient and inpatient care and genetic test ($200); no indirect costs	Drug acquisition, genetic test ($233.80), outpatient visits, hospitalization; no indirect	Medications, medication management visits, hospitalization for severe depression; no indirect costs	NR	Medication and test cost ($1000)
Key input parameters	Treatment as usual response rate at 8-12 weeks=24.7% Relative benefit ratio for response – CPGx = 1.71 Suicide rate: Responders=0.09%	Remission rate at 12 weeks (no genetic test): 0.33 (0.27-0.39); 5-HTTLPR effect on response: OR 2.37 (1.40-3.58); Hospitalization rate:	Remission rate at 12 weeks (no test): 0.33 (0.27-0.39) OR of 5-HTTLPR effect on response: 2.37 (1.40-3.58) Hospitalization rate:	Probability of remission at 3 mo. = 12%; Mortality rate =0.000538; Suicide rate=0.0009;	NR	Probability of responding to sertraline at 6 weeks=0.56; Utility of untreated depression = 0.32

	Nonresponders=0.16%	Euro A = 0.12, Euro B = 0.80, Euro C = 0.60	0.12	Relative risk of recovery = 1.28		
Results	94.5% probability of ICER values ≤ WTP threshold $50,000/QALY; GeneSight expected to save $3711 in direct medical costs per patient and $2553 in work productivity	Testing cost effective in high-income countries in Western Europe, not middle-income Eastern countries; ICER values: Euro A = $1147 Euro B= $1185 for Euro C = $117; Probability of ICER value below WHO threshold ($1926): Euro A = > 90% , Euro B = < 30%, Euro C = < 55% C	Unacceptable cost benefit for a single episode: ICER = $2890 ($1800-$4091), drops to $1392 ($837-$1982) after 2 recurrences; Probability ≤ ICER threshold of $1769 for 3rd episode > 80%	Test first and use bupropion for those at higher risk of nonresponse was not considered cost effective because it did not lead to ICER values ≤ WTP threshold $50,000/QALY. It cost $93,520/QALY relative to next best strategy of using an SSRI as first- and second-line without the test. Sensitivity analyses identified certain circumstances of benefit present, such as when testing OR for remission ~1.80-2.0	Initiating citalopram is dominant strategy: Cost $3,790 and produced 0.378 QALYs over 6 mo.; When cost of citalopram > $120/mo., gene testing most cost effective strategy; When clinical decision simplified to 2 treatment strategies (initiate paroxetine or test) gene testing strategy dominated no gene testing strategy up until the cost of genetic testing exceeded $100/patient	Testing does not save costs, even in optimistic "high correlation" scenario, unless expected treatment duration > 9 mo. Testing to guide medication choice cost $909 more than empiric therapy with a non-CYP medication, while using genetic testing to guide CYP dosing cost $882 *more*.

[1] High Gross Domestic Product [GDP] (Euro A: Austria), Middle GDP (Euro B: Slovakia), and middle-high GDP (Euro C: Hungary)
[2] Assumed to be same as general population
[3] Evaluated in recurrent episodes
Abbreviations: QALW=Quality-Adjusted-Life Weeks; QALY=Quality-adjusted life year; SSRI=Selective Serotonin Reuptake Inhibitor; ICER=Incremental cost-effectiveness ratio; WTP=Willingness-To-Pay; AD=Antidepressant; STAR*D=Sequenced Treatment Alternatives to Relieve Depression study; CYP=Cytochrome p450; NR=Not Reported; OR=Odds Ratio
Indirect costs related to productivity loss were not included in CUA, as recommended in guidelines for pharmacoeconomic analysis (Weinstein et al., 1996).

KEY FINDINGS

- Only 3 pharmacogenomics-guided treatment strategies have published studies that compare guided and usual care: (1) CNSDose (polygene panel of ABCB1, ABCC1, CYP2C19, CYP2D6, UGT1A1), not yet commercially available; (2) GeneSight (polygene panel of CYP2D6, CYPC19, CYP1A2, SLC6A4, HTR2A); and (3) ABCB1 genotyping added to weekly plasma monitoring. However, there is some doubt that the studies' findings are valid, because there is a single, small, short-term study of each strategy, and these studies have numerous minor methodological limitations. Also, most patients in these studies were females in their forties who lacked comorbidities, such as PTSD, that are common among Veterans who have depression. Some had refractory depression. Others were being treated as inpatients while participating in the Munich Antidepressant Response Signature (MARS) project, which included use of weekly plasma monitoring. Even if a pharmacogenomics-guided strategy worked in the specific populations tested, it might have different results in the VA.
    - Of the 3 pharmacogenomics-guided treatment strategies, CNSDose has the most favorable preliminary findings. One additional patient had a remission by 12 weeks for every 3 genotyped (95% CI, 1.7-3.5), and the effect on intolerability was also favorable (having an event where patient needed to reduce the dose or stop their antidepressant: usual care = 15% vs CNSDose-guided = 4%; RR 1.13, 95% CI 1.01 to 1.25; low SOE) compared to usual care.
    - ABCB1 genotyping also improved chance of remission, but less so – there was one additional remission at 5 weeks for every 3 to 20 patients genotyped. This difference could be due to the short duration of the study. Also, harms were not evaluated.
    - For GeneSight, the highest-quality study found its effects were not statistically significant and left unclear whether the chances were substantially *better* or *worse* than usual care for remission (HAM-D $\leq$ 7: 20% vs 8%; RR 2.40, 95% CI 0.51 to 11.21) and response ($\geq$ 50% HAM-D improvement: 36% vs 21%; RR 2.14, 95% CI 0.56 to 7.69). Harms were not evaluated.
- In establishing the clinical utility of pharmacogenomics-guided treatment, a first step is to demonstrate an improvement in the key outcomes of remission, response, and tolerability for the guided group overall versus usual care. An essential second step is also to demonstrate that the improvement on those key outcomes is due to a greater incidence in the guided group of actually implementing recommended medication changes to more genetically suitable regimens. At the time of this report, no pharmacogenomics-guided treatment strategy has met both of these criteria.
- We found no studies that evaluated the impact of pharmacogenomics-guided treatment on time to antidepressant effectiveness in patients with MDD or number of failed antidepressant trials.

- We found no studies that evaluated whether the impact of using pharmacogenomics-guided treatment on the effectiveness and harms of antidepressants differs according to the following key patient characteristics: demographics, psychiatric and medical comorbidities, depression symptomatology (*eg*, melancholic, atypical, psychotic, postpartum, anxiety features), depression severity and duration, history of antidepressant treatment resistance, concomitant medication, polypharmacy, medication side effects, nonadherence, or other health or lifestyle behaviors.

- The cost-effectiveness of pharmacogenomics-guided care versus usual care in Veterans with major depressive disorder is not clear. This is primarily because there is too much uncertainty about the effectiveness of pharmacogenomics-guided care in Veteran-representative patients whose primary diagnosis is major depressive disorder. The 2 available controlled cohort studies only measured cost savings and not cost-effectiveness, were comprised of populations using antidepressant medication primarily for diagnoses other than depression (*ie*, anxiety, ADHD, other mood disorder, dementia, personality disorder, 'all other psych'), and did not evaluate the subgroups of patients with depressive disorders (14%-39%). One modeling study found GeneSight testing to be cost-effective over a wide range of clinical scenarios, but, as with any modeling study, its reliance on inferences of likely outcomes rather than directly linking interventions to actual observed outcomes is a key limitation.

IMPLICATIONS FOR FUTURE RESEARCH

Findings from this review support the need for additional research in VA to better understand whether using pharmacogenomics-guided care can improve the effectiveness of available antidepressant medications in Veterans with major depressive disorder. Therefore, a study that could augment the Million Veteran Program's (MVP) capabilities, such as that proposed by the VA Office of Research and Development (ORD), has the potential to be very helpful toward their goals to (1) better understand the lifestyle, genomics, and pharmacogenomics of depression in Veterans, (2) develop individualized approaches to treat depression in Veterans, and (3) develop and implement a responsible and efficient process of returning genetic data to providers and patients to determine how to use genetic findings in the clinical setting.[6]

We did not find evidence that would help VA decide which genes to focus on, which variants, and how to translate results into clinical recommendations. To help guide ORD in ongoing learning and evidence development in depression pharmacogenomics, several conceptual frameworks are available that outline common challenges and identify important methodologic issues for consideration.[16,64-67] Although ORD's first goal of better understanding the genomics and pharmacogenomics of depression in Veterans – or clinical *validity* – was outside of this evidence brief's focus on clinical *utility*, a preliminary search suggested that there is the potential for additional studies to further improve our understanding of clinical *validity*. Our preliminary searching of several organizations that are internationally recognized for expertise in producing systematic reviews (see appendix F in supplemental materials) only identified one systematic review of CYP450 polymorphisms, conducted by the Agency for Healthcare Research and Quality's Duke Evidence-based Practice Center (EPC) in 2007.[16] It and other various, more recent nonsystematic reviews and meta-analyses of association studies have generally found that understanding the extent to which genetic variation is meaningfully associated with individual differences in antidepressant treatment outcomes continues to be a challenge due to these key

limitations of the evidence base: (1) individual studies failed to control for known clinical, behavioral, and environmental confounders, (2) small sample sizes, and (3) heterogeneity across studies in the direction and magnitude of effect sizes and with regard to patients' clinical characteristics (*eg*, depression type, severity, *etc*), medication regimen (*eg*, different types and classes, monotherapy versus combination therapy), and outcome measurement methods (*eg*, remission versus response, different end time points, different rating scales, *etc*).[16-24] Therefore, the VA ORD may consider that a possible first step toward better understanding the genomics and pharmacogenomics of depressive disorders in Veterans may be to conduct new research to better examine the association between genetic polymorphisms, patient behavioral and environmental factors, and antidepressant effectiveness. This first step may be in the form of conducting an updated evidence review that emphasizes Veteran relevancy prior to or in addition to undertaking new primary research to evaluate the potential association between genes and variants and antidepressant medication benefits and harms. As genetics research remains a rapidly moving area, the Duke EPC's 2007 review may reasonably be considered out-of-date. Therefore, a first step may be to update that systematic review, particularly with respect to Veteran relevancy. If an update still finds a need for better evidence, then the ORD may consider undertaking new research to better examine the association between genetic polymorphisms, patient behavioral and environmental factors, and antidepressant effectiveness.

To address ORD's second and third goals, there are several important factors to consider[48] in designing new research to evaluate the clinical utility of pharmacogenomics-guided treatment: (1) selection of genetic variants, (2) format of pharmacogenomic results delivery, (3) education, (4) ethical, legal, and social considerations**,** and (5) patient populations and outcome assessment methods.

Selection of genetic variants: In terms of selecting an already available pharmacogenomic testing platform, among those that have published studies that compare pharmacogenomics-guided care to usual care, the CNSDose polygene panel of CYP450, UGT1A1, and ABC transporter variants has the most favorable preliminary findings across the most complete set of outcomes. But it is not yet commercially available. Therefore, it is reasonable to consider using existing MVP genotyping data to create a pharmacogenomics-guided treatment process. Selection of markers should be informed by the above-described new research on clinical *validity*[29] and/or those included in the CNSDose polygene panel.

Format of pharmacogenomic results delivery: Another consideration for facilitating accurate translation of pharmacogenomics into clinical practice is the format and complexity of results delivery.[25] The complexity in interpreting results of gene-panel tests may increase as the numbers of genes and gene variants increase, and there may be challenges in finding the appropriate balance between level of detail in results delivery and information overload for busy practitioners and patients.[57] We noted that available pharmacogenomic testing results varied in (1) how much detail was provided about gene result, categorization of gene-drug interaction, therapeutic implications, and clinical impact, (2) the format of the interpretive information (*eg*, length of report, computer-based or paper-based components, *etc*), (3) turn-around time (*eg*, at point of care, days, weeks), and (4) whether or not a consult with a professional genetic counselor and/or a pharmacist was available. To assist with interpretation and replication, methods used to predict phenotype (*eg*, poor metabolizer) from genotype, algorithms used to combine phenotype information across multiple variants to make drug selection and dosing recommendations, and which guidelines are used to inform dosing recommendations should be

clearly specified. To assess if and how such differences in format of pharmacogenomic testing results delivery may affect the accuracy of their interpretation and use, we suggest testing a few different approaches. Potentially, incorporation of the VA clinician and Veteran perspectives in identifying the competencies needed, who needs education and training and what the priorities are, and preferences on the format of results further improve user satisfaction and the reliability of use.

Education about pharmacogenomic testing: Studies have shown that despite patients' expectations of clinicians' competency in explaining, interpreting, and applying pharmacogenomic test results in clinical decision making,[68] a majority of previously surveyed clinicians acknowledged that they may be inadequately informed to do so.[69] Therefore, there is likely a need for ORD to identify available, and ideally validated, educational materials on the utilization and potential harms of pharmacogenomic data in clinical decision-making. To explore whether competency and clinical expertise (*eg*, primary care, psychiatry) may affect skill in utilizing pharmacogenomic data and potentially antidepressant treatment outcomes, we also recommend that the VA study include a broad range of clinicians.

Ethical, legal, and social considerations: The Genetic Information Nondiscrimination Act of 2008 (GINA)[70] and VHA privacy laws[71] were created to address fears about and prevent genetic discrimination by health insurers or employers. Uncertainty remains, however, about the actual impact of genetic nondiscrimination laws on medical practice, participation in genetic testing, and associated ethical, legal, and social considerations, and may warrant exploration.[72] For example, compared to well-established medical procedures, extra scrutiny has been recommended for identifying informed consent requirements unique to pharmacogenomic testing. Among the CDC's ACCE Model List of 44 targeted questions aimed at a comprehensive review of genetic testing, those related to ethical, legal, and social considerations include: "What is known about stigmatization, discrimination, privacy/confidentiality, and personal/family social issues?", "Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements?", and "What safeguards have been described and are these safeguards in place and effective?" [48]

Patient populations, treatment, and outcome assessment issues: None of the pharmacogenomic testing platforms evaluated have yet included in their dosing recommendation algorithms any other patient characteristics that may also alter antidepressant efficacy and safety.[26] To improve clinical relevance and validity of findings, future studies should better-characterize and account for a broader range of patient characteristics, including depression symptomatology (*eg*, melancholic, atypical, psychotic, postpartum, anxiety features), depression severity, and duration; antidepressant medication types and regimens; history of antidepressant treatment resistance; concomitant medication and/or other non-psychotropic depression treatments; medical and psychiatric comorbidities; polypharmacy; nonadherence; and other health or lifestyle behaviors. In addition to remission and response outcomes, to best assess the overall net benefit of pharmacogenomics-guided care, future studies should simultaneously evaluate a more complete set of key outcomes, including their impact on quality of life, functional capacity, time to antidepressant effectiveness in patients with MDD or number of failed antidepressant trials, harms of antidepressant medication, harms of use the testing, and cost-effectiveness, *and* demonstrate that the improvement on those key outcomes is due to a greater incidence in the guided group of actually implementing recommended medication changes to more genetically suitable regimens and patient adherence to those regimens.

To clarify whether there are particular subpopulations that are more or less likely to benefit from pharmacogenomics-guided care, the ORD study should also seek to evaluate whether the impact of using pharmacogenomics-guided treatment on the effectiveness and harms of antidepressants differs according to the following key patient characteristics: demographics, psychiatric and medical comorbidities, depression symptomatology (*eg*, melancholic, atypical, psychotic, postpartum, anxiety features), depression severity and duration, history of antidepressant treatment resistance, concomitant medication, polypharmacy, medication side effects, nonadherence or other health or lifestyle behaviors, congruency of recommended genetically-suitable medication with patient preference/expectations about antidepressant choice, level of patient acceptability of using pharmacogenomics information to guide treatment decisions, and clinician characteristics (*eg*, specialty, satisfaction, and confidence).

As the duration of follow-up in available studies was only 5-12 weeks, the ORD study should also seek to obtain longer-term follow-up of at least 6 months to a year. Longer-term follow-up would facilitate evaluation of maintenance of effects, relapse, and whether pharmacogenomics-guided care could reduce number of failed antidepressant trials.

REFERENCES

1. Singh AB. Improved Antidepressant Remission in Major Depression via a Pharmacokinetic Pathway Polygene Pharmacogenetic Report. *Clinical Psychopharmacology and Neuroscience.* 2015;13(2):150-156.

2. Breitenstein B, Scheuer S, Pfister H, et al. The clinical application of ABCB1 genotyping in antidepressant treatment: a pilot study. *CNS Spectr.* Apr 2014;19(2):165-175.

3. 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.* Nov 2013;16(89):219-227.

4. Altar CA, Carhart J, Allen JD, Hall-Flavin D, Winner J, Dechairo B. Clinical Utility of Combinatorial Pharmacogenomics-Guided Antidepressant Therapy: Evidence from Three Clinical Studies. *Molecular Neuropsychiatry.* 2015;1(3):145-155.

5. The White House. The Precision Medicine Initiative. 2016; https://www.whitehouse.gov/precision-medicine. Accessed March, 2016.

6. Kilbourne A, Przygodzki R. VA Precision Medicine: A Pharmacogenomic Approach to Individualized Treatment of Depression. In: VHA Office of Research and Development, ed2016.

7. World Health Organization. Depression. 2016; http://www.who.int/topics/depression/en/. Accessed March, 2016.

8. SAMSHA. Mental Disorders: Depressive Disorders (Including Major Depressive Disorder). 2016; http://www.samhsa.gov/disorders/mental. Accessed March, 2016.

9. Trivedi RB, Post EP, Sun H, et al. Prevalence, comorbidity, and prognosis of mental health among US veterans. *American journal of public health.* 2015;105(12):2564-2569.

10. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR* D: implications for clinical practice. *Am J Psychiatry.* 2006;163(1):28-40.

11. Rost K, Nutting P, Smith JL, Elliott CE, Dickinson M. Managing depression as a chronic disease: a randomised trial of ongoing treatment in primary care. *BMJ.* 2002;325(7370):934.

12. Rush AJ, Trivedi M, Carmody TJ, et al. One-year clinical outcomes of depressed public sector outpatients: a benchmark for subsequent studies. *Biol Psychiatry.* 2004;56(1):46-53.

13. Tansey KE, Guipponi M, Hu X, et al. Contribution of common genetic variants to antidepressant response. *Biol Psychiatry.* Apr 1 2013;73(7):679-682.

14. Sinyor M, Schaffer A, Levitt A. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial: A Review. *Can J Psychiatry.* 2010;55(3):126-135.

15. National Institutes of Health. National Human Genome Research Institute: Advancing human health through genomics research. 2016; https://www.genome.gov/. Accessed March, 2016.

16. Matchar DB, Thakur ME, Grossman I, et al. Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs). 2007.

17. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *Eur Neuropsychopharmacol.* 2012;22(4):239-258.

18. Perlis RH. Pharmacogenomic testing and personalized treatment of depression. *Clin Chem.* Jan 2014;60(1):53-59.

19. Singh AB, Bousman CA, Ng C, Berk M. Antidepressant pharmacogenetics. *Curr Opin Psychiatry.* Jan 2014;27(1):43-51.

20. Howland RH. Pharmacogenetic Testing in Psychiatry: Not (Quite) Ready for Primetime. *Journal of psychosocial nursing and mental health services.* 2014;52(11):13-16.

21. Miller DB, O'Callaghan JP. Personalized medicine in major depressive disorder -- opportunities and pitfalls. *Metabolism.* Jan 2013;62 Suppl 1:S34-39.

22. Niitsu T, Fabbri C, Bentini F, Serretti A. Pharmacogenetics in major depression: a comprehensive meta-analysis.[Erratum appears in Prog Neuropsychopharmacol Biol Psychiatry. 2013 Dec 2;47:118-9]. *Prog Neuropsychopharmacol Biol Psychiatry.* Aug 1 2013;45:183-194.

23. Horstmann S, Binder EB. Pharmacogenomics of antidepressant drugs. *Pharmacol Ther.* Oct 2009;124(1):57-73.

24. Serretti A, Kato M. The serotonin transporter gene and effectiveness of SSRIs. *Expert rev.* Jan 2008;8(1):111-120.

25. Drozda K, Müller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy.* 2014;34(2):166-184.

26. Bousman CA, Hopwood M. Commercial pharmacogenetic-based decision-support tools in psychiatry. *The Lancet Psychiatry.* 2016.

27. ECRI Institute. *Pharmacogenetic Testing to Guide Treatment of Behavioral and Mental Health Disorders* 2015.

28. Food and Drug Administration. Content and Format of a 510(k) Summary 2015.

29. Food and Drug Administration. *Draft Guidance for Industry, Food and Drug Administraitno Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* 2014.

30. Jones P. FDA regulation of LDTs - an update. *Medical Laboratory Observer* 2015.

31. Philippidis A. Drawing Battle LInes over Lab Tests. *Genetic Engineering & Biotechnology News* 2015.

32. American Association for Clinical Chemistry. *Position Statement: Oversight of Laboratory Developed Tests* 2014.

33. Mertz A. Duplicative and unnecessary regulation of LDTs will hamper diagnostic innovation. *Medical Laboratory Observer*2014.

34. Genomind. Sample Genecept Assay Results Report. 2016; https://genomind.com/sample-results-report/. Accessed March, 2016.

35. PharmGKB. Dosing Guidelines - Royal Dutch Association for the Advancement of Pharmacy. 2011; https://www.pharmgkb.org/view/dosing-guidelines.do?source=DPWG. Accessed March, 2016.

36. Hicks J, Swen J, Thorn C, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther.* 2013;93(5):402-408.

37. PharmGKB. Dosing Guidelines - Clinical Pharmacogenetics Implementation Consortium. 2015-2016; https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC. Accessed March, 2016.

38. Berg AO, Piper M, Armstrong K, et al. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. *Genetics in Medicine.* 2007;9(12):819-825.

39. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry.* 2011;44(6):195-235.

40. International Society of Psychiatric Genetics. Genetic Testing Statement: Genetic Testing and Psychiatric Disorders. 2014; http://ispg.net/genetic-testing-statement/. Accessed March, 2016.

41. Bauer M, Whybrow PC, Angst J, Versiani M, Möller H-J. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance treatment of major depressive disorder - update 2015. *The World Journal of Biological Psychiatry.* 2015;16:76-95.

42. National Institute for Health and Care Excellence. *Depression in adults: recognition and management* 2009.

43. American Psychiatric Association. *Practice guideline for the treatment of patients with major depressive disorder* 2010.

44. Department of Veterans Affairs and Department of Defense: The Management of MDD Working Group. VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder2016.

45. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller H-J. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. *The World Journal of Biological Psychiatry.* 2013;14(5):334-385.

46. ECRI Institute. *GeneSight Pyschotropic Pharmacogenomic Testing (Assurex Health, Inc.) for Guiding Medication Selection for Patients with Neuropsychiatric Disorders* 2015.

47. Jonas DE, Wilt TJ, Taylor BC, Wilkins TM, Matchar DB. Challenges in and principles for conducting systematic reviews of genetic tests used as predictive indicators. *Journal of general internal medicine.* 2012;27(1):83-93.

48. Centers for Disease Control and Prevention, National Office of Public Health Genomics. ACCE Model Process for Evaluating Genetic Tests. 2007; http://www.cdc.gov/genomics/gtesting/ACCE/index.htm. Accessed March, 2016.

49. Rector TS, Taylor BC, Wilt TJ. Systematic review of prognostic tests. *Journal of general internal medicine.* 2012;27(1):94-101.

50. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the drug effectiveness review project. *BMC medical research methodology.* 2012;12(1):1.

51. Viswanathan M, Ansari M, Berkman ND, et al. *Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions:Methods Guide for Comparative Effectiveness Reviews*. Rockville, MD2012.

52. Berkman ND, Lohr KN, Ansari M, et al. *Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville MD2013.

53. 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.* Oct 2013;23(10):535-548.

54. Hall-Flavin DK, Winner JG, Allen JD, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. *Transl Psychiatry.* 2012;2:e172.

55. Brennan FX, Gardner KR, Lombard J, et al. A Naturalistic Study of the Effectiveness of Pharmacogenetic Testing to Guide Treatment in Psychiatric Patients With Mood and Anxiety Disorders. *The primary care companion for CNS disorders.* 2015;17(2).

56. Müller DJ, Kekin I, Kao AC, Brandl EJ. Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: update and report from a pharmacogenetic service clinic. *Int Rev Psychiatry.* 2013;25(5):554-571.

57. Hornberger J, Li Q, Quinn B. Cost-effectiveness of combinatorial pharmacogenomic testing for treatment-resistant major depressive disorder patients. *The American journal of managed care.* 2015;21(6):e357-365.

58. Olgiati P, Bajo E, Bigelli M, De Ronchi D, Serretti A. Should pharmacogenetics be incorporated in major depression treatment? Economic evaluation in high- and middle-income European countries. *Prog Neuropsychopharmacol Biol Psychiatry.* Jan 10 2012;36(1):147-154.

59. Serretti A, Olgiati P, Bajo E, Bigelli M, De Ronchi D. A model to incorporate genetic testing (5-HTTLPR) in pharmacological treatment of major depressive disorders. *World J Biol Psychiatry.* Oct 2011;12(7):501-515.

60. Perlis RH, Patrick A, Smoller JW, Wang PS. When is pharmacogenetic testing for antidepressant response ready for the clinic? A cost-effectiveness analysis based on data from the STAR D study. *Neuropsychopharmacology.* Sep 2009;34(10):2227-2236.

61. Pyne J. Genetic Testing Decision Analysis Model for Antidepressant Treatment. 2009.

62. Fagerness J, Fonseca E, Hess GP, et al. Pharmacogenetic-guided psychiatric intervention associated with increased adherence and cost savings. *The American journal of managed care.* 2014;20(5):e146-156.

63. Winner JG, Carhart JM, Altar CA, et al. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. *Current medical research and opinion.* 2015.

64. Faulkner E, Annemans L, Garrison L, et al. Challenges in the Development and Reimbursement of Personalized Medicine—Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research: A Report of the ISPOR Personalized Medicine Special Interest Group. *Value Health.* 2012;15(8):1162-1171.

65. Fiore LD, Brophy MT, Turek S, et al. The VA Point-of-Care Precision Oncology Program: Balancing Access with Rapid Learning in Molecular Cancer Medicine. *Biomarkers in Cancer.* 2016;8:9-16.

66. Serretti A, Kato M, Kennedy JL. Pharmacogenetic studies in depression: a proposal for methodologic guidelines. *Pharmacogenomics J.* Apr 2008;8(2):90-100.

67. Chambers DA, Feero W, Khoury MJ. Convergence of implementation science, precision medicine, and the learning health care system: A new model for biomedical research. *Jama.* 2016;315(18):1941-1942.

68. Squassina A, Manchia M, Manolopoulos VG, et al. Realities and expectations of pharmacogenomics and personalized medicine: impact of translating genetic knowledge into clinical practice. *Pharmacogenomics.* 2010;11(8):1149-1167.

69. Prainsack B, Wolinsky H. Direct-to-consumer genome testing: opportunities for pharmacogenomics research? *Pharmacogenomics.* 2010;11(5):651-655.

70. Genetic Alliance, Genetics and Public Policy Center, National Coalition for Health Professional Education in Genetics. *GINA & You* 2010.

71. Department of Veterans Affairs, Veterans Health Administration. Notice of Privacy Practices 2013.

72. Feldman EA. The Genetic Information Nondiscrimination Act (GINA): Public Policy and Medical Practice in the Age of Personalized Medicine. *Journal of general internal medicine.* 2012;27(6):743-746.