Pharmacogenomic testing for selected conditions

Draft evidence report

October 20, 2016
Pharmacogenomic Testing for Selected Conditions

A Health Technology Assessment

Prepared for Washington State Healthcare Authority

DRAFT REPORT

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Acknowledgement

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List of Abbreviations:

CGI-S, Clinical Global Impression of Severity
CYP450, Cytochrome P450 family of metabolic enzymes
HAM-D, Hamilton Depression Rating Scale
PGx, pharmacogenomics or pharmacogenomic testing
PHQ-9, Patient Health Questionnaire
QIDS-C16, Quick Inventory of Depressive Symptomatology-Clinician Rated

Definitions:

Allele, one of a number of alternative forms of the same gene or same genetic locus; every person has 2 alleles of each gene

Analytic validity, the technical performance of the test i.e., how accurately, precisely, and robustly the test detects what it is intended to detect

Clinical validity, the strength of association that determines the test's ability to accurately and reliably identify or predict the disorder of interest

Clinical utility, the balance of benefits and harms when the test is used to influence patient management

Pharmacogenetics: The study of variability in drug response due to heredity, largely used in relation to genes determining drug metabolism

Pharmacogenomics: A broad-based term that encompasses all genes in the genome that may determine drug response; the distinction, however, is arbitrary and both pharmacogenetics and pharmacogenomics can be used interchangeably

Polymorphism, see Variant, a version of a gene that varies at a particular region in its base-pair DNA sequence
EVIDENCE SUMMARY

The EVIDENCE SUMMARY summarizes background information, the methods and search results for this report, findings with respect to the Key Questions, and payer policies and practice guidelines. The EVIDENCE SUMMARY also includes conclusions and an assessment of the quality of the evidence for each Key Question. In general, references are not cited in the EVIDENCE SUMMARY. The EVIDENCE SUMMARY ends with an Overall Summary and Discussion. The TECHNICAL REPORT provides additional detail, with full citation, regarding background information, study results, and payer policies and guidelines, but does not include conclusions or quality assessment.

Summary of Clinical Background

In 2014, there were an estimated 43.6 million (18.1%) adults in the United States with a mental illness in the previous year. This includes approximately 9.8 million (4.2%) adults with serious mental illness. Based on data from 2002, the National Institute of Mental Health (NIMH) estimates that the total direct and indirect costs of serious mental illness exceeds $300 billion per year. In 2010, neuropsychiatric disorders, which include mental and behavioral disorders, accounted for the largest proportion of health-related disability in the United States. In 2008, 13.4% of adults in the United States received treatment for a mental health problem. This includes all adults who received care in inpatient or outpatient settings and/or used prescription medication for mental or emotional problems. Therefore, the societal burden of mental and behavioral disorders is high. Pharmacotherapy is an important part of treatment but is considered effective for only 30% to 60% of patients (Pouget et al., 2014). Adverse events in small proportions of patients results in poor medication adherence. For many drugs, treatment selection is empirical and multiple failed trials occur before obtaining an acceptable response without any, or with tolerable, side effects. The following mental and behavioral illnesses are the focus of this report: depression, psychosis, anxiety, mood disorders, attention deficit/hyperactivity disorder (ADHD), and substance use disorder. Substance abuse will focus specifically on opioid and alcohol abuse.

- **Depressive disorders** include disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. In 2014, an estimated 10.2 million adults aged 18 years or older in the United States (4.3% of all adults) had at least one major depressive episode with severe impairment limiting the ability to carry out major life activities. Depression is usually treated with medications, psychotherapy, or a combination of these treatments. Patients who do not respond after 4 to 8 weeks of treatment, dose adjustment, and additional monitoring may be changed to an antidepressant from the same pharmacological class or to one from a different class.
• **Schizophrenia spectrum and other psychotic disorders** include schizophrenia, other psychotic disorders, and schizotypal (personality) disorder. Schizophrenia affects approximately 1% of the U.S. population and is ranked among the top 20 leading causes of global disability. Schizophrenia is typically treated with a combination of antipsychotic medication and psychosocial treatment. Most medications are only effective in 30% to 60% of patients, with 7% of patients experiencing a serious adverse event. Antipsychotic medication nonadherence in schizophrenia patients is prevalent.

• **Anxiety disorders** are characterized by excessive and persistent fear or worry that is difficult to control and substantially interferes with daily functioning. Anxiety disorders include: panic disorder, generalized anxiety disorder (GAD), phobias, and separation anxiety disorder. Anxiety disorders are the most common class of mental disorder in the United States, affecting approximately 40 million adults, or 18% of the population. Treatments for anxiety may involve a combination of both medication and counseling but only 34.3% of patients with an anxiety disorder receive minimally adequate healthcare treatment.

• **Bipolar disorder** is a chronic mood disorder that causes recurrent, dramatic shifts in mood, energy, and activity levels. There are 4 basic types, each defined by the pattern of episodes a patient commonly experiences. In the United States, the combined prevalence of bipolar I disorder, bipolar II disorder, and cyclothymic disorder for adolescents (ages 13 to 18) and adults are 11.2% and 2.6%, respectively. Bipolar disorder ranks among the top 20 leading causes of global disability and is associated with a high rate of suicide attempts. Bipolar disorder is typically treated with a combination of medication and psychotherapies, but 20% and 60% of patients with bipolar disorder are nonadherent to medication, leading to increased hospitalization.

• **Attention-deficit/hyperactivity disorder (ADHD)** is characterized by symptoms of inattention and/or hyperactivity with impulsivity that manifest as poor concentration, overall disorganization, propensity to not complete tasks or projects, poor school/work performance, and issues with time management and mood control. ADHD is one of the most common childhood-onset neurobehavioral, psychiatric disorders, affecting approximately 9% of children aged 13 to 18 years in the United States. For 60% to 85% of affected children, ADHD persists into adulthood. ADHD symptoms can negatively impact a person’s ability to function in more than one domain. Treatments include medication, psychotherapy, education or training, or a combination of treatments. Approximately 70% to 80% of children with ADHD respond to stimulant medications with improvement in at least some domains. Patients may need to try more than one medication or dose to find the treatment with the highest efficacy and fewest side effects.

• **Substance use disorders** involve excessive use of drugs that directly activate the brain’s reward system, which is involved in behavior reinforcement and memory production.
  – **Alcohol use disorder (AUD)** is characterized by an excessive use of alcohol that increases an individual’s risk of developing serious health problems associated with intoxication behaviors and withdrawal symptoms. In the United States, AUDs affect approximately 16.3
million adults and 679,000 adolescents (aged 12 to 17 years). Alcohol use increases the risk of acute injury and traffic-related injuries and deaths, as well as the risk for liver disease, cardiovascular disease, neurological deficits, several types of cancer, and psychiatric illnesses. A number of service components, including medication, are often used in combination as a multimodal approach for the treatment of substance use disorders. Several medications have shown efficacy in adults for the treatment of AUD, helping to maintain abstinence. Despite success, only 25% of people seek treatment for AUDs.

- **Opioid use disorder** (OUD) involves the excessive use of opioids, which increase a person’s risk for serious medical complications, including overdose. In 2014, an estimated 1.9 million people in the United States had an OUD involving prescription pain relievers and 568,000 people had an OUD involving heroin; opioid overdose deaths hit a record high, reaching 9.0 per 100,000 people. Several medications are used for the treatment of OUDs in order to reduce cravings and withdrawal symptoms. Limitations include the availability of treatment programs.

**Pharmacogenomics**

Pharmacogenomics aims to identify relationships between base sequence variants in genes that ultimately identify patients likely to respond to treatment or experience adverse events from specific medications. The products of such genes are most likely to be involved in drug uptake and metabolism (pharmacokinetics) or may have specific function at the target of drug action (pharmacodynamics). Sequence variants of these genes may result in products with altered function.

For example the CYP2D6 cytochrome P450 (CYP450) enzyme plays a role in the metabolism of 80% of antidepressant and antipsychotic drugs and the CYP2C19 CYP450 enzyme plays a role in the metabolism of certain antidepressants such as citalopram, escitalopram, amitriptyline, and sertraline. Variants in each of these genes may result in phenotypes of normal metabolizers (fully functional enzyme activity), poor metabolizers (little to no activity), intermediate metabolizers (decreased activity, between normal and poor), and rapid/ultrarapid metabolizers (increased enzyme activity) (Caudle et al., 2016). A patient who is a poor metabolizer treated with an antidepressant may have greater-than-expected drug exposure with more potential for side effects whereas an ultrarapid metabolizer given the same drug may experience insufficient exposure and poor response. Note that these predicted results apply to an active drug and would be opposite for a prodrug (a version of a drug that must first be metabolized into its pharmacologically active form).

The dopaminergic and serotonergic neurotransmitter systems are central to antipsychotic drug efficacy; therefore, much research has centered on the impact of genetic variants in the dopamine D2 receptor (*DRD2*), the dopamine D3 receptor (*DRD3*), the serotonin 1A receptor (*HTR1A*), and the serotonin 2A receptor (*HTR2A*) genes (Pouget et al., 2014), all examples of pharmacodynamic gene products. Variants in these genes, and many others, are hypothesized to alter response to and clinical efficacy of psychotropic drug treatment as well as likelihood of adverse effects.
In order to personalize individual patient prescribing and improve pharmacotherapy outcomes, a number of clinical pharmacogenomic laboratories are available, many of which offer testing services that purport to address a range of psychotropic drugs. The primary evidence supporting the development of these tests is evidence associating gene variants with treatment outcomes, which is just one aspect of the clinical validity of a test. Measures of association are often reported as odds ratios (OR), the value indicating the relative strength of association. ORs can also be converted to the standardized mean difference, or Cohen’s d, a common measure of effect size that can be compared across studies. For example, an OR of 2 equates to a Cohen’s d of approximately 0.2. At this value, 92% of the gene variant–positive and gene variant–negative groups are predicted to overlap, and the number needed to treat to have one more favorable outcome in the treatment group compared with control is predicted to be 16.5. Using general guidelines, a Cohen’s d of 0.2 is small, 0.5 is medium, and 0.8 is large, although these cutoff values are arbitrary and should not replace consideration of specific study details. Predictors of small effect size are likely to perform poorly as clinical laboratory tests. Where possible and biologic plausibility and/or statistical analysis suggests, several predictors of small effect size may be combined in test panels to generate larger effect sizes.

**Clinical Validity of Pharmacogenomic Testing for Pharmacotherapy of Selected Psychiatric Disorders**

The vast majority of the published literature supporting and promoting the uptake of clinical pharmacogenomic testing does not report on clinical utility data but rather reports associational or clinical validity data. Clinical validity data was not included as evidence in the systematic Literature Review section of this report. However, as important context to the key question of clinical utility, a search for high-level evidence of clinical validity of pharmacogenomic gene-outcome associations was conducted for inclusion in this background section and 38 systematic reviews were identified as pertinent to the indications of interest for this report. Of 38, 12 reported only descriptive results and 26 reported meta-analysis of association results where sufficient studies were available. In the latter case, this means that for each gene variant (or in some cases, all variants combined for a single gene) and a selected outcome, a meta-analysis across all published studies reporting that combination was reported. In addition, several inheritance models may be reported depending on what is and is not known about the variant. Across all meta-analysis publications, and considering only the indication of schizophrenia, many genes were examined for gene-outcome associations, highlighting the complexity in the biological models used to choose candidate genes for this psychiatric condition. Therefore, we elected to summarize genes that were reported in more than one publication, and for each gene-outcome association we selected only the model with the most significant OR, whether or not it was statistically significant. The selections cover a range of models and give an indication of a range of ORs that have been reported as relevant to the selected indication. A full description of the genes reported for the chosen example of schizophrenia can be found in [APPENDIX I](#).

For schizophrenia, the highest OR reported is for the *TNFa* gene and weight gain at a protective value of 0.23 (*P*=0.34). Inverted, this corresponds to an OR of 4.3 and a Cohen’s d of approximately 0.35. The highest statistically significant OR greater than 1 is 2.08 (*P*=0.008; Cohen’s d, 0.18), reported for CYP2D6.
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...and tardive dyskinesia. The highest statistically significant OR less than 1 is for the association of *MnSOD* Ala-9Val and tardive dyskinesia, OR equals 0.37 (\(P\)=0.009), inverted equals 2.7, Cohen’s d 0.24. Therefore, despite a large number of association studies and several meta-analyses combining results across studies, effect sizes for relevant gene-outcome associations tend to be relatively small. These results can be compared with an opposite extreme, those for genetic variants predicting high-risk adverse events. For example, in Han Chinese, presence of *HLA-B*¹⁵:02 predicts life-threatening Steven-Johnson syndrome at a highly statistically significant OR of 97.6, Cohen’s d 1.1.

No meta-analyses combined results for more than one gene for the same outcome to show improved effect size. Published examples describe the selection of a group of genes with the strongest effect sizes and briefly summarize algorithms that “prioritize and apply differential weight to potential clinical outcomes” in order to arrive at overall treatment recommendations. Commercial pharmacogenomic panels use patented or otherwise proprietary algorithms to synthesize the results from individual gene variants and arrive at treatment recommendations, see examples in the Literature Review of this report.

Additional confounders of gene-outcome association studies include variation in race/ethnicity, multiple metabolic and effector pathways that may influence outcomes, and concomitant medication and patient comorbidity interactions with psychotropic drugs. Study designs may lack corrections for multiple testing, large and representative populations, and may introduce additional confounders of clinical history when enrolling chronically treated instead of psychotropic drug-naïve patients.

Taken together, information regarding the clinical validity of pharmacogenomic testing for the indications of interest for this report is limited to associational evidence of small effect size for single genes/gene variants and selected outcomes, lacks information on how these gene variants are combined to make treatment recommendations, and may not take full account of common potential confounders of these relationships. For these reasons, a report focusing on the preponderance of available association studies would be limited in its usefulness and evidence regarding the use of pharmacogenomic testing to prospectively guide the selection of treatment drug or dosing, compared with treatment as usual, with measured impact on appropriate outcomes is of greater use and is the focus of the Literature Review section of this report.

**Analytic Validity of Pharmacogenomic Testing for Pharmacotherapy of Selected Psychiatric Disorders**

Analytic validity for laboratory tests refers to the technical performance of the test, how accurately, precisely, and robustly the test detects what it is intended to detect. For additional context, we searched for information on the analytic validity of pharmacogenomic tests used in the clinical validity studies outlined above and in those studies included in the Literature Review. One systematic review, published in 2010, assessed 46 studies that reported on the analytic validity of genotyping 11 different *CYP450* gene variants, almost half of which were related to *CYP2D6*. All studies reported concordance of 95% or more, regardless of the *CYP* gene tested or the methods used. Few studies reported on quality control or assay robustness. In most studies, both sensitivity and specificity were 100%. Testing for *CYP450* gene...
variants appears highly accurate but not all aspects of analytic validity have been reported. The current search found no analytic validity evidence for genotyping non-CYP450 genes or for commercially available gene panels.

**Policy Context**
A growing number of new laboratory tests and computer-based predictive algorithms are available to assess an individual patient’s potential metabolic response to various drugs. Potential benefits include better application of the drugs or chemotherapy choices that will work for a specific individual. Concerns relate to whether specific tests result in improved treatment decisions and health outcomes, as well as rapid emergence and uptake of pharmacogenomic tests generally. Concerns are considered low for safety of these tests, high for efficacy, and medium/high for cost-effectiveness.

**Summary of Review Objectives and Methods**

**Review Objectives**

**Population:** People any age who are being prescribed medications for treatment of depression, mood disorder, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), substance use disorder

**Interventions:** Clinical laboratory tests for genetic variants in targeted genes or in panels of genes to inform the selection or dose of psychotropic medications relevant to the conditions of interest

**Comparisons:** Usual care/no genetic testing

**Outcomes:** Patient Management: physician and patient decision-making regarding drug choice and/or dose; improved patient adherence to treatment regimen; clinically meaningful improvement in patient response to informed treatment and reduction in adverse events as a result of informed treatment;
Costs: cost-effectiveness or cost

**Key Questions**

1. Effectiveness: What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorders, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), or substance use disorder?
   a. Does genetic testing to inform the selection or dose of medications change the drug or dose selected by physicians and/or patients compared with usual care/no genetic testing?
   b. Do decisions about selection or dose of medications guided by genetic testing result in clinically meaningful improvement in patient response to treatment or reduction in adverse events as a result of treatment compared with decisions based on usual care/no genetic testing?
2. Harms: What direct harms are associated with conducting genetic testing when it is used to inform the selection or dose of medications?

3. Special populations: Compared with usual care/no genetic testing, do decision-making, patient outcomes, or harms following genetic testing to inform the selection or dose of medications vary by:
   a. Clinical history (e.g., prior treatments, whether the diagnosis is initial or recurrent, duration of diagnosis, severity of illness, or concurrent medications); or
   b. Patient characteristics (e.g., such as age, sex, or comorbidities)?

4. Costs: What are the costs and cost-effectiveness of genetic testing to guide the selection or dose of medications?

**Analytic Framework**

See TECHNICAL REPORT, Review Objectives and Analytic Framework.
Methods
See the Methods section of the TECHNICAL REPORT, APPENDIX II, and APPENDIX III for additional detail.

Search Strategy and Selection Criteria
Before conducting a search for primary data to answer the key questions of interest, core databases, PubMed, and the websites of relevant specialty societies were searched for systematic reviews, meta-analyses, economic evaluations, and practice guidelines published in the last 10 years. Systematic reviews were to be selected if they reviewed studies considered eligible for answering the Key Questions or if they provided useful background information. The PubMed (January 1, 2000 to August 15, 2016), OVID-Embase (1996 to 2016, week 33) and PsycINFO (1987 to July, week 4, 2016) databases were searched for primary studies and economic evaluations designed to answer the Key Questions.

Inclusion Criteria
- Population
  - People any age who are being prescribed medications for treatment of any of the conditions of interest
- Interventions
  - Clinical laboratory tests for genetic variants in targeted genes or in panels of genes to inform the selection or dose of psychotropic medications relevant to the conditions of interest
- Comparators
  - Usual care/no genetic testing
- Outcomes
  - Patient Management (KQ1)
    - Physician and patient decision-making regarding drug choice and/or dose
    - Improved patient adherence to treatment regimen
    - Clinically meaningful improvement in patient response to treatment and reduction in adverse events as a result of treatment
  - Costs (KQ2)
    - Cost
    - Cost-effectiveness

More detailed aspects of these criteria and the rationale for these criteria are presented in the METHODS section of the TECHNICAL REPORT.

Exclusion Criteria
- Population
– Patients being treated for any other condition for which pharmacogenomics testing may be considered

• Interventions
  – Non-DNA–based laboratory tests

• Comparators
  – Treatment decisions based on other stipulated patient characteristics in addition to clinical laboratory tests for genetic variants

• Outcomes
  – Outcomes other than those measuring treatment response, adverse events or related outcomes; cost outcomes not related to genetic testing

More detailed aspects of these criteria and the rationale for these criteria are presented in the METHODS section of the TECHNICAL REPORT.

Quality Assessment
The process used by Hayes for assessing the quality of primary studies and bodies of evidence is in alignment with the methods recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. Like the GRADE Working Group, Hayes uses the phrase quality of evidence to describe bodies of evidence in the same manner that other groups, such as the Agency for Healthcare Research and Quality (AHRQ), use the phrase strength of evidence. A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. See the Methods section of the TECHNICAL REPORT and APPENDIX III for details on quality assessment methods.

Summary of Search Results
Fourteen studies were selected for detailed analysis as evidence pertaining to the Key Questions. These include 4 studies addressing Key Question 1a (clinical utility, medical decision-making), 9 studies addressing Key Question 1b (clinical utility, patient outcomes), which were also assessed for Key Question 3 (subgroups), and 7 studies addressing Key Question 4 (economic outcomes). No unique studies were identified for Key Question 2 (harms of testing).

See APPENDIX IV for a list of the 19 studies that were excluded from analysis after full-text review.
Twelve practice guidelines, that had any language regarding pharmacogenomic testing and were published in the last 10 years, were identified. Several other guidelines, from prominent professional organizations, that had no such language are also listed.

**Findings**

Summary of Findings tables follow each Key Question. See EVIDENCE SUMMARY, Methods, Quality Assessment and the corresponding section in the TECHNICAL REPORT, as well as APPENDIX III, for further details regarding the assessment of bodies of evidence. See APPENDIX V for full evidence tables.

**Key Question #1: Effectiveness: What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorders, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), or substance use disorder?**

**a. Does genetic testing to inform the selection or dose of medications change the drug or dose selected by physicians and/or patients compared with usual care/no genetic testing?**

Four studies reported results of using pharmacogenomic genotyping to aid in clinical decision-making. All studies enrolled patients diagnosed with depressive disorder.

See Table 1 for a summary of findings.

Two prospective double-blind randomized controlled trials of fair quality, 1 prospective open-label cohort study of poor quality, and 1 retrospective comparative study of poor quality reported that pharmacogenomic test results, either single-gene or multiple-gene panels, consistently led medication treatment prescribers to change their treatment compared with treatment as usual. Sample sizes were small and some study populations were limited by race/ethnicity, which reduces the risk for confounding but limits generalizability of the results. Outcomes were measured differently across studies, so the amount of change and precision of the result is unknown. The overall quality of the body of evidence to answer Key Question 1a was considered to be of low quality. The limited results regarding clinical decision-making suggest that pharmacogenomic test results, whether derived from single-gene tests or interpretive panels, may change prescribing patterns in favor of pharmacogenomic recommendations compared with treatment as usual. Evidence that pharmacogenomic testing informs the selection and/or dose of medications is an intermediate outcome of clinical utility and does not in itself demonstrate improved patient outcomes. This is addressed in **Key Question 1b.**

**Table 1. Impact of Pharmacogenomic Testing on Clinical Decision-Making**

**Key:** Ctl, control group for which genotyping results were available to the prescribing physician at the end of the treatment period or not available at all, depending on study design; Exp, experimental or genotyped treatment group for which results were immediately available to prescribing physicians; PGx, pharmacogenomic; PICO, population, intervention, comparator, outcome; RCT, randomized controlled trial
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### Number, Size, and Quality of Studies

<table>
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<td>Winner 2013 (RCT, fair)</td>
</tr>
<tr>
<td>Hall-Flavin 2012 (controlled trial, fair)</td>
</tr>
<tr>
<td>Breitenstein 2014 (comparative, poor)</td>
</tr>
</tbody>
</table>

**Outcome: Remission**

Four studies reported on remission from a depressive disorder, comparing patients whose prescribing physicians had access to pharmacogenomic information to control patients treated as usual. These were 2 randomized controlled trials (RCT) of fair quality, 1 (non-randomized) prospective controlled trial of

---

**Key Question #1: Effectiveness: What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorders, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), or substance use disorder?**

**b. Do decisions about selection or dose of medications guided by genetic testing result in clinically meaningful improvement in patient response to treatment or reduction in adverse events as a result of treatment compared with decisions based on usual care/no genetic testing?**

Nine studies reported results of using pharmacogenomic genotyping and subsequent effects on patient outcomes. Six studies enrolled patients with depressive disorders, 2 enrolled patients with any psychiatric disorder, and 1 enrolled patients with alcohol use disorder. Outcomes reported were remission, response to treatment, outcomes related to adverse effects (adherence, tolerance, adverse events) and hospital stay/healthcare utilization.

See Table 2 for a summary of findings.

---

**Pharmacogenomic Studies of Treatment of Depressive Disorders**

**Outcome: Remission**

Singh 2015 (Exp n=74)

- Treatment prescribers indicated that in 65% of cases, a PGx panel interpretive report led to medication dosing different from their usual practice.

Winner 2013 (Exp n=26 vs Ctl n=25; all genotyped, see Key)

- 100% of baseline medications that a PGx panel interpretive report indicated should be used with caution and frequent monitoring were changed in the Exp group; 50% of similarly classified medications were changed/dose adjusted in Ctls.

Hall-Flavin 2012 (Exp n=25 vs Ctl n=26; all genotyped, see Key)

- At 8 wks, 5.9% of Exp cases were prescribed a medication designated “use with caution” on PGx panel interpretive report vs 21.4% of controls (P=0.02).

Breitenstein 2014 (Exp n=58)

- By 5 wks, prescribers increased dose of appropriate antidepressants 1.63-fold for genotyped pts (Exp) with an unfavorable ABCB1 genotype (P=0.012) and changed antidepressant prescribed more often (P=0.011) compared with other genotypes.
fair quality, and 1 retrospective comparative study of poor quality. Follow-up times were reasonable for all studies. All studies used generally accepted definitions of minimal clinically important differences (MCID) for outcomes reported, although 1 study may fall short of validated definitions.

Results suggest improved remission rates as a result of genotyping but there were several limitations to the body of evidence. The results of the comparative study may lack clinical relevance due to the MCID used. The prospective controlled trial had a high risk for bias due to high losses to follow-up (27%) and reliance on data imputation for statistical significance for 2 of 3 depression scores, reducing our confidence that the groups were comparable. One RCT was underpowered to discriminate between groups. The other RCT reports the most statistically significant results for the outcome of remission using a commercial pharmacogenomic panel test that is not currently available in the United States. In summary, despite consistency of results favoring improved remission rates as a result of genotyping, the quality of the evidence is low and our confidence that the results represent a true effect is therefore also low. Notably, because the methods used to generate interpretations of the individual genetic variant results and the methods used to derive overall clinical recommendations for drug selection and dose are not known, the clinical utility performance of one specific panel test is not generalizable to that of any other pharmacogenomic test.

**Outcome: Response to Treatment**

Four studies reported on response to treatment of depressive disorders. These were 2 RCTs of fair quality, 1 prospective controlled trial of fair quality, and 1 comparative study of very poor quality.

Response to treatment of depression is typically measured as a reduction in score of 50% or more for well-validated instruments. Overall, the results for response to treatment, comparing pharmacogenomic testing–informed prescribing with treatment as usual, lack consistency, are limited in some cases by lack of acceptable measures of response, or were underpowered. The overall quality of the evidence is low. Best results are reported by a fair-quality prospective controlled trial that used 3 such measures of response and showed that patients whose prescribing physicians had access to results from a U.S.-based pharmacogenomic genotyping panel were statistically significantly more likely to respond than control patients who were prescribed treatment as usual for 8 weeks. These results were obtained both for remaining patients after 27% loss to follow-up and for imputed data, except for one imputed instrument score. As already noted, pharmacogenomic panel test results are not generalizable to other pharmacogenomic tests, as the methods used to generate interpretations of the individual genetic variant results are not known.

The same U.S.-based assay was used in a second fair-quality prospective controlled trial and obtained statistically significant reductions in depression severity scores, but did not use a criterion to define response, rendering results less clinically interpretable. Power analyses assumed only 20% to 25% reductions in scores. A poor-quality retrospective comparative study also did not use usual criteria for defining response to treatment; did not define the clinical relevance of measures used to compare response; and in most comparisons, did not obtain statistically significant results. The RCT was
underpowered and results favoring improved response of genotyped patients were not statistically significant.

Outcome: Adherence, Tolerance, Adverse Events; Hospital Stay

One fair-quality RCT reported on tolerance of medications, finding that non-genotyped control patients were less tolerant of medications, statistically significantly more often requiring dose reduction or cessation. In addition, genotyped patients took sick leave less often, and took leave times of shorter duration when needed, compared with non-genotyped patients.

In a poor-quality retrospective comparative study, patients who were prescribed dose increases for genotype-appropriate antidepressants had statistically significantly shorter hospital stays, which were reduced by an average of 4.7 weeks if the antidepressant dose was increased by more than 1.5-fold.

While favoring pharmacogenomic genotyping, the evidence supporting pharmacogenomic impact on outcomes related to adverse events and to duration of hospital stay is of very low quality, limited to 1 trial each and, as such, is insufficient for conclusions.

Pharmacogenomic Studies of Treatment of Any Psychiatric Disorder

Two retrospective comparative studies of poor quality (overall, very-low-quality body of evidence) enrolled patients diagnosed with any psychiatric disorder. In both studies, one group was selected because attending physicians had ordered pharmacogenomic testing. Similar control groups were selected from the same source of patients. One study used propensity score matching to choose an equivalent control group.

One study, using a large commercial pharmacogenomic assay panel developed in Spain and not available in the U.S., reported global severity scores statistically significantly lower than baseline when pharmacogenomic testing results informed treatment compared with treatment as usual. The other study used a U.S.-based panel assay to provide interpretations to prescribing physicians compared with treatment as usual, and reported a statistically significant average increase in drug treatment adherence with pharmacogenomic testing.

Pharmacogenomic Studies of Treatment of Alcohol Use Disorder

One fair-quality prospective observational study of patients with alcohol use disorder and treated in an RCT with naltrexone versus placebo was stratified by OPRM1 gene variants asp40 (predicted to improve naltrexone response) and asn40. While results were not statistically significant, their direction was opposite to that expected in that the naltrexone-asp40 group was more likely to drink heavily. Therefore, very-low-quality evidence from 1 fair-quality study is insufficient evidence to draw conclusions.
Overall Summary of Key Question #1 Evidence

Only 9 studies were included for Key Question #1 and these do not address all the indications of interest for this report. In some cases, populations were limited by race and ethnicity, which reduces potential genotype confounders, but also reduces generalizability of results. Four studies were rated fair quality, 4 poor quality, and 1 very poor quality. Only the fair-quality studies were prospectively designed. Of these, 1 RCT was seriously underpowered, as evidenced by a power analysis, which concluded that 92 to 115 patients were needed in each trial arm whereas 25 and 26 were enrolled. Therefore, all results had no statistical significance. One reasonably well-designed RCT, with statistically significant treatment response and remission results supporting pharmacogenomic testing for patients with major depressive disorder, used a commercial interpretive panel assay that is not available in the United States. As noted, pharmacogenomic panel tests are not generalizable to other pharmacogenomic tests, as the methods used to generate clinical interpretations and treatment recommendations from the individual genetic variant results are not known.

Two prospective controlled (nonrandomized) trials conducted using the same U.S.-based commercial interpretive pharmacogenomic panel both reported statistically significant remission and/or response to treatment results. Only one of these appropriately defined clinical measures of remission and response but lacked some consistency of results between those calculated from the remaining patients (27% lost to follow-up) and those calculated using imputed data. Among poor-quality studies, all were retrospective and some did not define the clinical relevance of treatment response measures. For the 2 studies that enrolled patients with any psychiatric disorder and the pharmacogenomic assays used in these studies, patient numbers were too few, study quality poor, and results too sparse for conclusions regarding the impact of pharmacogenomic testing on treatment response or adverse event-related outcomes. The authors of the single study on pharmacogenomic variant testing to improve response to naltrexone for alcohol use disorder concluded that the variant in question likely did not moderate the response.

In summary, the evidence base for pharmacogenomic testing for the psychiatric disorders of interest for this report is extremely limited and compromised and considered to be of low to very low quality, depending on the outcome measured. As such, the evidence is insufficient for conclusions regarding clinical use.

Table 2. Impact of Pharmacogenomic Testing on Patient Outcomes

Key: asp40 and asn40, genetic variants of the OPRM1 gene; CGI-S, Clinical Global Impression of Severity; Ctl, control group for which genotyping results were available at the end of the treatment period or not available at all, depending on study design; Exp, experimental or genotyped treatment group for which results were immediately available to prescribing physicians; HAM-D, Hamilton Depression Rating Scale (21 items unless otherwise specified); PGx, pharmacogenomic; PHQ-9, Patient Health Questionnaire (9 items); PICO, population, intervention, comparator, outcome; pt(s), patient(s); QIDS-C16, Quick Inventory of Depressive Symptomatology-Clinician Rated (16 items); RCT, randomized controlled trial
<table>
<thead>
<tr>
<th>Number, Size, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results (statistically significant results bolded)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ #1b. Impact of pharmacogenomic testing on patient outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KQ #1b. Outcome: Remission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 studies</td>
<td>OVERALL: LOW</td>
<td></td>
<td>Winner 2013 (Exp n=26 vs Ctl n=25, see Key)</td>
</tr>
<tr>
<td>Exp n=272 Ctl n=270</td>
<td>Study quality: Poor-Fair</td>
<td>• At 10 wks 20% of Exp pts vs 8.3% of Ctl pts achieved remission (Ham-D17 &lt;7) (OR=2.75; 95% CI, 0.48-15.8; P=NS).</td>
<td></td>
</tr>
<tr>
<td><strong>Depressive disorders</strong></td>
<td>Quantity and precision: Few studies, small sample sizes, studies do not address all indications of interest, some pt populations limited by race/ethnicity; precision unknown</td>
<td></td>
<td>Singh 2015 (Exp n=74 vs Ctl n=74, see Key)</td>
</tr>
<tr>
<td>Winner 2013 (RCT, fair)</td>
<td>Consistency: Remission outcomes range from highly statistically significant to not significant, may be related to study size; not all measured similarly</td>
<td>• At 12 wks, Exp pts more often obtained remission (HAM-D17 &lt;7) (OR=2.52; 95% CI, 1.71-3.73; P&lt;0.0001). Number needed to test for remission=3 (95% CI, 1.7-3.5).</td>
<td></td>
</tr>
<tr>
<td>Singh 2015 (RCT, fair)</td>
<td>Applicability to PICO: ✓</td>
<td></td>
<td>Hall-Flavin 2013 (Exp n=114 vs Ctl n=113, see Key)</td>
</tr>
<tr>
<td>Hall-Flavin 2013 (controlled trial, fair)</td>
<td>Reference standard: ✓</td>
<td>• At 8 wks, more Exp pts obtained remission (QIDS-C16&lt;6) compared with Ctl pts (OR=2.42; 95% CI, 1.09-5.39; P=0.03).</td>
<td></td>
</tr>
<tr>
<td>Breitenstein 2014 (comparative, poor)</td>
<td>Publication bias: Unknown</td>
<td>• HAM-D17 and PHQ-9 results were not significantly different except for results using data imputation to account for 27% lost to follow-up.</td>
<td></td>
</tr>
<tr>
<td>6 studies</td>
<td>OVERALL: LOW</td>
<td></td>
<td>Breitenstein 2014 (Exp n=58 vs Ctl n=58, see Key)</td>
</tr>
<tr>
<td>Exp n=365 Ctl n=413</td>
<td>Study quality: Very poor-Fair</td>
<td>• Exp pts more often in remission (HAM-D &lt;10) at treatment wk 4 compared with Ctl pts (83.6% vs 62.1%; P=0.005). HAM-D at admission &gt;14. Required change in score may not be clinically relevant.</td>
<td></td>
</tr>
<tr>
<td><strong>Depressive disorders</strong></td>
<td>Quantity and precision: Studies limited in quantity and size, studies do not address all indications of interest, some pt populations limited by race/ethnicity; precision unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winner 2013 (RCT, fair)</td>
<td>Consistency: Response outcomes range from highly statistically significant to not significant; not all measured similarly; studies may not define clinically significant response; better study designs tend to obtain statistically significant results, depending on size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hall-Flavin 2013 (controlled trial, fair)</td>
<td>Applicability to PICO: ✓</td>
<td>Results are in the direction of improved response for genotyped patients. Only 1 study used defined measures of response and obtained statistically significant results.</td>
<td></td>
</tr>
<tr>
<td>Hall-Flavin 2012 (Exp n=25 vs Ctl n=26; all genotyped, see Key)</td>
<td>Reference standard: ✓</td>
<td>In the naltrexone trial for alcohol use, results were opposite those of prior studies, although not statistically significant.</td>
<td></td>
</tr>
<tr>
<td>Rundell 2011 (Exp n=29 vs Ctl n=17, see Key)</td>
<td>Publication bias: Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oslin 2015</td>
<td></td>
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</tbody>
</table>

**Pharmacogenomic testing for selected conditions: Draft report**

**Page 15**
### KQ #1b. Outcome: Adherence, tolerance, adverse events

<table>
<thead>
<tr>
<th>Number, Size, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results (statistically significant results bolded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(observational within RCT, fair)</td>
<td>Applicability to PICO: ✓  Reference standard: ✓  Publication bias: Unknown</td>
<td></td>
<td>• 5-HTTLPR categories: L/L genotype pts had greater PHQ-9 score improvement than other genotypes at times 4 and 5 (P=0.02 to P=0.05).  • Adjusted post-day 14 PHQ-9 scale slopes and differences in pre- to post-baseline scale slopes were not significantly different among genotype categories.</td>
</tr>
</tbody>
</table>

**Espadaler 2016 (Exp n=89 vs Ctl n=93, see Key)**

- At 3 months, 93% (Exp) vs 82% (Ctl) had CGI-S scores lower than baseline (adjusted OR=3.86; 95% CI, 1.36-10.95; P=0.011).

**Oslin 2015 (Exp n=38 naltrexone + 44 placebo, all asp40 see Key)**

(Ctl n=73 naltrexone + 66 placebo, all asn40 see Key)

- Exp (asp40, favorable genotype) pts: OR for heavy drinking in the naltrexone group was 1.10 (95% CI, 0.52-2.31; P=0.80) compared with placebo.
- Ctl (asn40, unfavorable genotype) pts: OR for heavy drinking in the naltrexone group was 0.69 (95% CI, 0.41-1.18; P=0.17) compared with placebo.

**Singh 2015 (Exp n=74 vs Ctl n=74, see Key)**

- Ctl pts were less able to tolerate medications, requiring dose reduction or cessation (OR=1.13; 95% CI, 1.01-1.25; P=0.0272).
- Exp pts took sick leave less often (4% vs 15%; P=0.0272) and of less duration when needed (4.3 vs 7.7 days; P=0.014).

**Espadaler 2016 (Exp n=89 vs Ctl n=93, see Key)**

- Equal numbers of adverse events were reported in each group.

**Fagerness 2014 (Exp n=111 vs Ctl n=222, see Key)**

- Exp pts showed an average increase in drug treatment adherence of 6.3% compared with 0.3% in Ctl pts (P=0.0016).

**Oslin 2015 (Exp n=38 naltrexone + 44 placebo, all asp40 see Key)**

(Ctl n=73 naltrexone + 66 placebo, all asn40 see Key)

Adherence (at least 80% of 12 wks of treatment days):
- asn40: naltrexone, 72.6%; placebo, 66.7%
- asp40: naltrexone, 50.0%; placebo, 79.6%

Serious and severe adverse events were infrequent and unrelated to group assignment.

### KQ #1b. Outcome: Hospital stay/Healthcare utilization

<table>
<thead>
<tr>
<th>Number, Size, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(observational within RCT, fair)</td>
<td>Applicability to PICO: ✓  Reference standard: ✓  Publication bias: Unknown</td>
<td></td>
<td>Breitenstein 2014 (Exp n=58 vs Ctl n=58, see Key)</td>
</tr>
<tr>
<td>1 study</td>
<td></td>
<td>Results indicate PGx</td>
<td>• Dose increases in genotype-appropriate antidepressants</td>
</tr>
</tbody>
</table>

**Breitenstein 2014 (Exp n=58 vs Ctl n=58, see Key)**

- Dose increases in genotype-appropriate antidepressants.
### Number, Size, and Quality of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results (statistically significant results bolded)</th>
</tr>
</thead>
</table>
| Ctl n=58  
**Depressive disorders**  
Breitenstein 2014  
(comparative, poor) | **Quantity and precision:** Only 1 small study of pts with depressive disorders in 1 European country  
**Consistency:** Cannot be addressed  
**Applicability to PICO:** ✓  
**Reference standard:** ✓  
**Publication bias:** Unknown | for ABCB1 variants may result in better anti-depressant dosing and shorter hospital stays; not generalizable | were associated with shorter hospital stays (P=0.009). Hospital stay for pts with unfavorable ABCB1 genotype was reduced by 4.7 wks if dose was increased more than 1.5-fold. |

### Key Question #2: What direct harms are associated with conducting genetic testing when it is used to inform the selection or dose of medications?

No studies were found that address the direct harms of pharmacogenomic testing. DNA may be collected from a whole blood sample, which involves an invasive procedure, or for some tests it may be collected from a cheek swab or from saliva, which is noninvasive.

### Key Question #3: Compared with usual care/no genetic testing, do decision-making, patient outcomes, or harms following genetic testing to inform the selection or dose of medications vary by:

- **a. Clinical history** (e.g., prior treatments, whether the diagnosis is initial or recurrent, duration of diagnosis, severity of illness, or concurrent medications); or
- **b. Patient characteristics** (e.g., such as age, sex, or comorbidities)?

All included studies were reviewed for presentation of results by clinical history or patient characteristic parameters. Only 1 study investigated predictors of the response to medications among pharmacogenomic tested versus untested patients, the remaining 8 of 9 studies attempted, by study design, to construct similar experimental (treatment informed by pharmacogenomic testing) and control (treatment as usual) study arms according to a variety of clinical history and patient characteristic parameters. Testing for differences among these parameters at baseline found few statistically significant differences with one exception. One very-poor-quality comparative study that retrospectively selected patient groups based on whether they did (experimental) or did not (control) have pharmacogenomic testing ordered found that tested patients had greater degrees of psychiatric predisposition and depression severity at baseline.

One poor-quality, retrospective comparative study, compared pharmacogenomically tested versus untested groups using multivariate logistic regression and found that neither clinical history variables nor patient characteristic variables were statistically significant predictors of the response to medication as measured by a depression severity scale. No other studies adjusted for or reported results of
subgroups analyses according to clinical history or patient characteristic variables. Taken together, the evidence is insufficient for forming conclusions.

**Key Question #4: What are the costs and cost-effectiveness of genetic testing to guide the selection or dose of medications?**

The literature search identified 7 economic assessments that compared the cost of pharmacogenomic testing versus usual care for psychiatric conditions. The results of 3 cost-comparison studies suggest that employment of pharmacogenomic testing is associated with reduced total costs for healthcare. Medication costs in tested patients were greater than non-tested patients in 1 study and less in another study. Two studies reported that medication adherence was higher in patients who were tested versus those who were not tested. Of the 2 cost-effectiveness studies, 1 reported that pharmacogenomics testing was not cost-effective and the other found that it was moderately cost-effective. One additional study found that patients were willing to pay for pharmacogenomic testing if it reduced the number of medication trials or the amount of time for correct dosing to be achieved. The studies are summarized in the following paragraphs.

See Table 3 for a summary of findings.

The economic evidence base includes studies of different designs and study populations each incorporating different pharmacogenomic tests that were compared with no-test treatment regimens. Results in some cases suggested cost-effectiveness but lacked consistency overall. There were indications that results may depend at least partly on test cost and on the effect size of the clinical validity evidence supporting the pharmacogenomic test. In a survey of non-patients, the utility of testing increases with decreases in the number of changes in medications or reduced times for dosage adjustments.

**Table 3. Cost-Effectiveness of Pharmacogenomic Testing**

<table>
<thead>
<tr>
<th>Number and Type of Studies</th>
<th>Limitations</th>
<th>Direction of Findings</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-comparison studies</td>
<td>Results are not comparable across studies. Each used different types of sources, enrolled pts with different indications, and used different measures for cost comparison.</td>
<td>Results of 3 of 4 cost-comparison studies suggest that employment of PGx testing is associated with reduced total costs for healthcare; however, results in 1 study suggested that significant cost</td>
<td><strong>Winner 2015</strong>, GeneSight PGx test panel (n=1662) vs propensity-matched Ctl (n=10,880): Avg med cost ↑ $690 PGx vs $1725 Ctl; P&lt;0.0001 Med adherence rate +0.11 PGx vs -0.01 Ctl; P&lt;0.0001 Meds congruent with PGx test results had net annual cost savings of $2775 vs incongruent meds; P&lt;0.0001</td>
</tr>
<tr>
<td>4 studies Exp n=1921 Ctl n=11253</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winner 2015 (Pharmacy benefits provider database; mixed psychiatric diagnoses) Fagerness 2014</td>
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<td></td>
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</table>

Pharmacogenomic testing for selected conditions: Draft report
<table>
<thead>
<tr>
<th>Number and Type of Studies</th>
<th>Limitations</th>
<th>Direction of Findings</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Medical and pharmacy claims database; mixed psychiatric diagnoses)</td>
<td>benefits of PGx testing may be limited to extreme metabolizers (poor or ultrarapid).</td>
<td></td>
<td>Fagerness 2014, Geneceopt Assay PGx test panel (n=111) vs propensity-matched controls (n=222): Avg med cost ↑ $886 PGx vs $222 Ctl; P&lt;0.108 Med adherence 6.3% PGx vs 0.3% Ctl; P&lt;0.001 Outpatient visits ↓ by 1.2 (PGx) and 0.1 (Ctl) visits Total costs increased by 5.9% (PGx) and 15.4% (Ctl) Relative cost savings for PGs $562 (9.5%)</td>
</tr>
<tr>
<td>Herbild 2013 (Danish pt registers; schizophrenia)</td>
<td></td>
<td></td>
<td>Herbild 2013, CYP2D6 and CYP2C19 PGx test (n=103) vs standard care controls (n=104), total healthcare costs, currency reference yr 2010: Mean total costs/yr USD*18.4k PGx vs $21.6k Ctl, very wide CIs, both estimates affected by high outliers. Mean med costs/yr USD3052 PGx vs $3170 Ctl. Modeling suggests PGx testing significantly reduced costs for extreme metabolizers.</td>
</tr>
<tr>
<td>Rundell 2011 (Mayo Clinic database; depression)</td>
<td></td>
<td></td>
<td>Rundell 2011, PGx testing (≤1 of CYP2D6, CYP2C19, CYP2C9, 5-HTTLPR; n=45) vs standard care controls (n=47), total healthcare costs, currency reference yr 2010: Mean total costs $5010 PGx vs $6693 Ctl; P=0.08. After adjusting for all patient variables; P&gt;0.07.</td>
</tr>
</tbody>
</table>

**Cost-effectiveness studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Findings</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 modeling studies</td>
<td>Both studies modeled pt cohorts from the STAR*D study results but incorporated PGx tests for different genes and presented different result measures making comparison of results difficult; in 1 study, cost-effectiveness outcomes depended on the effect size of the underlying test clinical validity; in the other study, the authors consider whether the incremental benefit in QALWs offsets the incremental increase in cost of PGx testing.</td>
<td>One study found PGx testing not to be cost-effective; 1 modeling study of a hypothetical pt cohort estimated an increased overall cost of healthcare with PGx vs Ctl for an incremental benefit in QALW.</td>
<td>Fagerness 2014, Geneceopt Assay PGx test panel (n=111) vs propensity-matched controls (n=222): Avg med cost ↑ $886 PGx vs $222 Ctl; P&lt;0.108 Med adherence 6.3% PGx vs 0.3% Ctl; P&lt;0.001 Outpatient visits ↓ by 1.2 (PGx) and 0.1 (Ctl) visits Total costs increased by 5.9% (PGx) and 15.4% (Ctl) Relative cost savings for PGs $562 (9.5%)</td>
</tr>
<tr>
<td>Perlis 2009 (Patient data based on STAR*D study)</td>
<td></td>
<td></td>
<td>Herbild 2013, CYP2D6 and CYP2C19 PGx test (n=103) vs standard care controls (n=104), total healthcare costs, currency reference yr 2010: Mean total costs/yr USD*18.4k PGx vs $21.6k Ctl, very wide CIs, both estimates affected by high outliers. Mean med costs/yr USD3052 PGx vs $3170 Ctl. Modeling suggests PGx testing significantly reduced costs for extreme metabolizers.</td>
</tr>
<tr>
<td>Oligiati 2012 (Hypothetical cohort of Caucasian adults modeled from the STAR*D study)</td>
<td></td>
<td></td>
<td>Rundell 2011, PGx testing (≤1 of CYP2D6, CYP2C19, CYP2C9, 5-HTTLPR; n=45) vs standard care controls (n=47), total healthcare costs, currency reference yr 2010: Mean total costs $5010 PGx vs $6693 Ctl; P=0.08. After adjusting for all patient variables; P&gt;0.07.</td>
</tr>
</tbody>
</table>

**Cost-utility studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Findings</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study</td>
<td>Questionnaire based upon expert opinion, literature review, and focus group interviews; focus group members were not psychiatric</td>
<td>Utility increases with decreases in the number of changes in meds or ↓ times for dosage adjustments.</td>
<td>Perlis 2009, HTR2A PGx testing either before first-line tx (Test 1st) or after first-line tx failure (Test 2nd) vs no testing (Ctl), direct costs: Test 1st + bupropion tx for test-negative pts ↑ cost by $505/pt but provided 0.0054 QALY for ICER of $93,520/QALY; therefore, not cost-effective.</td>
</tr>
<tr>
<td>Herbild 2009 (Web-based)</td>
<td></td>
<td></td>
<td>Oligiati 2012, 5-HTTLPR PGx testing vs none in high income W European countries, direct costs: Incremental benefit of PGx 0.062 QALWs for clinical response plus 0.016 QALWs for side effect burden. Overall incremental benefit of PGx 0.156 QALWs. Estimated overall cost of healthcare Intl.$2242 (PGx) vs Intl.$2063 (Ctl). Incremental cost of PGx testing was Intl.$179 and the ICER was Intl.$1147.</td>
</tr>
<tr>
<td>Number and Type of Studies</td>
<td>Limitations</td>
<td>Direction of Findings</td>
<td>Study Results</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>discrete choice questionnaire administered to Danes</td>
<td>pts.</td>
<td></td>
<td>test cost in Denmark.</td>
</tr>
</tbody>
</table>

*Costs were converted from the value of the Danish krone in 2010 to USD 2016.

**Practice Guidelines**

The search of the core sources and relevant specialty groups identified 12 guidelines that mention pharmacogenomic testing published within the past 10 years. The general recommendations provided by the guidelines are summarized in Table 4. Additional details, by guideline, are presented in APPENDIX VIa.

Most guidelines make no formal recommendations for use of pharmacogenomic testing. Those that mention pharmacogenomic testing indicate a need for future research to help determine the optimal choice of pharmacotherapy based on the gene or genes involved in the etiology of treatment responsiveness. Pharmacogenomic testing may help guide identification of particular patient populations that will benefit from specific therapeutic options. In addition, some guidelines suggest that pharmacogenomic testing in combination with therapeutic drug monitoring may be beneficial in certain circumstances.

The goal of the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health’s Pharmacogenomics Research Network and the Pharmacogenomics Knowledge Base is to provide peer-reviewed, evidence-based, accessible guidelines for gene-drug associations in order to facilitate the translation of pharmacogenomic knowledge from bench to bedside. CPIC guidelines include dosing recommendations for tricyclic antidepressants and selective serotonin reuptake inhibitors based on CYP2D6 and CYP2D6 gene phenotypes (e.g., ultrarapid metabolizer, extensive metabolizer, intermediate metabolizer, or poor metabolizer). However, these guidelines state that recommendations are based on clinical validity evidence, most of which relies on drug plasma concentration outcomes and includes case reports and pharmacokinetic studies of healthy individuals. No evidence is presented linking plasma concentration to clinical outcomes in these guidelines.

A number of other guidelines from authoritative organizations are listed in APPENDIX VIb. None of these guidelines made any reference to pharmacogenomic testing.

**Table 4. Summary of Practice Guidelines with Any Mention of Pharmacogenomic Testing**

**Key:** AGNP, Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie; APA, American Psychiatric Association; BAP, British Association for Psychopharmacology; CPIC, Clinical Pharmacogenetics Implementation Consortium; DoD, Department of Defense; EPA, European Psychiatric Association; GL(s), guideline(s); ICSI, Institute for Clinical Systems Improvement; PGx,
pharmacogenomic; SSRIs, selective serotonin reuptake inhibitors; TDM, therapeutic drug monitoring; VA, Department of Veterans Affairs; WFSBP, World Federation of Societies for Biological Psychiatry

<table>
<thead>
<tr>
<th>Quantity of Individual GLs</th>
<th>Individual GL Quality</th>
<th>Pharmacogenomics Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (beyondblue; EPA; ICSI; VA/DoD; WFSBP)</td>
<td>2 Good 2 Fair 1 Poor</td>
<td>Four of 5 GLs present no formal recommendations for the use of PGx testing. WFSBP recommends: In possibly nonadherent patients (e.g., low drug plasma levels despite high doses of the antidepressant), a combination of TDM and genotyping may be informative. Such analyses can aid in identifying those individuals who are slow or rapid metabolizers of certain antidepressants.</td>
</tr>
<tr>
<td><strong>Schizophrenia Spectrum and Other Psychotic Disorders</strong></td>
<td></td>
<td>No GLs addressing PGx testing specific to schizophrenia spectrum disorders were identified.</td>
</tr>
<tr>
<td><strong>Bipolar Disorder and Related Disorders</strong></td>
<td></td>
<td>No GLs addressing PGx testing specific to bipolar disorder and related disorders were identified.</td>
</tr>
<tr>
<td><strong>Anxiety Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (APA)</td>
<td>1 Fair</td>
<td>No formal recommendations for use of PGx testing.</td>
</tr>
<tr>
<td><strong>Attention Deficit/Hyperactivity Disorder</strong></td>
<td></td>
<td>No GLs addressing PGx testing specific to attention deficit/hyperactivity disorder were identified.</td>
</tr>
<tr>
<td><strong>Substance Use Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (APA; BAP)</td>
<td>1 Fair 1 Poor</td>
<td>No formal recommendations for use of PGx testing.</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (AGNP; BAP; CPIC)</td>
<td>2 Fair 2 Poor</td>
<td>Two of 4 GLs present no formal recommendations for the use of PGx testing. Two CPIC GLs provide dosing recommendations for tricyclic antidepressants or SSRIs based on CYP2D6 or CYP2D6 gene phenotypes (e.g., ultrarapid metabolizer, extensive metabolizer, intermediate metabolizer, or poor metabolizer). In general, for CYP2D6 or CY2C19 ultrarapid metabolizers with increased metabolism of a medication (e.g., tricyclic antidepressants or SSRI), an alternative drug not predominantly metabolized by the either the CYP2D6 or CY2C19 gene phenotype should be selected. For CYP2D6 or CY2C19 extensive metabolizers with normal metabolism of tricyclic antidepressants or SSRIs or CYP2D6 or CY2C19 intermediate metabolizers with reduced metabolism of tricyclic antidepressants or SSRIs compared with extensive metabolizers, CPIC recommends initiating therapy with the recommended starting dose. An exception to this recommendation is for CYP2D6 intermediate metabolizers with reduced metabolism of tricyclic antidepressants; for this treatment group, CPIC recommends consideration of a 25% reduction of the recommended starting dose and using TDM to guide dose adjustments. For CYP2D6 or CY2C19 poor metabolizers with greatly reduced metabolism of tricyclic antidepressants or SSRIs, CPIC recommends considering a 25% to 50% reduction of the recommended starting dose and using TDM to guide dose adjustments.</td>
</tr>
</tbody>
</table>
Selected Payer Policies

At the direction of WA State HCA, the coverage policies for the following organizations were reviewed: Aetna, Centers for Medicare & Medicaid Services (CMS), Oregon Health Evidence Review Commission (HERC), GroupHealth, and Regence Blue Cross/Blue Shield.

Commercial pharmacogenomic gene panels such as GeneSight and Genecept Assay, which test for several genes and gene polymorphisms to deliver an interpretive report, are considered experimental, investigational, and/or not medically necessary for managing psychiatric conditions by Aetna, Group Health Cooperative, and Regence Group due to insufficient evidence that these genetic testing panels result in improved patient health outcomes. The Oregon HERC does not yet have guidance in this area but plans it for the near future. The CMS have no National Coverage Determinations in this topic area. Noridian Healthcare Solutions LLC, a Medicare contractor in the State of Washington, issued a Local Coverage Decision on October 1, 2015, for GeneSight Psychotropic, providing limited coverage when licensed psychiatrists or neuropsychiatrists contemplating an alteration in neuropsychiatric medication for patients diagnosed with major depressive disorder (MDD) who are suffering with refractory moderate to severe depression after at least one prior neuropsychiatric medication failure.

Specific gene tests are covered in certain cases. Noridian Healthcare Solutions LLC, a Medicare contractor in the state of Washington, issued a Local Coverage Decision effective July 8, 2016 in which genetic testing for the CYP2D6 gene is considered medically necessary to guide medical treatment and/or dosing for individuals for whom initial therapy is planned with amitriptyline or nortriptyline for treatment of depressive disorders.

A CMS Local Coverage Decision provides limited coverage for patients of Asian and Oceanian ancestry prior to initial treatment with carbamazepine, an antiepileptic drug. This class of drugs was excluded from this report. Carbamazepine is sometimes used in conjunction with other medications to treat schizophrenia and is a secondary treatment in bipolar disorder. Our literature search did not specify drug names, and only 1 study of the potential clinical utility of HLA-B*15:02 genetic testing for carbamazepine was found in our literature search. The patients in that study were being newly treated with antiepileptic drugs; therefore, the study was excluded as not enrolling patients with an indication of interest.

See Selected Payer Policies in the TECHNICAL REPORT for additional details and links to policy documents.

Overall Summary and Discussion

**Evidence-Based Summary Statement**

In general, the evidence base is of low to very low quality and is insufficient to support recommendations regarding the clinical use of pharmacogenomic testing to aid in the treatment of the psychiatric disorders of interest for this report. Key summary points of interest are as follows:
• As described in the Background, a wealth of data have been generated associating many genetic variants with treatment outcomes; most, if not all, are of low effect size. Such data are important and hypothesis-generating, but incompletely represent clinical validity, and are insufficient to support clinical use. Moreover, few data are available to show how a combination of gene variant tests may be interpreted and how the results are used to categorize drug and dose recommendations for individual patients.

• Pharmacogenomic test results consistently led medication treatment prescribers to change their treatment decisions compared with treatment as usual but the overall quality of evidence was low. While management change is a necessary step toward improving patient outcomes, it is not sufficient to support a conclusion of clinical benefit.

• The evidence supporting the use pharmacogenomic test results for patient management and their impact on patient outcomes is extremely limited and compromised and is considered to be of low to very low quality, depending on the outcome measured. As such, the evidence is insufficient for conclusions regarding clinical use.

• Economic study results in some cases suggested cost-effectiveness but lacked consistency overall. Furthermore, economic analyses are limited by the low quality of the available evidence base and the applicability of the evidence selected to create the various models employed.

• Of the practice guidelines that mention pharmacogenomic testing at all, most make no formal recommendations for use, but rather indicate a need for future research. Some guidelines suggest that pharmacogenomic testing in combination with therapeutic drug monitoring may be beneficial in certain circumstances.

• Few payer policies provide general coverage for pharmacogenomic testing; specific gene tests may be covered in certain cases.

**Gaps in the Evidence**

The following evidence is needed to better answer the Key Questions of this report:

• The populations of patients affected with the disorders of interest is large; answering questions about pharmacogenomic testing in such large and potentially diverse populations is difficult in very small trials of little more than 100 per treatment arm and often much less. For the indications examined in this report, large, well-designed (e.g., retrospective-prospective designs based on already-completed clinical trials) are needed to answer the following questions:
  – Which genes/variants or combinations of genes/variants best address specific clinical indications and outcomes of interest?
  – Selecting the most promising genes/variants and/or combinations, which potential confounders must be addressed and how in the testing process, considering, for example:
    ▪ Race/ethnicity
    ▪ Common and potentially interacting concomitant medications
    ▪ Relevant comorbidities
    ▪ Prior treatment history
Clinical Background

In 2014, there were an estimated 43.6 million (18.1%) adults in the United States with a mental illness in the previous year. This includes approximately 9.8 million (4.2%) adults with serious mental illness. Based on data from 2002, the National Institute of Mental Health estimates that the total direct and indirect costs of serious mental illness exceeds $300 billion per year (NIMH, 2002). In 2010, neuropsychiatric disorders, which include mental and behavioral disorders, accounted for the largest proportion of health-related disability in the United States. In 2008, 13.4% of adults in the United States received treatment for a mental health problem (NIMH, 2008). This includes all adults who received care in inpatient or outpatient settings and/or used prescription medication for mental or emotional problems. Therefore, the societal burden of mental and behavioral disorders is high. Pharmacotherapy is an important part of treatment but is considered effective for only 30% to 60% of patients (Pouget et al., 2014). Adverse events in small proportions of patients result in lack of adherence. For many drugs, treatment selection is empirical and multiple failed trials occur before obtaining an acceptable response without any or with tolerable side effects. The following mental and behavioral illnesses are the focus of this report: depression, psychosis, anxiety, mood disorders, attention deficit/hyperactivity disorder (ADHD), and substance use disorder. Substance abuse will focus specifically on opioid and alcohol abuse.

Depressive Disorders

Definition. Depressive disorders include disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. A major depressive episode is defined as a period of 2 weeks or longer during which there is either depressed mood, or loss of interest or pleasure, and at least 4 other symptoms that reflect a change in functioning, such as problems with sleep, eating, energy, concentration, and self-image (APA, 2013).

Burden. Of the various types of depression, major depression carries the heaviest burden of disability among mental and behavioral disorders (Murray et al., 2013). In 2014, an estimated 10.2 million adults aged 18 years or older in the United States had at least one major depressive episode with severe impairment limiting ability to carry out major life activities (SAMHSA, 2015a). This number represented 4.3% of all U.S. adults.

Initial treatment and results. Depression is usually treated with medications, psychotherapy, or a combination of these treatments. A selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, mirtazapine, or bupropion is recommended first-line medication (APA, 2000 [Reaffirmed 2015]). Full therapeutic dose depends on the patient’s age, the treatment setting, and the presence of co-occurring illnesses, concomitant pharmacotherapy, or medication side effects. Patients
who do not respond after 4 to 8 weeks of treatment, dose adjustment, and additional monitoring may be changed to an antidepressant from the same pharmacological class or to one from a different class. Despite available options, only 20% of those treated receive adequate treatment (Wang et al., 2005), and only 30% of those who receive adequate treatment reach remission (Trivedi et al., 2006). The remaining 70% will either have a response without remission (approximately 20%) or not respond at all (50%) (Trivedi et al., 2006).

**Schizophrenia Spectrum and Other Psychotic Disorders**

**Definition.** Schizophrenia spectrum and other psychotic disorders include schizophrenia, other psychotic disorders, and schizotypal (personality) disorder. These disorders are characterized by a range of cognitive, behavioral, and emotional abnormalities that present in 1 or more of 5 key symptom domains, including: (1) delusions; (2) hallucinations; (3) disorganized thinking (speech); (4) extremely disorganized or abnormal motor behavior (including catatonia); and (5) negative symptoms such as diminished emotional expression, reduced feelings of pleasure, poverty of speech, and a decreased ability to engage in self-initiated activities (APA, 2013).

**Burden.** Schizophrenia affects approximately 1% of the United States population (SAMHSA, 2015b) and is ranked among the top 20 leading causes of global disability (Murray et al., 2013). While disease onset typically occurs from 16 to 30 years of age, childhood-onset schizophrenia, which manifests before age 13 years, affects approximately 0.01% of children (SAMHSA, 2015b).

**Initial treatment and results.** Schizophrenia is typically treated with a combination of antipsychotic medication and psychosocial treatment. Second-generation agents, also known as atypical antipsychotic medications, are considered first-line treatment options for patients in the acute phase of illness due to the reduced risk of extrapyramidal side effects (i.e., parkinsonism, dystonia, akathisia, and tardive dyskinesia) compared with treatment with first-generation agents; however, for some patients, a first-generation antipsychotic medication may also be appropriate (Lehman et al., 2004). Most medications are only effective in 30% to 60% of patients, with 7% of patients experiencing a serious adverse event (Pouget et al., 2014). Several factors may impact long-term medication adherence, including lack of insight, medication beliefs, substance abuse, and unpleasant side effects such as weight gain, excessive sedation, and tardive dyskinesia (Higashi et al., 2013). Agranulocytosis is a rare (cumulative incidence 0.8% to 1.5% within the first year of treatment) but potentially fatal adverse effect of clozapine treatment (Pouget et al., 2014). Antipsychotic medication nonadherence in schizophrenia patients is prevalent, with rates in the literature ranging from 20% to 89% (Barkhof et al., 2012). For patients that discontinue taking medication, relapse rates are up to 5 times higher than those who continue treatment (Lehman et al., 2004). In addition, nonadherent patients have 4 to 7 times greater risk of suicide (Higashi et al., 2013).

**Anxiety Disorders**

**Definition.** Anxiety disorders are characterized by excessive and persistent fear or worry that is difficult to control and substantially interferes with daily functioning (SAMHSA, 2015b). There are several types
of anxiety disorders, including: panic disorder, generalized anxiety disorder (GAD), phobias, and separation anxiety disorder (CDC, 2013a).

**Burden.** Anxiety disorders are the most common class of mental disorder in the United States, affecting approximately 40 million adults, or 18% of the population (Kessler et al., 2009). Typically, anxiety disorders have an earlier onset than other disorders, with phobias and GAD presenting around age 11 (SAMHSA, 2015b). Women are 60% more likely to experience an anxiety disorder over their lifetime compared with men (Kessler et al., 2005). Anxiety disorders rank in the top 10 leading causes of global disability (Murray et al., 2013; Baxter et al., 2014) and are associated with a significant impairment in family, social, and work role functioning (Wittchen, 2002; Hoffman et al., 2008).

**Initial treatment and results.** Treatments for anxiety typically involve pharmacotherapy, psychosocial interventions such as cognitive-behavioral therapy, mindful therapy, and exposure therapy, or a combination of both medication and counseling. Antianxiety drugs (benzodiazepines), antidepressants, and beta-blockers may be prescribed as part of a treatment approach (SAMHSA, 2015c). Medications are occasionally prescribed as a first-line treatment for an anxiety disorder or are used if there is insufficient improvement with psychotherapy (NIMH, 2016a). Although anxiety disorders are treatable, only 34.3% of patients with an anxiety disorder receive minimally adequate healthcare treatment (Wang et al., 2005).

**Bipolar and Related Disorders**

**Definition.** Bipolar disorder is a chronic mood disorder that causes recurrent, dramatic shifts in mood, energy, and activity levels. It is characterized by a range of discrete mood episodes, including: manic episodes (defined by abnormally elevated, unrestrained, or irritable mood); hypomanic episodes (defined by less severe manic periods that are unlikely to cause significant social or occupational issues); major depressive episodes (distinguished by lasting depressed mood or loss of interest or pleasure); or mixed state (defined by symptoms, including elements of both manic and depressive states) (SAMHSA, 2015b). The four basic types of bipolar disorder include: bipolar I disorder, bipolar II disorder, cyclothymic disorder, and other specified and unspecified bipolar and related disorders (NIMH, 2016b). Each type is defined by the pattern of episodes a patient commonly experiences. For example, individuals with bipolar I disorder experience manic episodes that persist for at least 7 days or are so extreme that the individual requires immediate medical attention (NIMH, 2016b).

**Burden.** In the United States, the combined prevalence of bipolar I disorder, bipolar II disorder, and cyclothymic disorder for adolescents (ages 13 to 18) and adults are 11.2% and 2.6%, respectively (SAMHSA, 2015b). The median age of bipolar disorder onset is 25 years and men typically experience earlier onset than women; however, women have 3.2 times greater risk of developing bipolar disorder compared with men (CDC, 2013a). Symptoms of bipolar disorder are severe and create a substantial burden on employers due to absenteeism and presenteeism (Laxman et al., 2008). Bipolar disorder ranks among the top 20 leading causes of global disability (Murray et al., 2013). Furthermore, 25% to 50% of patients with bipolar disorder attempt suicide at least once (Jamison, 2000).
Initial treatment and results. Bipolar disorder is typically treated with a combination of medication and psychotherapies, such as cognitive-behavioral therapy, interpersonal and family therapies, and psychoeducation. Several medications may be prescribed to help control the symptoms of bipolar disorder, including mood stabilizers, antipsychotic agents, and antidepressants (SAMHSA, 2015c). Only 38.8% of patients with bipolar disorder receive minimally adequate healthcare treatment (Wang et al., 2005) and from 20% to 60% of patients with bipolar disorder are nonadherent to medication leading to increased hospitalization (Gaudiano et al., 2011).

Attention Deficit/Hyperactivity Disorder

Definition. Attention-deficit/hyperactivity disorder (ADHD) is characterized by symptoms of inattention and/or hyperactivity with impulsivity that manifest as poor concentration, overall disorganization, propensity to not complete tasks or projects, poor school/work performance, and issues with time management and mood control. Hyperactivity in children may specifically manifest as fidgeting or constant movement, and impulsivity as a lack of patience or lack of emotional control. Adults with ADHD may seek treatment due to an associated complaint, such as procrastination, disorganization, lack of motivation, insomnia, rage attacks, and/or mood swings. There are 3 subtypes of the disorder, including: (1) predominantly hyperactive/impulsive presentation; (2) predominantly inattentive presentation; and (3) combined hyperactive inattentive presentation (SAMHSA, 2015b).

Burden. ADHD is one of the most common childhood-onset neurobehavioral, psychiatric disorders, affecting approximately 9% of children aged 13 to 18 years in the United States (SAMHSA, 2015b). For 60% to 85% of affected children, ADHD persists into adulthood. In the United States, prevalence estimates of ADHD in adults range from 4% to 5% (Kessler et al., 2006; Pliszka, 2007; Lis et al., 2010; Safren et al., 2010). Although the disorder can affect both sexes, it appears more frequently among men than women (Benkert et al., 2010; Lis et al., 2010). The disorder may be accompanied by comorbidities, including learning disabilities, substance use disorders, mania, depression, anxiety, conduct disorder, and oppositional defiant disorder. ADHD symptoms can negatively impact a person’s ability to function in more than one domain (e.g., school, home, work) and can impair self-esteem, interpersonal relationships, and school or work performance (Pliszka, 2007; MFMER, 2016).

Initial treatment and results. Treatments include medication, psychotherapy, education or training, or a combination of treatments. Medications called stimulants (e.g., methylphenidate [Ritalin, Concerta, Methylin, Quillivant XR, and others], amphetamine [Adderall], dextroamphetamine [Dexedrine, ProCentra], and lisdexamfetamine dimeylate [Vyvanse]) are commonly prescribed for the treatment of ADHD. Non-stimulant medications (e.g., atomoxetine [Strattera], clonidine [Kapvay], guanfacine [Intuniv]) may be prescribed to patients who experience side effects from stimulants or for whom stimulants are not effective. Combinations of stimulant and non-stimulant medications may also be considered. Approximately 70% to 80% of children with ADHD respond to stimulant medications with improved attention span, reduced impulsivity, and improved on-task behavior (SAMHSA, 2015c). However, it is not clear if stimulant medications benefit cognition, behavior, mood, or school performance in the long term. Patients may need to try more than one medication or dose to find the treatment with the highest efficacy and fewest side effects.
Substance Use Disorders

Definition. Ten separate classes of drugs comprise substance-related disorders, including: alcohol; caffeine; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics, and anxiolytics; stimulants; tobacco; and other substances (SAMHSA, 2015b). These drugs directly activate the brain’s reward system, which is involved in behavior reinforcement and memory production (Koob, 2006).

Alcohol use disorder (AUD) is characterized by an excessive use of alcohol that increases an individual’s risk of developing serious health problems associated with intoxication behaviors and withdrawal symptoms. AUD may be mild, moderate, or severe, depending on the number of symptoms that meet diagnostic criteria. Some symptoms of AUD include: difficulty controlling alcohol intake; persistent alcohol use despite issues resulting from drinking; development of tolerance; or the development of withdrawal symptoms (SAMHSA, 2015b).

Opioids are a type of medication used to relieve pain. Opioid use disorder (OUD) involves the excessive use of opioids, such as oxycodone, hydrocodone, morphine, and heroin. These drugs increase a person’s risk for serious medical complications, including overdose. Some symptoms of OUD include: a strong desire for opioid use; inability to control or reduce use; continued use despite interference with major obligations or social functioning; use of large amounts of opioids over time; development of tolerance; spending large amounts of time obtaining and using opioids; and development of withdrawal symptoms (SAMHSA, 2015b).

Burden. Substance use disorders rank among the top 10 leading causes of global disability (Murray et al., 2013) and can contribute too many work-performance problems, including premature death/fatal accidents, injury, absenteeism, and loss of production.

In the United States, AUDs affect approximately 16.3 million adults and 679,000 adolescents (aged 12 to 17 years) (SAMHSA, 2014; NIAAA, 2016). Alcohol use increases the risk of acute injury and traffic-related injuries and deaths. In addition, alcohol dependence and excessive drinking are associated with increased risk for liver disease, cardiovascular disease, neurological deficits, several types of cancer, and psychiatric illnesses, particularly mood and anxiety disorders and drug abuse (Cargiulo, 2007; Rehm, 2011). Approximately 88,000 deaths are attributed to alcohol use per year (CDC, 2013b; SAMHSA, 2015b). Compared with individuals with treated AUDs, untreated AUDs use twice as much healthcare (Holder, 1998).

With an estimated 1.9 million people having an OUD involving prescription pain relievers and 568,000 people having an OUD involving heroin, opioid overdose deaths in the United States hit a record high in 2014, reaching 9.0 per 100,000 people (Rudd et al., 2016). Natural and semisynthetic opioid pain relievers (e.g., morphine, oxycodone) accounted for the most opioid-related deaths. Since 1999, rates of opioid overdose-related deaths have risen by 265% and 400% among men and women, respectively (SAMHSA, 2015b).

Initial treatment and results. A number of service components are often used in combination as a multimodal approach for the treatment of substance use disorders. These service components include:
medication; individual or group counseling; inpatient and residential treatment; intensive outpatient treatment; partial hospital programs; case or care management; recovery support services; 12-Step fellowship; and peer support (SAMHSA, 2015c). Due to the chronic nature of substance use disorders, patients typically require long-term treatment, although the intensity and specific components of treatment may change over time (Kleber et al., 2006).

Several medications have shown efficacy in adults for the treatment of AUD, including acamprosate, disulfiram, and naltrexone. Acamprosate helps individuals with AUDs that have achieved abstinence maintain abstinence for several weeks to months by reducing the symptoms of protracted withdrawal. Disulfiram alters alcohol metabolism, resulting in flushing, nausea, vomiting and other unpleasant symptoms after alcohol consumption. Naltrexone blocks the effects of opioids and reduces alcohol cravings (SAMHSA, 2015c). Positive outcomes from AUD treatment have been documented in many studies, with improved health status and reductions in the number of drinking days within 6 months of starting treatment (Kleber et al., 2006). Despite success, only 25% of people seek treatment for AUDs (Dawson et al., 2006).

Medications used for the treatment of OUDs include methadone, buprenorphine, or extended-release injectable naltrexone. Methadone and buprenorphine act as opioid agonists and reduce cravings and withdrawal symptoms. Extended-release injectable naltrexone helps control cravings and reduces the risk of relapse and is often used in situations where an opioid agonist is not available or appropriate (SAMHSA, 2015c). Treatments for OUDs can be highly effective; however, success is often limited by the availability of treatment programs (Kleber et al., 2006).

**Pharmacogenomics**

Because drugs for psychiatric conditions (and many other important medical conditions) are selected and dosed empirically, with less than a desirable response in all cases, and sometimes moderate to serious adverse events, advance predictors of response or adverse events in individual patients have been sought. Pharmacogenomics aims to identify relationships between base sequence variants in genes that ultimately identify patients likely to respond to treatment or experience adverse events from specific medications. The products of such genes are most likely to be involved in drug uptake and metabolism (pharmacokinetics) or may have specific function at the target of drug action (pharmacodynamics). Sequence variants of these genes may result in products that have slightly or greatly reduced function, or none at all. Replication of these specific genes may amplify function, increasing, for example, the metabolic function of a pharmacokinetic product.

An example of pharmacokinetic genetic variation is the cytochrome P450 (CYP450) superfamily, a large group of enzymes that have an essential role in drug metabolism. In particular, the CYP2D6 CYP450 enzyme plays a role in the metabolism of 80% of antidepressant and antipsychotic drugs and the CYP2C19 CYP450 enzyme plays a role in the metabolism of certain antidepressants such as citalopram, escitalopram, amitriptyline, and sertraline (Muller et al., 2013). Variants in each of these genes may result in enzymes with variable activity, and phenotypes of normal metabolizers (fully functional activity), poor metabolizers (little to no activity), intermediate metabolizers (decreased activity, from
normal to poor), and rapid/ultrarapid metabolizers (increased enzyme activity) (Caudle et al., 2016). A patient who is a poor metabolizer treated with an antidepressant may have greater-than-expected drug exposure with more potential for side effects, whereas an ultrarapid metabolizer given the same drug may experience insufficient exposure and poor response. Note that these predicted results apply to an active drug and would be opposite for a prodrug (a version of a drug that must first be metabolized into its pharmacologically active form).

The dopaminergic and serotonergic neurotransmitter systems are central to antipsychotic drug efficacy; therefore, much research has centered on the impact of genetic variants in the dopamine D2 receptor (DRD2), the dopamine D3 receptor (DRD3), the serotonin 1A receptor (HTR1A), and the serotonin 2A receptor (HTR2A) (Pouget et al., 2015), all examples of pharmacodynamic gene products. Variants in these genes and many others are hypothesized to alter response to and clinical efficacy of psychotropic drug treatment as well as likelihood of adverse effects.

Methodologic approaches to identifying genomic predictors of drug response or adverse effects include candidate gene studies, whereby genes are selected based on biologic plausibility, as described in the preceding examples. The majority of evidence supporting the association of gene variants with drug treatment outcomes is based on candidate gene studies. The other approach is a genome-wide association study(ies) (GWAS), which uses a hypothesis-free approach to test an enormous number of single nucleotide polymorphisms across the genome for significant and relevant associations. For example, the Genome-Based Therapeutic Drugs for Depression (GENDEP) project was a randomized pharmacogenomic trial with 2 active treatment arms; 87% of patients were included in a genome-wide analysis. The results of this GWAS were combined with 2 other similar GWAS in a meta-analysis to increase the power for detecting significant associations. Interestingly, however, only modest evidence was found that common genetic variation contributes to individual differences in antidepressant response (GENDEP, 2013).

In order to personalize individual patient prescribing and improve pharmacotherapy outcomes, a number of clinical pharmacogenomic laboratories are available, many of which offer testing services that purport to address a range of psychotropic drugs. The primary evidence supporting the development of these tests is gene variant treatment outcome associational evidence, one aspect of the clinical validity of a test. A strong association supports a test’s ability to predict response or occurrence of adverse effects. Weak individual pharmacogenomic associations may indicate complicated pharmacokinetic or pharmacodynamics pathways within which the influence of a single gene is insufficient for strong predictive ability. Moreover, a strong association may be a poor predictor if the frequencies of the predictive genetic variant and/or the outcome are low in the target population (Tonk et al., 2016).

Associational evidence has been used, in many cases exclusively, to support the addition of genetic information to drug labels by the U.S. Food and Drug Administration (FDA). Wang et al. (2014) evaluated biomarker information in 119 drug labels from the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, a publicly accessible database, using guidelines from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group to define strength of evidence for clinical validity and
clinical utility. In total, 43 (36.1%) of 119 labels provided convincing clinical validity evidence. Sixty-one (51.3%) of 119 labels made recommendations for clinical decision-making based on biomarker test results; 36 (30.3%) of these were based on convincing clinical utility data. The authors concluded that adding biomarker testing recommendations to drug labels may be premature when convincing data linking testing to patient outcomes is lacking. Note, the indications for these drug labels were not limited to those selected for this report.

Because association evidence has been widely used as primary evidence to support the use of pharmacogenomic testing, it is important to examine the value of the information contained within such evidence. Measures of association are often reported as odds ratios (OR), the value indicating the relative strength of association. If the measure of association for a particular genetic variant and the outcome of tardive dyskinesia when a patient is treated with antipsychotic drugs is a statistically significant OR of 2, then patients with that particular variant may be twice as likely to experience tardive dyskinesia when treated with antipsychotic drugs as patients who do not have that genetic variant (or compared with the base rate in the population if the frequency of the genetic variant is small). ORs can also be converted to the standardized mean difference, or Cohen’s d, a common measure of effect size that can be compared across studies. Using published formulas, an OR of 2 equates to a Cohen’s d of approximately 0.2 (Hasselblad and Hedges, 1995). At this value, 92% of the gene variant–positive and gene variant–negative groups are predicted to overlap (see Figure 2), and the number needed to treat to have one more favorable outcome in the treatment group compared with control group is predicted to be 16.5. Using general guidelines, a Cohen’s d of 0.2 is small, 0.5 is medium, and 0.8 is large, although these cutoff values are arbitrary and should not replace consideration of specific study details (Cohen, 1988).

Predictors of small effect size are likely to perform poorly as clinical laboratory tests. Where possible and biologic plausibility and/or statistical analysis suggests, several predictors of small effect size may be combined in test panels to generate larger effect sizes. However, overall effect sizes for specific applications of individual pharmacogenomic tests combined into panels (e.g., for specific clinical disorder indications and outcomes) are often lacking.
Clinical Validity of Pharmacogenomic Testing for Pharmacotherapy of Selected Psychiatric Disorders

The vast majority of the published literature supporting and promoting the uptake of clinical pharmacogenomic testing does not report on clinical utility data but rather reports associational or clinical validity data. As noted, some effect sizes can be very large and in high-risk clinical settings may stimulate highly directed clinical translation studies to support routine testing (Martin and Kroetz, 2013). As context for the clinical utility evidence presented in this report, it is important to provide a sense of the scientific landscape in relation to the question of clinical validity, including the size, nature, and strength of pharmacogenomic associational data for the indications of interest for this report. Therefore, a search for summary evidence of pharmacogenomic gene-outcome associations in the form of systematic reviews and meta-analyses was conducted. Search details are summarized in APPENDIX II; note that this search was not exhaustive and discussion of clinical validity data is restricted to the background section of this report.

Thirty-eight systematic reviews were identified as pertinent to the indications of interest for this report. Of 38, 12 reported only descriptive results and 26 reported meta-analysis of gene-outcome association results where sufficient studies were available. In the latter case, this means that for each gene variant
(or in some cases, all variants combined for a single gene) and a selected outcome, a meta-analysis across all published studies reporting that combination was reported. In addition, several models (allele only, dominant, recessive, homozygous, heterozygous) may be reported, depending on what is and is not known about the variant and its inheritance. Across all meta-analysis publications, many genes were examined for gene-outcome associations, highlighting the complexity in the biological models used to choose candidate genes for various psychiatric conditions. To report the results of all meta-analyses, including the various models for each gene, would be excessive and uninformative. Therefore, the indication of schizophrenia was selected as an example. **APPENDIX I** first lists all of the genes studied. Next, gene-outcome associations reported in more than one of of the 8 applicable meta-analyses are shown. For each, only the model with the most significant OR, whether or not it was statistically significant, was chosen. The selections cover a range of models and give an indication of a range of ORs that have been reported for the genes (or GWAS variants) as relevant to schizophrenia.

For the provided example of schizophrenia (see **APPENDIX I**), the highest OR reported is for the TNFa gene and weight gain at a protective value of 0.23 (Zhang et al., 2016). Inverted, this corresponds to an OR of 4.3 and a Cohen’s d of approximately 0.35, but the original result was not statistically significant ($P=0.34$). The highest statistically significant OR greater than 1 is 2.08 ($P=0.008$; Cohen’s $d$, 0.18), reported for CYP2D6 (all variants combined) and tardive dyskinesia (Fleeman et al., 2010; Fleeman et al., 2011). The highest statistically significant OR less than 1 is for the association of MnSOD Ala-9Val and tardive dyskinesia, OR equals 0.37 ($P=0.009$), inverted equals 2.7, Cohen’s $d$ 0.24 (Bakker et al., 2008).

Therefore, despite a large number of association studies and several meta-analyses combining results across studies, effect sizes for relevant gene-outcome associations tend to be relatively small. These results can be compared with an opposite extreme, those for genetic variants predicting high-risk adverse events. For example, in Han Chinese, presence of HLA-B*15:02 predicts life-threatening Steven-Johnson syndrome at a highly statistically significant OR of 97.6, Cohen’s $d$ 1.1 (Hsiao et al., 2014). The presence of HLA-B*57:01 predicts immunologically confirmed hypersensitivity reaction to abacavir in patients with clinically suspected reactions at ORs of 900 to 1945, Cohen’s $d$ 1.6 to 1.8 (Saag et al., 2008). These are both routinely used pharmacogenomic tests in applicable populations.

No meta-analyses combined results for more than one gene for the same outcome to show improved effect size. Published examples describe the selection of a group of genes with the strongest effect sizes and briefly summarize algorithms that “prioritize and apply differential weight to potential clinical outcomes” in order to arrive at overall treatment recommendations (Salloum et al., 2014). Commercial pharmacogenomic panels use patented or otherwise proprietary algorithms to synthesize the results from individual gene variants and arrive at treatment recommendations (see examples in the Literature Review of this report).

Other complexities that may not be accounted for in pharmacogenomic profiles include variation in race/ethnicity, which can result in different associations due to different linkage profiles with other genes, different gene-environment interactions, and different frequencies of variants alleles. Rare alleles in one ethnic group can be mistaken for variant pharmacogenomic alleles but may be common in other ethnic groups; gene variants may even appear to be protective in one ethnic group but causative in...
another due to confounding genetic influences (Risselada et al., 2011). An example of this can be seen in the table Meta-analyses for Clinical Validity—Schizophrenia: Shen et al. (2014) show results for a variant in the leptin gene (LEP) and its association with weight gain, for all study populations together (OR, 1.25), for studies of Asian populations (OR, 1.62), and for studies of European populations (OR, 0.78), here displayed using the recessive model. Only the results for the Asian populations, however, are statistically significant.

The table also emphasizes the number of different genes and gene variants that have been considered plausibly related to drug response and adverse effects, reflecting the possibility of multiple metabolic and effector pathways that may influence outcomes; fractional pathways may differ for specific drugs even within classes. In addition, concomitant medications and patient comorbidities may interact with the psychotropic drug, altering pharmacokinetics and/or pharmacodynamics.

Finally, not all individual study designs share good-quality criteria, which include correcting results for multiple testing and conducting studies in large and representative populations (Risselada et al., 2011). In addition, studies often do not study psychotropic drug-naïve patients, in which case clinical history may also confound results. The study of antipsychotic drug use and genetic influences on weight gain is one example.

Taken together, information regarding the clinical validity of pharmacogenomic testing for the indications of interest for this report is limited to associational evidence of small effect size for single genes/gene variants and selected outcomes, lacks information on how these gene variants are combined to make treatment recommendations, and may not take full account of common potential confounders of these relationships. For these reasons, a report focusing on the preponderance of available association studies would be limited in its usefulness. Evidence regarding the use of pharmacogenomic testing to prospectively guide the selection of treatment drug or dosing, compared with treatment as usual, with measured impact on appropriate outcomes is of greater use and is evaluated in the Literature Review section of this report.

Analytic Validity of Pharmacogenomic Testing for Pharmacotherapy of Selected Psychiatric Disorders

Analytic validity for laboratory tests refers to the technical performance of the test, how accurately, precisely, and robustly the test detects what it is supposed to detect. The FDA conducts a detailed and publicly available review of the analytic validity of any clinical laboratory test submitted for clearance, which covers most laboratory tests in general. The exception is genetic tests, which are primarily laboratory-developed tests not currently required to be submitted to the FDA as long as the test is not manufactured and sold in kit form to other laboratories. Validation data for these types of tests are not publicly available and, unless published in the medical literature, (rare) are not reported.

For additional context, we searched for information on the analytic validity of pharmacogenomic tests used in the clinical validity studies outlined above and in those studies included in the Literature Review. One systematic review (Fleeman et al., 2010) reported on 46 studies that reported on the analytic
validity of genotyping 11 different CYP450 gene variants, almost half of which were related to CYP2D6. CYP2C19 and CYP2C9 were also included in several studies. Real-time polymerase chain reaction (PCR) was the most frequent genotyping method, although microarray methods (including the commercially available AmpliChip) were also applied. PCR plus restriction fragment length polymorphism analysis and sequencing were the most common reference methods, but sequencing was used sparingly, usually as a second reference method. The majority of studies were conducted in Europe. Study size varied from 40 subjects to 428 for the test method. Few studies reported on the ethnic origin of test subjects. All studies reported concordance of 95% or more, regardless of the CYP gene tested or the methods used. Few studies reported on quality control or assay robustness. In most studies, both sensitivity and specificity were 100%. Comprehensive data were available for AmpliChip (microarray testing for CYP2D6 and CYP2C19 variants), which was submitted to and cleared by the FDA for marketing in 2005. For this assay, concordance was 100% and sensitivity and specificity were near or at 100%. Thus, testing for CYP450 gene variants appears highly accurate but not all aspects of analytic validity have been reported. The current search found no analytic validity evidence for genotyping non-CYP450 genes or for commercially available gene panels.
Washington State Agency Utilization and Costs

Related Medical Codes
Review Objectives and Analytic Framework

Scope
The scope of this report is defined as:

**Population:** People any age who are being prescribed medications for treatment of depression, mood disorder, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), substance use disorder.

**Interventions:** Clinical laboratory tests for genetic variants in targeted genes or in panels of genes to inform the selection or dose of psychotropic medications relevant to the conditions of interest.

**Comparisons:** Usual care/no genetic testing.

**Outcomes:**
- Patient Management (KQ1): physician and patient decision-making regarding drug choice and/or dose; improved patient adherence to treatment regimen; clinically meaningful improvement in patient response to treatment and reduction in adverse events as a result of treatment;
- Costs (KQ2): cost-effectiveness or cost.

Key Questions
The following key questions will be addressed:

1. **Effectiveness:** What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorders, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), or substance use disorder?
   a. Does genetic testing to inform the selection or dose of medications change the drug or dose selected by physicians and/or patients compared with usual care/no genetic testing?
   b. Do decisions about selection or dose of medications guided by genetic testing result in clinically meaningful improvement in patient response to treatment or reduction in adverse events as a result of treatment compared with decisions based on usual care/no genetic testing?
2. **Harms:** What direct harms are associated with conducting genetic testing when it is used to inform the selection or dose of medications?
3. **Special populations:** Compared with usual care/no genetic testing, do decision-making, patient outcomes, or harms following genetic testing to inform the selection or dose of medications vary by:
   a. Clinical history (e.g., prior treatments, whether the diagnosis is initial or recurrent, duration of diagnosis, severity of illness, or concurrent medications); or
b. Patient characteristics (e.g., such as age, sex, or comorbidities)?

4. Costs: What are the costs and cost-effectiveness of genetic testing to guide the selection or dose of medications?

**Analytic Framework**

Figure 1 depicts the relationship of the PICO statement with the Key Questions

*Figure 1. Analytic Framework: Pharmacogenomic Testing for Selected Conditions*

(Key Questions referenced by number in the graphic)
Methods

Search Strategy and Selection Criteria
See APPENDIX II for additional search details.

Before conducting a search for primary data to answer the key questions of interest, the following sources were searched on August 16, 2016, for systematic reviews, meta-analyses, economic evaluations, and practice guidelines published in the last 10 years:

- Core online databases such as the Agency for Healthcare Research and Quality (AHRQ), Centre for Reviews and Dissemination (York University), National Institute for Health Research Health Technology Assessment Programme (UK), Institute for Clinical Systems Improvement, and National Guidelines Clearinghouse (NGC).
- Websites of relevant professional societies.

Systematic reviews were not selected for inclusion in the Literature Review section of this report (since they did not report on clinical utility) but rather formed the basis for the summary information on the clinical validity of pharmacogenomic testing already outlined in the background section of this report. Included systematic reviews were categorized into those that were only descriptive and those that included quantitative meta-analyses for gene-outcome associations where sufficient numbers of studies were available. This search was not exhaustive and was intended to exemplify the extent and type of data that is available to support many pharmacogenomic tests for the indications of interest. Additional details on the selection of the data presented in the background section of the report are described in the Clinical Validity of Pharmacogenomic Testing for Pharmacotherapy of Selected Psychiatric Disorders in APPENDIX I.

Since reports of analytic validity are rare in the clinical literature and information on the topic was restricted to the background section of the report, no search criteria specific to analytic validity were developed and the search is not considered systematic or exhaustive. In addition to systematic reviews reviewed for clinical validity, and primary studies included in the Literature Summary, websites of commercial gene panels used in the studies reviewed in the Literature Review sections of this report were searched for information regarding analytic validity, but none were found.

Primary Studies

PubMed (January 1, 2000 to August 15, 2016), OVID-Embase (1996 to 2016, week 33) and PsycINFO (1987 to July, week 4, 2016) databases were searched for primary studies and economic evaluations designed to answer the Key Questions. Specific search strings are documented in APPENDIX II.
Inclusion/Exclusion Criteria

Detailed inclusion and exclusion criteria, along with their rationale, are presented in Table 5.

Table 5. Inclusion/Exclusion Criteria

Key: ADHD, attention deficit/hyperactivity disorder

<table>
<thead>
<tr>
<th>For Clinical Utility studies include if all of the following were true:</th>
<th>Rationale:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population was composed of people any age who were being prescribed medications for treatment of depression, mood disorder, psychosis, anxiety, ADHD, or substance use disorder.</td>
<td>This describes the appropriate clinical population in which the intervention of interest would be used and excludes patients being treated for any other condition for which pharmacogenomics testing may be considered.</td>
</tr>
<tr>
<td>The interventions consisted of clinical laboratory tests for genetic variants in targeted genes or in panels of genes. Test results were available to the medication prescriber in the experimental arm of the study.</td>
<td>Only DNA-based pharmacogenomics tests were acceptable interventions; non–DNA-based laboratory tests such as enzyme activity functional testing was excluded. Available test results could be used to inform the selection or dose of psychotropic medications relevant to the conditions of interest.</td>
</tr>
<tr>
<td>Use of pharmacogenomic testing was compared with usual care/no genetic testing.</td>
<td>Studies without control groups cannot measure the impact of a pharmacogenomic strategy.</td>
</tr>
<tr>
<td>Outcomes could be categorized as follows: Patient Management (KQ1): Physician and patient decision-making regarding drug choice and/or dose; improved patient adherence to treatment regimen; clinically meaningful improvement in patient response to treatment and reduction in adverse events as a result of treatment; Costs (KQ2): Cost-effectiveness or cost.</td>
<td>Physician and patient decision-making regarding pharmacogenomic testing represents the first potential impact of test results and is measurable; clinically meaningful measures of response to treatment comparing use versus no use of pharmacogenomic testing, as well as cost, summarize the results of those decisions and whether or not they are meaningfully different.</td>
</tr>
<tr>
<td>Settings were inpatient and outpatient facilities in any country</td>
<td>Utility of pharmacogenomic testing for the indications of interest is not expected to differ by setting or country.</td>
</tr>
<tr>
<td>The study design was limited to the following: Patient Management (KQ1): Randomized and nonrandomized controlled trials, prospective and retrospective cohort studies with eligible comparison groups, case-control studies. Costs (KQ2): Economic evaluations (e.g., cost outcomes reported in comparative studies, systematic reviews, and meta-analyses that included cost information</td>
<td>Study designs were chosen to minimize bias as much as possible but to also recognize the limitations of the evidence and allow for some flexibility.</td>
</tr>
</tbody>
</table>
Quality Assessment

Clinical Studies

APPENDIX III outlines the process used by Hayes for assessing the quality of individual primary studies and the quality of bodies of evidence. This process is in alignment with the methods recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. Quality checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Additional items were added that pertain specifically to this topic area. Individual studies are labeled as good, fair, poor, or very poor.

Like the GRADE Working Group, Hayes uses the phrase quality of evidence to describe bodies of evidence in the same manner that other groups, such as the Agency for Healthcare Research and Quality (AHRQ), use the phrase strength of evidence. The Hayes Evidence-Grading Guides ensure that assessment of the quality of bodies of evidence takes into account the following considerations:

- Methodological quality of individual studies, with an emphasis on the risk of bias within studies.
- Applicability to the population(s), intervention(s), comparator(s), and outcome(s) of interest, i.e., applicability to the PICO statement.
- Consistency of the results across studies. Quantity of data (number of studies and sample sizes).
- Publication bias, if relevant information or analysis is available.

NOTE: Two terms related to applicability are directness and generalizability. Directness refers to how applicable the evidence is to the outcomes of interest (i.e., health outcomes versus surrogate or intermediate outcomes) or to the comparator of interest (indirect comparison of 2 treatments versus head-to-head trials). Generalizability usually refers to whether study results are applicable to real-world practice. If the setting is not specified in a PICO (population-interventions-comparator-outcomes) statement, the issue of generalizability to real-world settings is not typically treated as an evidence quality issue. Another term used by some organizations is imprecision, which refers to findings based on such a small quantity of data that the CI surrounding a pooled estimate includes both clinically important benefits and clinically important harms, or such a small quantity of data that any results other than large statistically significant effects should be considered unreliable.

Bodies of evidence for particular outcomes are labeled as being of high, moderate, low, or very low quality. Very-low-quality bodies of evidence are deemed to be insufficient to permit conclusions. These labels can be interpreted in the following manner:

**High**: Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.
Moderate: Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies.

Low: We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and possibly the direction of the results.

Very low: Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

Economic Evaluations
A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. Sources are listed in APPENDIX III.

Guidelines
The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Enterprise, 2013), along with a consideration of the items related to commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. Use of the AGREE tool was limited to these areas because they relate most directly to the link between guideline recommendations and evidence.

Search Results

Included Studies
Fourteen studies were selected for detailed analysis as evidence pertaining to the Key Questions. Figure 3 summarizes the systematic identification and selection of these studies, which include 4 studies addressing Key Question 1a (clinical utility, medical decision-making), 9 studies addressing Key Question 1b (clinical utility, patient outcomes), which were also assessed for Key Question 3 (subgroups), and 7 studies addressing Key Question 4 (economic outcomes). No unique studies were identified for Key Question 2 (harms of testing).

Excluded Studies
See APPENDIX IV for a listing of the 19 studies that were excluded from analysis after full-text review.
Figure 3. Summary of Search Results

744 PubMed hits
1323 Embase hits

581 duplicates removed
1465 studies excluded based on title/abstract review

33 full-text articles retrieved

19 studies excluded based on full-text review
Not a comparative study (6)
Not a pharmacogenomics study (2)
Study of physician ordering practices (2)
Case report (1)
Review (1)
Medications adjusted for other reasons in addition to pharmacogenomic test (1)
Report of an error (1)
Non-psychiatric indications (1)
Economic study of a single drug (2)
Physician prescribing concentration (1)
Study superseded by another (1)

14 studies analyzed for clinical utility
5 clinical decision-making studies (KQ#1a)
9 patient outcome studies (includes all 5 decision-making studies) KQ#1b, 2, 3)
7 economic studies (includes 2 of the 9 patient outcome studies) (KQ#4)

1 study added from guidelines citation
1 study added from systematic review/guidelines search

Literature Review

Key Question #1: Effectiveness: What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorders, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), or substance use disorder?

a. Does genetic testing to inform the selection or dose of medications change the drug or dose selected by physicians and/or patients compared with usual care/no genetic testing?

Four studies reported results of using pharmacogenomic genotyping to aid in clinical decision-making. All studies enrolled patients diagnosed with depressive disorder. Study details are presented in APPENDIX Va.
Two studies were prospective double-blind randomized controlled trials (RCTs) of fair quality (Winner et al., 2013; Singh, 2015), 1 was a prospective controlled trial of poor quality (Hall-Flavin et al., 2012), and 1 was a retrospective comparative study of poor quality (Breitenstein et al., 2014).

Singh (2015) randomized 74 white patients to a pharmacogenomic genotyping arm and 74 similar patients to a control arm, in which a DNA sample was obtained for patient blinding but was not analyzed. A commercial genotyping assay detecting genetic variation in genes coding for the serotonin transporter linked promoter region (5-HTTLPR), which may impact response to antidepressants, ABC active efflux transporters at the blood brain barrier (ABCB1, ABCC1), and enzymes that metabolize antidepressants (CYP2D6, CYP2C19, UGT1A1) was utilized. Results of the test were provided in the form of an interpretive report with recommended dose ranges; prescribers were allowed to use their judgment in choice of treatment medication. In the genotyping arm, all treatment prescribers were verified to have viewed the pharmacogenomic interpretive report. In 65% of cases, prescribers indicated that pharmacogenomic results changed medication dosing compared with their usual practice, as conveyed by confidential feedback form.

In a similarly designed study, Winner et al. (2013) randomized 26 patients to pharmacogenomic genotyping and 25 to treatment as usual. Control patients were genotyped but no results were provided to attending physicians. A proprietary commercial test measuring variation in genetic sequence among genes that are believed to influence antidepressant and antipsychotic drug metabolism (CYP2D6, CYP2C19, CYP1A2) and response (SLC6A4, HTR2A) was utilized to provide an interpretive report and recommendations for medication selection and dose. In the genotyping arm, 100% of baseline medications that the assay interpretive report indicated should be used with caution and frequent monitoring were changed. In the control arm, only 50% of similarly classified medications were altered when the genotyping report was evaluated after the fact.

Breitenstein et al. (2014) conducted a retrospective comparative study of 116 patients undergoing a moderate to severe depressive episode at hospital admission. ABCB1 genotyping had been available to treatment prescribers for 58 of these patients. Among genotyped patients, those found to have an identified “unfavorable” genotype, antidepressant dose was increased 1.63-fold compared with other genotypes (P=0.012). A change to a different antidepressant also occurred more often in patients with an unfavorable genotype than in other genotypes (P=0.011).

Finally, Hall-Flavin et al. (2012) conducted a prospective controlled trial using the same genotyping assay as Winner et al. (2013). Twenty-five consecutively selected adults were genotyped with results immediately returned to their physicians; 26 similar controls were also genotyped but results were not provided to their physicians until after 8 weeks of treatment. At 8 weeks, only 5.9% of genotyped patients were prescribed a medication that the pharmacogenomic interpretive report labeled “use with caution” compared with 21.4% of controls (P=0.02).

The overall quality of the body of evidence to answer Key Question 1a was considered to be of low quality. All studies were moderately to very small and limited to patients with depressive disorders; only 2 studies were randomized clinical trials. The limited results regarding clinical decision-making suggest
that pharmacogenomic test results, whether derived from single-gene tests or interpretive panels, may change prescribing patterns in favor of pharmacogenomic recommendations compared with treatment as usual. This is a necessary but not sufficient step toward improving patient outcomes.

**Key Question #1: Effectiveness: What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorders, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), or substance use disorder?**

b. Do decisions about selection or dose of medications guided by genetic testing result in clinically meaningful improvement in patient response to treatment or reduction in adverse events as a result of treatment compared with decisions based on usual care/no genetic testing?

Nine studies reported results of using pharmacogenomic genotyping and subsequent effects on patient outcomes. Six studies enrolled patients with depressive disorders, 2 enrolled patients with any psychiatric disorder, and 1 enrolled patients with alcohol use disorder. Study details are presented in **APPENDIX Va**.

**Pharmacogenomic Studies of Treatment of Depressive Disorders**

Two studies were prospective double-blind RCTs of fair quality (Winner et al., 2013; Singh, 2015); 2 were prospective controlled trials, 1 of fair quality (Hall-Flavin et al., 2013) and 1 of poor quality (Hall-Flavin et al., 2012); 2 were retrospective comparative studies, 1 of poor quality (Breitenstein et al., 2014; Fagerness et al., 2014; Espadaler et al., 2016) and 1 of very poor quality (Rundell et al., 2011).

**Outcome: Remission**

Four studies reported on remission from a depressive disorder, comparing patients whose prescribing physicians had access to pharmacogenomic information to control patients treated as usual. In an RCT, Singh (2015) reported that at 12 weeks after treatment based on pharmacogenomic results, tested patients (blinded to physician use of test results) statistically significantly more often obtained remission as defined by a 17-item Hamilton Depression Rating Scale (HAM-D17) score of less than 7 (OR=2.52; 95% CI, 1.71-3.73; \( P<0.0001 \)) and that the number needed to test to obtain remission was 3. This trial used a commercial pharmacogenomic assay panel (CNSDose) that tests for variants in several genes and uses proprietary technology to provide an interpretive report with recommended antidepressants and dose ranges. Detail on how individual variant genotype results are combined to generate recommendations is not available. The test is not currently available in the United States but may be available at a later date (Venkatesh, 2016).

Winner et al. (2013), in an RCT, and Hall-Flavin et al. (2013), in a prospective controlled trial, both employed the same U.S.-based commercial pharmacogenomic assay panel (GeneSight) to compare remission outcomes for patients treated with pharmacogenomic information available versus patients treated as usual. Patented proprietary technology is used to translate the several GeneSight panel gene variant genotype results for each patient into an interpretive report in which 26 psychiatric medications
are placed in categories of “use as directed,” “use with caution,” and “use with caution and with more frequent monitoring.” In the underpowered Winner et al. RCT, results suggested greater likelihood of remission for tested patients but were not statistically significant. In the Hall-Flavin et al. controlled trial, tested patients were statistically significantly more likely to obtain remission compared with controls at 8 weeks, as defined by a Quick Inventory of Depressive Symptomatology (Clinician Rated) (QIDS-C16) score < 6. However, similar results were not obtained using HAM-D17 or the 9-item Patient Health Questionnaire (PHQ-9) depression severity score, except for results using data imputation to account for 27% of patients lost to follow-up.

Finally, in a retrospective comparative study testing for variants in a single gene, Breitenstein et al. (2014) reported that genotyped patients were statistically significantly more likely to be in remission (HAM-D score < 10) at hospital discharge compared with non-genotyped patients (83.6% versus 62.1%; P=0.005).

**Summary of Remission Outcomes:**

It has been reported that approximately one-third of those who ultimately respond to treatment of a depressive episode and half of those who entered remission did so after 6 weeks while 40% of those who entered remission required 8 or more weeks (Gaynes et al., 2008). All studies reporting remission outcomes followed patients for 8 or more weeks, except Breitenstein et al. (results reported at discharge; hospital stays averaged approximately 10 to 15 weeks). Thus follow-up times appear reasonable.

In all studies, enrolled patients had minimum HAM-D scores of 14 to 18 whereas remission was defined as HAM-D score of less than 7 to 10. Thus, for remission, scores were required to change by 4 to 11 points, depending on the study. The National Institute for Health and Clinical Excellence (NICE) guidelines for depression (NICE, 2009) defines the minimal clinically important difference (MCID) in HAM-D as 3 points but do not reference this value. In a letter to the editor, Masson and Tejani (2013) report a systematic review of studies that identified the MCID of depression rating scales. For the HAM-D17 (17 item) and HAM-D (21 item) scales, approximately 4.5- and 5.7-point differences, respectively, are needed for clinical relevance. Only the Breitenstein et al. (2014) study does not meet this criterion. Culpepper et al. (2015) recently stated that a HAM-D17 cutoff of 7 to define remission is no longer considered acceptable because global psychosocial functioning and quality of life are still impaired. Thus, although using accepted definitions, these studies may not be measuring full remission.

In summary, despite consistency of results favoring improved remission rates as a result of genotyping, the quality of the evidence is low and our confidence that the results represent a true effect is therefore also low. The results of Breitenstein et al. (2014) may lack clinical relevance. Hall-Flavin et al. (2013) lacks consistency of results due to high losses to follow-up (27%) and reliance on data imputation for statistical significance for 2 of 3 depression scores. The Winner et al. (2013) RCT is underpowered to discriminate between groups. The most statistically significant results for the outcome of remission are reported by Singh (2015) using a test that is not currently available in the United States. Because the methods used to generate interpretations of the individual genetic variant results and derive overall
clinical recommendations for drug selection and dose are not known, the clinical utility performance of one specific panel test is not generalizable to that of any other pharmacogenomic test.

Outcome: Response to Treatment

Four studies reported on response to treatment of depressive disorders. In the RCT reported by Winner et al. (2013), nonsignificant results in the direction of improved treatment response (> 50% reduction in HAM-D17 score from baseline) were seen at 10 weeks. In a prospective controlled trial, Hall-Flavin et al. (2013) reported consistent and statistically significantly improved response (> 50% reduction in score from baseline) for 3 different commonly used measures of depression symptoms among genotyped patients compared with controls. Odds ratios ranged from 2.06 to 2.58. In a similarly designed, fair-quality, prospective controlled trial that also used the GeneSight pharmacogenomic test, Hall-Flavin et al. (2012) reported improved response for a statistically significantly larger proportion of genotyped patients than controls using QIDS-C16 and HAM-D17 depression severity scores. In a very-poor-quality retrospective comparative study, Rundell et al. (2011) reported inconsistent but primarily nonsignificant results for response to treatment. Clinical interpretation of some of the measures investigated (e.g., pre-to post-baseline PHQ-9 scale slopes) was not provided.

Summary of Response to Treatment Outcomes:

Response to treatment of depression is typically measured as a reduction in score of 50% or more for well-validated instruments such as HAM-D, QIDS-C16, and PHQ-9 (Culpepper et al., 2015). In fact, a 50% or greater reduction in the PHQ-9 is a National Quality Measures Clearinghouse clinical quality measure (NQMC, 2005). Overall, the results for response to treatment, comparing pharmacogenomic testing informed prescribing to treatment as usual, lack consistency, are limited in some cases by lack of acceptable measures of response, or were underpowered. The overall quality of the evidence is low. Best results are reported by Hall-Flavin et al. (Hall-Flavin et al., 2013), which used such measures of response and showed that patients whose prescribing physicians had access to GeneSight pharmacogenomic genotyping results were statistically significantly more likely to respond than control patients who were prescribed treatment as usual for 8 weeks. These results were obtained both for remaining patients after 27% loss to follow-up and for imputed data with the exception of the imputed QIDS-C16 score. As noted for the CNSDose assay, pharmacogenomic panel tests are not generalizable to other pharmacogenomic tests as the methods used to generate interpretations of the individual genetic variant results are not known.

Hall-Flavin et al. (2012) also used the GeneSight assay and obtained statistically significant reductions in depression severity scores, but did not use a criterion to define response. Power analyses assumed only 20% to 25% reductions in scores. Lack of an accepted criterion for response renders the results less clinically interpretable. Rundell et al. (2011) also did not use usual criteria for defining response to treatment and further did not define the clinical relevance of measures used to compare response. Most comparisons were not statistically significant. In this retrospective study, any one or more of four different genes were required to have been genotyped, so pharmacogenomic comparisons between patient groups were likely not equivalent. While Winner et al. reported the results of an RCT with a well-
defined response to treatment, the study was underpowered and results favoring improved response of genotyped patients were not statistically significant.

**Outcome: Adherence, Tolerance, Adverse Events; Hospital Stay**

Only Singh (2015) reported on tolerance of medications in an RCT, finding that non-genotyped control patients were less tolerant of medications, statistically significantly more often requiring dose reduction or cessation (OR=1.13; 95% CI, 1.01-1.25; P=0.0272). In addition, genotyped patients took sick leave less often (4% versus 15%; P=0.0272) and took leave times of shorter duration when needed compared with non-genotyped patients (4.3 versus 7.7 days; P=0.014).

Breitenstein et al. (2014), in a poor-quality retrospective comparative study, reported that patients who were prescribed dose increases for genotype-appropriate antidepressants had shorter hospital stays (P=0.009). Moreover, hospital stays for patients with an unfavorable ABCB1 genotype were reduced by an average of 4.7 weeks if the antidepressant dose was increased by more than 1.5-fold.

While favoring pharmacogenomic genotyping, the evidence supporting pharmacogenomic impact on outcomes related to adverse events and to duration of hospital stay is of very low quality, limited to 1 trial each, and, as such, is insufficient for forming conclusions.

**Pharmacogenomic Studies of Treatment of Any Psychiatric Disorder**

Two retrospective comparative studies of poor quality (overall, very-low-quality body of evidence) enrolled patients diagnosed with any psychiatric disorder. In 1 study, patients had failed a previous treatment regimen due to lack of efficacy and/or poor tolerability (Espadaler et al., 2016). Primary diagnoses were major depression, psychotic disorder, and bipolar disorder. In another study (Fagerness et al., 2014), primary diagnoses were ADHD, anxiety disorder, depression, and mood disorder. In both studies, one group was selected because attending physicians had ordered pharmacogenomic testing. Similar control groups were selected from the same source of patients. Fagerness et al. (2014) used propensity score matching to choose an equivalent control group.

One study reported on response to treatment outcomes using a large commercial pharmacogenomic assay panel (Neuropharmagen) developed in Spain and not available in the United States (Espadaler et al., 2016). Espadaler et al. reported that at 3 months, 93% of genotyped patients versus 82% of control patients treated as usual had Clinical Global Impression of Severity (CGI-S) scores statistically significantly lower than baseline, a common global measure of response (adjusted OR=3.86; 95% CI, 1.36-10.95; P=0.011).

Espadaler et al. (2014) and Fagerness et al. (2014), using a pharmacogenomic panel assay developed and available in the United States (Genecept Assay), reported outcomes related to adverse events. The Genecept Assay determines genotypes of several gene variants, reports on those individual gene variants and their therapeutic implications, and provides a drug interaction summary categorizing medications as “use as directed,” “therapeutic options,” or “use with caution,” based on the patient overall genotype. The method for this categorization is not provided. Espadaler et al. noted only that
equal numbers of adverse events were reported in each group. Fagerness et al. found that genotyped patients showed an average increase in drug treatment adherence of 6.3% compared with 0.3% in patients treated as usual ($P=0.0016$).

**Pharmacogenomic Studies of Treatment of Alcohol Use Disorder**

Oslin et al. (2015) was a prospective observational study conducted within an RCT of fair quality. The asn40asp variant of the OPRM1 gene had been identified in prior work as modifying the response to naltrexone in the treatment of alcohol use disorder, with asp40 predicted to improve response. While genotyping information was not used to modify treatment in this study, fixed-dose naltrexone and placebo groups were stratified by asn40 and asp40 variant category to determine impact on treatment. With regard to treatment response, the naltrexone-asp40 group was more likely to drink heavily (OR=1.10; 95% CI, 0.52-2.31; $P=0.80$) than the naltrexone-asn40 group (OR=0.69; 95% CI, 0.41-1.18; $P=0.17$), a result opposite to that expected, although not statistically significant. While serious and severe adverse events were infrequent and unrelated to group assignment, adherence (at least 80% of 12 weeks of treatment days) was worse for the naltrexone-asp40 group than for all others.

The authors of this study suggested that it was unlikely the OPRM1 asn40asp variant significantly modulates naltrexone treatment. Thus, very-low-quality evidence from 1 fair-quality study is insufficient evidence to draw conclusions.

**Overall Summary of Key Question #1 Evidence**

A systematic search for the best available evidence uncovered just 9 studies that met inclusion criteria for Key Question 1, and that did not address all indications of interest for this report. In some cases, populations were limited by race and ethnicity, which reduces potential genotype confounders but also reduces generalizability of results. Four studies were rated fair quality, 4 poor quality, and 1 very poor quality. Only the fair-quality studies were prospectively designed. Of these, 1 RCT (Winner et al., 2013) was seriously under-powered, as evidenced by a power analysis, which concluded that 92 to 115 patients were needed in each trial arm whereas 25 and 26 were enrolled. Therefore, all results had no statistical significance. One reasonably well-designed RCT (Singh, 2015), with statistically significant treatment response and remission results supporting pharmacogenomic testing for patients with major depressive disorder, used a commercial interpretive panel assay that is not available in the United States. As noted, pharmacogenomic panel tests are not generalizable to other pharmacogenomic tests, as the methods used to generate clinical interpretations and treatment recommendations from the individual genetic variant results are not known.

Two prospective controlled (nonrandomized) trials (Hall-Flavin et al., 2012; Hall-Flavin et al., 2013) conducted using the same U.S.-based commercial interpretive pharmacogenomic panel both reported statistically significant remission and/or response to treatment results. Only one of these (Hall-Flavin et al., 2013) appropriately defined clinical measures of remission and response but lacked some consistency of results between those calculated from remaining patients (27% lost to follow-up) and those calculated using imputed data. Among poor-quality studies, all were retrospective, some did not
define the clinical relevance of treatment response measures, or may have lacked equivalency of comparison groups. For the 2 studies that enrolled patients with any psychiatric disorder and the pharmacogenomic assays used in these studies, patient numbers were too few, study quality poor, and results too sparse for conclusions regarding the impact of pharmacogenomic testing on treatment response or adverse event–related outcomes. The authors of the single study on pharmacogenomic variant testing to improve response to naltrexone for alcohol use disorder concluded that the variant in question likely did not moderate the response.

In summary, the evidence base for pharmacogenomic testing for the psychiatric disorders of interest for this report is extremely limited and compromised and is considered to be of low to very low quality, depending on the outcome measured. As such, the evidence is insufficient for forming conclusions regarding clinical use.

**Key Question #2: What direct harms are associated with conducting genetic testing when it is used to inform the selection or dose of medications?**

No studies were found that address the direct harms of pharmacogenomic testing. DNA may be collected from a whole blood sample, which involves an invasive procedure, or for some tests, it may be collected from a cheek swab or from saliva, which is noninvasive.

**Key Question #3: Compared with usual care/no genetic testing, do decision-making, patient outcomes, or harms following genetic testing to inform the selection or dose of medications vary by:**

- **Clinical history (e.g., prior treatments, whether the diagnosis is initial or recurrent, duration of diagnosis, severity of illness, or concurrent medications); or**
- **Patient characteristics (e.g., such as age, sex, or comorbidities)?**

All 9 included studies were reviewed for presentation of results by clinical history or patient characteristic parameters. Study details are presented in APPENDIX Vb.

Two studies were RCTs (Winner et al., 2013; Singh, 2015) and a third was conducted within an RCT (Oslin et al., 2015). Two retrospective comparative studies matched control patients according to age, sex, and varying clinical history parameters to pharmacogenomically tested patients (Breitenstein et al., 2014; Fagerness et al., 2014). Two prospective controlled trials selected 2 consecutive groups from the same population (Hall-Flavin et al., 2012; Hall-Flavin et al., 2013). A third retrospective comparative study drew 2 groups from the same population but did not actively match (Espadaler et al., 2016). One retrospective comparative study selected pharmacogenomically tested versus untested patients (Rundell et al., 2011).

All studies compared pharmacogenomically tested groups with control groups at baseline and 8 of 9 studies found few statistically significant differences. The exception is Rundell et al. (2011), a very-poor-quality study that retrospectively enrolled patients who did and did not have pharmacogenomic testing.
ordered. Tested patients had greater degrees of psychiatric predisposition and depression severity at baseline as evidenced by differences in several related variables. After adjustment for these clinical history variables, no significant differences for the PHQ-9 depression severity scores were found among genotypes. Outcomes for specific subgroups were not reported.

Espadaler et al. (2016), in a poor-quality retrospective comparative study, compared pharmacogenomically tested versus untested groups using multivariate logistic regression and found that neither clinical history variables nor patient characteristic variables were statistically significant predictors of the response to medication as measured by the QIDS-C16.

No other studies adjusted for or reported results of subgroup analyses according to clinical history or patient characteristic variables. Taken together, the evidence is of very low quality for detecting subgroups and therefore insufficient for forming conclusions.

**Key Question #4: What are the costs and cost-effectiveness of genetic testing to guide the selection or dose of medications?**

The literature search identified 7 economics assessments that compared the cost of pharmacogenomic testing versus usual care for psychiatric conditions. The results of 3 cost-comparison studies suggest that employment of pharmacogenomic testing is associated with reduced total costs for healthcare. Medication costs in tested patients were greater than non-tested patients in 1 study and less in another study. Two studies reported that medication adherence was higher in patients who were tested versus those who were not tested. Of the 2 cost-effectiveness studies, 1 reported that pharmacogenomics testing was not cost-effective and the other found that it was moderately cost-effective. One additional study found that patients were willing to pay for pharmacogenomic testing if it reduced the number of medication trials or the amount of time for correct dosing to be achieved. The studies are summarized in the following paragraphs.

NOTE: For the following currency conversions, the CCEMG-EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values was used on September 28, 2016, with the specified price year and 2016 as the target price year: CCEMG-EPPI-Centre Cost Converter (last updated on April 29, 2016) (Shemilt et al., 2010). These conversions represent an approximate translation of the procedural cost and/or product price values to current U.S. values. These conversions do NOT provide an estimate of the current cost and do not directly reflect the U.S. healthcare system.

**Cost-Comparison Studies**

*Winner et al. (2015)* – Pharmacy benefits provider database (September 2011 to December 2013) used to select patients prescribed psychiatric medication in multiple U.S. practice settings; pharmacogenomic testing (n=1662) versus propensity-matched controls (n=10,880), mixed psychiatric diagnoses, 1-year total medication costs, currency reference year was not reported:
The average medication costs per member per year increased by $1725 in the standard care control group versus $690 in the pharmacogenomic testing group from the pretest period to the study end, resulting in a cost savings of $1035 for the tested group ($P<0.0001). The proportion of days covered ratio indicated that the medication adherence rate increased by 0.11 in the tested group and decreased by 0.01 in the standard care group, resulting in a net improvement of 0.123 in the tested group ($P<0.0001). Of the patients in the tested group, 78% received medications that were congruent with the test results and 22% received incongruent medications. Treatment with medications that were congruent with pharmacogenomics testing outcomes was associated with a net annual cost savings of $2775 versus treatment with incongruent medications ($P<0.0001). When analyzed by psychiatric diagnosis, treatment with congruent medications was associated with net annual cost savings of $6875 in patients with anxiety disorder ($P<0.0001), $3580 in patients with depressive disorder ($P<0.007), and $4795 in patients with bipolar disorder ($P=0.14) compared with treatment with incongruent medications.

Fagerness et al. (2014) – U.S.-based medical and pharmacy claims database (September 2010 to September 2012), pharmacogenomic testing (n=111) versus propensity-matched controls (n=222), mixed psychiatric diagnoses, medication and outpatient medical visit costs, currency reference year was not reported:

The average medication costs per patient increased by $886 (14.2%) in the pharmacogenomic testing group versus $222 (5.5%) in the standard care control group from the pretest period to 4 months posttest, resulting in a $664 lesser cost for the control group ($P<0.108). The average increase in medication adherence was 6.3% in the test group versus 0.3% in the control group, resulting in a statistically significant difference in adherence favoring the test group (6%; $P=0.001). Outpatient private practitioner visits declined by an average of 1.2 and 0.1 visits from the pretest to posttest period in the test group and control group, respectively. Private practitioner costs were reduced by $425 (~26.8%) per patient in the test group and increased by $537 (63.4%) in the control group ($P=0.105). Overall, total costs increased by 5.9% in the test group and 15.4% in the control group. The relative cost savings for patients who received pharmacogenomics testing was $562 (9.5%) per patient versus the control patients.

Herbild et al. (2013) – Danish patient registers, pharmacogenomic testing (n=103) versus standard care controls (n=104), schizophrenia, total healthcare costs (medications, primary care services, hospital services, and psychiatric services), currency reference year 2010:

Mean total costs for 1 year were DKK 131,141 (USD 18,440 in 2016) in the test group (range, DKK 1702 to 1,189,742 [USD 239 to 167,295 in 2016]) and DKK 153,536 (USD 21,589 in 2016) in the control group (range, DKK 12,032 to 1,052,956 [USD 1691 to 148,061 in 2016]). Both means were affected by a few patients with very high healthcare costs—median costs were DKK 86,388 (USD 12,147 in 2016) for the test group and DKK 105,392 (USD 14,819 in 2016) for controls. Mean psychiatric costs for 1 year were DKK 100,433 (USD 14,122 in 2016) in the test group (range DKK 1642 to 1,189,742 [USD 230 to 167,295 in 2016]) and DKK 121,648 (USD 17,105 in 2016) in the control group (range DKK 1642 to 1,030,560 [USD 230 to 144,912 in 2016]). Psychiatric care means were also affected by a few patients with very high
psychiatric costs—median costs were DKK 47,618 (USD 6695 in 2016) for the test group and DKK 76,348 (USD 10,735 in 2016) in the control group. Mean medication costs for 1 year were DKK 21,709 (USD 3052 in 2016) in the test group and DKK 22,544 (USD 3170 in 2016) in the control group. Incorporating the data into various models of total medical care and psychiatric care, which stratified patients based on metabolizer genotype, suggested that pharmacogenomics testing significantly reduced healthcare costs among patients who were classified as extreme metabolizers (either poor or ultrarapid metabolizers).

NOTE: Costs were converted from the value of the Danish krone in 2010 to USD 2016.

*Rundell et al. (2011)* – Mayo Clinic database (January 2006 to June 2010), pharmacogenomic testing (n=45) versus standard care controls (n=47), depression, total healthcare costs, currency reference year 2010:

The mean healthcare costs from the pretest period to posttest period were $5010 in the pharmacogenomics test group and $6693 in the control group (P=0.08). The difference between groups was statistically significant after adjusting for diagnosis of major depressive disorder (P=0.049) and the numbers of psychotropic drug trials (P=0.02) but not after adjusting for baseline depression severity, family history of mood disorder, or practice setting (all analyses, P>0.07).

**Cost-Effectiveness Studies**

*Perlis et al. (2009)* – Data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, pharmacogenomics testing either before first-line treatment (test first) or after first-line treatment failure (test second) versus no testing (control), depression, direct costs (outpatient treatment, hospitalization, and antidepressant medications), currency reference year 2006:

Cost-effectiveness analyses were performed using state-transition probability models incorporating probabilities from the STAR*D study. Costs and quality-adjusted life-years (QALY) were compared for sequential trials of antidepressants with or without guidance from a pharmacogenomics test. The base case was a 40-year-old with major depressive disorder. Compared with treating all patients with a selective serotonin reuptake inhibitor as first- or second-line therapy, testing patients first and assigning bupropion to those testing negative increased costs by $505.50 per patient but provided an additional 0.0054 QALY to yield an incremental cost-effectiveness ratio (ICER) of $93,520 per QALY. Based on the commonly used threshold of $50,000 per QALY, pharmacogenomics testing would not be cost-effective. In one-way sensitivity analyses to examine the impact of individual model parameters, the ICER for testing was in the $80,000 to $100,000 range. Test cost, which ranged from $100 to $1000, had a large effect on cost-effectiveness. When the response risk ratio was varied over its 95% confidence interval, the ICER decreased from $218,000 to $59,000 per QALY.

*Olgiati et al. (2012)* – Hypothetical cohort of white adults modeled from the STAR*D study, pharmacogenomics testing versus no testing in high-income Western European countries, depression, direct costs, currency (international dollars [Intl]) reference year 2009:
Cost-effectiveness analyses were performed using state-transition probability models. Costs for outpatient and inpatient care were obtained from World Health Organization data. The incremental benefit of the pharmacogenomic approach is 0.062 quality-adjusted life-weeks (QALW) for clinical response plus 0.016 QALWs for side effect burden. Assuming that patients will have 2 recurrent episodes, the overall incremental benefit of pharmacogenomic testing is 0.156 QALWs. The estimated overall cost of healthcare was Intl $2242 with pharmacogenomics testing and Intl $2063 without testing. The incremental cost of pharmacogenomic testing was Intl $179 and the ICER was Intl $1147. Multivariate sensitivity analyses were performed using estimated ICER values ranging from Intl $638 to Intl $1738 (representing the 10th to 90th percentiles). Cost-effectiveness acceptability curves revealed that the probability of having an ICER value below the Intl $1926 cost-effectiveness threshold suggested by the World Health Organization was 90%, suggesting that pharmacogenomics testing was moderately cost-effective.

**Cost-Utility Study**

*Herbild et al. (2009)* – Web-based discrete choice questionnaire of Danes (n=323), pharmacogenomics testing versus no testing, depression, willingness to pay for pharmacogenomics testing, currency reference date was not reported:

A fractional factorial experimental design was employed to assess the willingness of Danish people to pay for pharmacogenomic testing upon diagnosis of depression. The questionnaire was based on expert opinion, literature review, and focus group interviews. Conditional logistic regression analyses determined that the coefficient on the price attribute was negative, indicating decreasing utility as the cost of the test increases. The coefficients of the effect attributes were positive, indicating that utility increases with decreases in the number of changes in medications or reduced times for dosage adjustments. The willingness-to-pay estimate for a 10% probability of a reduction of 1 in the number of antidepressant changes was DKK 1571 (USD 229 in 2016) and for the reduction of 1 month in the time for dosage adjustments was DKK 604 (USD 88 in 2016). The pharmacogenomics test price was DKK 1630 (USD 237 in 2016); therefore, the willingness to pay exceeds the cost of the test.

NOTE: Costs were converted from the value of the Danish krone in 2008 to USD 2016.

**Summary of Economic Studies**

The economic evidence base includes studies of different designs and study populations, each incorporating different pharmacogenomic tests that were compared with no-test treatment regimens. Results in some cases suggested cost-effectiveness but lacked consistency overall. Cost analyses were limited by the available evidence base and the applicability of the evidence selected to create the various models for economic analyses. There were indications that results may depend at least partly on test cost and on the effect size of the clinical validity evidence supporting the pharmacogenomic test. In a survey of non-patients, the utility of testing increases with decreases in the number of changes in medications or reduced times for dosage adjustments.
Practice Guidelines

The search of the core sources and relevant specialty groups identified 12 guidelines that mention pharmacogenomic testing and published within the past 10 years. The general recommendations provided by the guidelines are summarized in Table 4 of the Evidence Summary and are presented in detail in APPENDIX VIa.

Most guidelines made no formal recommendations for use of pharmacogenomic testing. Those that mentioned pharmacogenomic testing indicate a need for future research to help determine the optimal choice of pharmacotherapy based on the gene or genes involved in the etiology of treatment responsiveness. Pharmacogenomic testing may help guide identification of particular patient populations that will benefit from specific therapeutic options. In addition, some guidelines suggest that pharmacogenomic testing in combination with therapeutic drug monitoring may be beneficial in certain circumstances.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health’s Pharmacogenomics Research Network and the Pharmacogenomics Knowledge Base is to provide peer-reviewed, evidence-based, accessible guidelines for gene-drug associations in order to facilitate the translation of pharmacogenomic knowledge from bench to bedside. CPIC guidelines include dosing recommendations for tricyclic antidepressants and selective serotonin reuptake inhibitors based on CYP2D6 and CYP2D6 gene phenotypes (e.g., ultrarapid metabolizer, extensive metabolizer, intermediate metabolizer, or poor metabolizer). However, these guidelines state that recommendations are based on clinical validity evidence, most of which relies on drug plasma concentration outcomes and includes case reports and pharmacokinetic studies of healthy individuals. No evidence is presented linking plasma concentration to clinical outcomes in these guidelines.

We also searched a number of other guidelines from authoritative organizations that are listed in APPENDIX VIb. None of these guidelines made any reference to pharmacogenomic testing.

Selected Payer Policies

Centers for Medicare & Medicaid Services (CMS)

The keywords genetic or genomic or antidepressant or antipsychotic were used to search for CMS National Coverage Determination (NCD) or, in the absence of an NCD, Local Coverage Determination (LCD) documents on pharmacogenomic testing for the psychiatric conditions of interest or for relevant genes/gene variants. No CMS NCD for pharmacogenetics or pharmacogenomic testing was identified on September 23, 2016 at: CMS Advanced Search Database.

An LCD for CYP2C19, CYP2D6, CYP2C9 and VKORC1 genetic testing (L36312), effective July 8, 2016, was issued by Noridian Healthcare Solutions LLC, a Medicare contractor in the state of Washington. The LCD states:

- Genetic testing for the CYP2C19 gene is considered investigational for:
  - Amitriptyline
• Selective serotonin reuptake inhibitors.
  
  Genetic testing of the CYP2D6 gene is considered medically necessary to guide medical treatment and/or dosing for individuals for whom initial therapy is planned with Amitriptyline or Nortriptyline for treatment of depressive disorders.

There is insufficient evidence to demonstrate that genetic testing for the CYP2D6 gene improves clinical outcomes. Consequently, genetic testing for the CYP2D6 gene is considered investigational including but not limited to the following medications:

  o Antidepressants other than those listed above
  o Antipsychotics
  o Codeine
  o Donepezil
  o Galantamine

• Genetic testing for the CYP2C9 gene is considered investigational as there is currently no proven clinical utility related to any medication (except warfarin).

• Genetic testing for the VKORC1 gene is considered investigational for all medications (except warfarin).

An LCD on MolDX: GeneSight Assay for Refractory Depression (L36324), effective October 1, 2015, was issued by Noridian Healthcare Solutions LLC, a Medicare contractor in the state of Washington. It states: “This LCD provides limited coverage for the GeneSight Psychotropic (AssureRx Health Inc.) gene panel. GeneSight testing may only be ordered by licensed psychiatrists or neuropsychiatrists contemplating an alteration in neuropsychiatric medication for patients diagnosed with major depressive disorder (MDD) who are suffering with refractory moderate to severe depression after at least 1 prior neuropsychiatric medication failure.”

An LCD on MolDX: HLA-B*15:02 Genetic Testing (L36149), effective April 1, 2016, was issued by Noridian Healthcare Solutions LLC. The policy provides limited coverage for HLA-B*15:02 genotype testing for patients of Asian and Oceanian ancestry when initial treatment with carbamazepine is planned.

The following private payer sites were searched using keywords pharmacogenetics or pharmacogenomic or antidepressant or depression or antipsychotic during the time frame of September 13 through September 23, 2016.

Aetna

Aetna considers CYP2D6 genotyping experimental and investigational for identifying individuals with Alzheimer disease with different clinical response to donepezil (Aricept) because its clinical value has not been established.

Aetna considers genotyping for other cytochrome P450 (CYP450) polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system, including opioid analgesics, antipsychotic medications, and SSRIs) experimental and investigational because the clinical value of this type of genetic testing has not been established.
Aetna considers genotyping for HLA-B*15:02 medically necessary for persons of Asian ancestry before commencing treatment with carbamazepine (Tegretol).

Aetna considers genotyping for methylenetetrahydrofolate reductase (MTHFR) for guiding antidepressant therapy experimental and investigational because its clinical value has not been established.

Aetna considers GeneSightRx testing for the management of individuals treated with antidepressant and/or antipsychotic medications experimental and investigational because its clinical value has not been established.

Aetna considers the Genecept Assay (Genomind) experimental and investigational for managing psychiatric conditions.


**GroupHealth**


GHC considers genetic testing panels medically necessary when the results are expected to directly affect treatment, management, surveillance, or reproductive decisions and when all genes or genetic variants included in the panel have high-quality, evidence-based guidelines established to direct clinical management based on results.

Testing for individual components of a panel may be medically necessary in some clinical situations. Separate clinical criteria for these components may apply.

GHC considers the following genetic panels not medically necessary:

- Genecept Assay for Psychotropic Treatment
- GeneSight ADHD
- GeneSight Psychotropic test
- Proove Pharmacogenetic Panels:
  - Drug Metabolism
  - Opioid Response
- YouScript Personalized Prescribing System

The current scientific evidence is not yet sufficient to establish how test results from all components of these panels should be used to direct treatment decisions. There is also insufficient evidence to establish that use of these genetic panels to guide treatment decisions results in improved patient health outcomes. See Genetic Panels using Next Generation Sequencing (Clinical Review Criteria).
The GHC policy on pharmacogenomic/pharmacological testing refers to MCG guidelines for the following genetic testing coverage criteria:

- Carbamazepine Pharmacogenetics – *HLA-B*15:02 Allele
- Psychotropic Medication Pharmacogenetic Testing
- Selective Serotonin Reuptake Inhibitors (SSRIs) – Cytochrome P450 Polymorphism Testing (only covers CYP2D6 and CYP2C19)

See Pharmacogenomic/Pharmacological Testing for Predicting Response of Chemotherapeutic Agents (Clinical Review Criteria).

**Oregon Health Evidence Review Commission (HERC)**

No coverage guidance for pharmacogenomics or pharmacogenetics was identified on the Oregon HERC website (Oregon HERC Coverage Guidances). However, the website indicates that a new coverage guidance will be developed to address “Genetic Tests for Selection of Antidepressant Therapy,” based on HERC and Oregon Health Authority priorities and subject to available resources.

**Regence**

Regence Group considers the identified genetic panels investigational because the evidence base is insufficient to demonstrate how comprehensive test results from all genes and/or gene mutations included in the panels listed below may be used to manage treatment decisions and improve net health outcomes. The panels listed below are identified in the policy, Evaluating the Utility of Genetic Panels (Regence Group Medical Policy No. 64):

- Empowering Personalized Medicine (EPM) Panel
- Genecept Assay for Psychotropic Treatment
- GeneSight ADHD, GeneSight Analgesic, GeneSight Psychotropic Genetic Testing
- Informed PGx ADHD, Informed PGx Depression, Informed PGx Psychotropic
- Mental Health DNA Insight
- Proove Drug Metabolism Panel, Opioid Response Panel
- STA²R SureGene Test for Antipsychotic and Antidepressant Response
- YouScript Personalized Prescribing System
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APPENDIX I. Meta-analyses of Clinical Validity – Schizophrenia

Systematic Reviews with Meta-analyses for Clinical Validity – Schizophrenia

Key: GWAS: genome-wide association studies; MA, meta-analyses; rs, reference SNP cluster—denotes base position within the human genome DNA sequence; SNP, single nucleotide polymorphism

<table>
<thead>
<tr>
<th>Indication Medication Type</th>
<th># MA</th>
<th>Gene (Polymorphism) Information Evaluated</th>
</tr>
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<tbody>
<tr>
<td>Schizophrenia Antipsychotics</td>
<td>8</td>
<td>CYP450 (2D6, 2C19, 1A2, 17, 3A4, 3A5), DRD2 (rs1799732), DRD3 (rs6280), DRD4, DRD3 (Ser9Gly), LEP (2548G/A); HTR2A (rs6313, rs6311, rs6314), HTR2C (rs6318), HTR3A (rs1062613), TNFa (rs1800629), 5-HTTLPR, GNB3, ADRA1A, ADRA2A, ADRB3, H2, DRD1, COMT, MnSOD, ANKK1, BDNF, CNR1, FTO, HTR6, INSIG2, LEPR, MC4R, MDR1, PPARG, SNAP25, GWAS SNPs</td>
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</table>

Meta-analyses for Clinical Validity – Schizophrenia

The most significant results are recorded from each meta-analysis for each gene-outcome association; however, not every result is statistically significant.

Key: AIMS, abnormal involuntary movement scale; Assn, association; BMI, body mass index; CLZ, clozapine; Del, deletion; Ins, insertion; MA, meta-analysis; mut, mutation; NR, not reported; NS, not significant; OR, odds ratio; pts, patients; rs, reference SNP cluster—denotes base position within the human genome DNA sequence; SAS score, Simpson-Angus Scale (for measuring drug-related extrapyramidal side effects); WMD, weighted mean difference; wt, wild type

<table>
<thead>
<tr>
<th>Gene(^1)-Outcome Assn</th>
<th>Author, Yr</th>
<th>Comparison</th>
<th># Studies in MA</th>
<th># Pts in MA</th>
<th>Effect Size (95% CI); (i^2)</th>
<th>P Value</th>
<th>Genotype Favored by Result</th>
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<tr>
<td>CYP2D6 genotype and tardive dyskinesia</td>
<td>Fleeman(^2) et al., 2010 and 2011</td>
<td>wt/mut vs wt/wt</td>
<td>4</td>
<td>282</td>
<td>OR (fixed) 2.08 (1.21, 3.57)</td>
<td>0.008</td>
<td>wt/wt</td>
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<td>Comparison</td>
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<td># Pts in MA</td>
<td>Effect Size (95% CI); $I^2$</td>
<td>$P$ Value</td>
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<tr>
<td>CYP2D6 genotype and SAS score</td>
<td>Fleeman et al., 2010 and 2011</td>
<td>mut/mut vs wt/wt</td>
<td>2</td>
<td>96</td>
<td>WMD (random) -0.41 (-1.84, 1.02); 74.9%</td>
<td>$P=0.58$</td>
<td>mut/mut</td>
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<td>CYP2D6 genotype and dystonia</td>
<td>Fleeman et al., 2010 and 2011</td>
<td>mut/mut+wt/mut vs wt/wt</td>
<td>2</td>
<td>195</td>
<td>OR (fixed) 0.83 (0.38, 1.81); 35.8%</td>
<td>$P=0.64$</td>
<td>mut/mut+wt/mut</td>
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<td>CYP2D6 genotype and akathisia</td>
<td>Fleeman et al., 2010 and 2011</td>
<td>mut/wt vs wt/wt/mut</td>
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<td>OR (random) 1.08 (0.05, 22.74); 63.6%</td>
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<td>CYP2D6 genotype and AIMS score</td>
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<td>WMD (fixed) 1.80 (0.40, 3.19); 0%</td>
<td>$P=0.01$</td>
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<tr>
<td>CYP2D6 genotype and dystonia</td>
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<td>mut/mut+wt/mut vs wt/wt</td>
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<td>OR (fixed) 1.64 (1.04, 2.58); 30.9%</td>
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<td>CYP1A2*1F genotype and tardive dyskinesia</td>
<td>Fleeman et al., 2010 and 2011</td>
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<td>OR (random) 1.05 (0.50, 2.2); 65.6%</td>
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<td>COMT (val158met) and tardive dyskinesia</td>
<td>Bakker et al., 2008</td>
<td>Heterozygote (Val-Met) vs Homozygote (Val-Val)</td>
<td>4</td>
<td>NR</td>
<td>OR (fixed) 0.63 (0.46, 0.86); 46.9%</td>
<td>$P=0.004$</td>
<td>Protective effect for Val-Met heterozygotes</td>
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<td>Taq1A in DRD2 and tardive dyskinesia</td>
<td>Bakker et al., 2008</td>
<td>A2 variant vs A1 variant (allelic model)</td>
<td>4</td>
<td>1528</td>
<td>OR (fixed) 1.30 (1.03, 1.65); 0.0%</td>
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<td>Risk increasing effect for A2 variant</td>
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<td>MnSOD Ala-9Val and tardive dyskinesia</td>
<td>Bakker et al., 2008</td>
<td>Ala-Val heterozygotes vs Ala-Ala homozygotes</td>
<td>4</td>
<td>680</td>
<td>OR (fixed) 0.37 (0.17, 0.79); 0.0%</td>
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<td>Protective effect for Ala-Val heterozygotes</td>
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<td>DRD1 (rs4532) and antipsychotic response</td>
<td>de Matos et al., 2015</td>
<td>G vs A (allelic model)</td>
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<td>1300</td>
<td>OR (fixed) 1.17 (0.90, 1.52); 51%</td>
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<td>DRD1 (rs4532) and CLZ response</td>
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<td>AA vs G-allele</td>
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<td>OR (fixed) 0.79 (0.51, 1.23); 55%</td>
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<td>DRD2 –141C Ins/Del (rs1799732) and CLZ response</td>
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<td>Del carriers vs Ins/Ins (All)</td>
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<td>OR 0.96 (0.48, 1.94); 60%</td>
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<td>Del Carrier vs Ins/Ins Genotype</td>
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<td>OR (fixed) 0.65 (0.43, 0.97); 46%</td>
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<td>Ins/Ins</td>
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<td>DRD2 –141C Ins/Del (rs1799732) and weight gain</td>
<td>Zhang et al., 2016</td>
<td>Del/Del vs Ins</td>
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<td>247</td>
<td><strong>BMI or weight change &gt;7% or 10%:</strong> OR (0.65, 5.76); 0%</td>
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<td>DRD3 Ser9Gly allele (rs6280) and CLZ response</td>
<td>Hwang et al., 2010</td>
<td>Ser vs Gly (allelic model)</td>
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<td>Gressier et al., 2016</td>
<td>Ser vs Gly (allelic model)</td>
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<td>P Value</td>
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<td>HTR2A (rs6311) and CLZ response</td>
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<td>GG vs A carriers</td>
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<td>HTR2A (rs6313) and CLZ response</td>
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<td>P=0.02</td>
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<td>HTR2A (rs6313, SNP 102T/C) and weight gain</td>
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<td>CC vs T carriers</td>
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<td>HTR2A (rs6314) and CLZ response</td>
<td>Gressier et al., 2016</td>
<td>C allele vs T allele (All)</td>
<td>5</td>
<td>671</td>
<td>OR (random) 1.75 (1.20, 2.56); 0%</td>
<td>P=0.004</td>
<td>Favors C allele carrier as responder</td>
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<td>HTR2A (rs6314, SNP His452Tyr) and weight gain</td>
<td>Zhang et al., 2016</td>
<td>Tyr/Tyr vs His</td>
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<td>246</td>
<td><strong>BMI or weight change &gt;7% or 10%:</strong> OR 1.62 (0.23, 11.38); 32%</td>
<td>P=0.63</td>
<td>His</td>
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<td>HTR2C (rs6318) and CLZ response</td>
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<td>C(+) vs C(-) (All)</td>
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<td>OR 1.74 (0.86, 3.53); 48%</td>
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<td><strong>BMI or weight change &gt;7% or 10%:</strong> OR 1.47 (1.03, 2.11); 0%</td>
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<td>HTR2C (rs3813929, 759C/T) and weight gain</td>
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<td>CC vs T</td>
<td>18</td>
<td>1738</td>
<td><strong>BMI or weight change &gt;7% or 10%:</strong> OR 1.96 (1.19, 3.22); 67%</td>
<td>P=0.009</td>
<td>T carriers favored to avoid weight gain</td>
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<td>HTR3A (rs1062613) and CLZ response</td>
<td>Gressier et al., 2016</td>
<td>C allele vs T allele</td>
<td>4</td>
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<td>OR 0.47 (0.24, 0.93); 50%</td>
<td>P=0.03</td>
<td>T allele carriers favored as responders</td>
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<td>LEP (rs7799039, 2548G/A) and weight gain</td>
<td>Shen et al., 2014</td>
<td>Recessive genetic model: AA vs GA+GG (All)</td>
<td>7</td>
<td>1019</td>
<td>OR (fixed) 1.25 (0.96, 1.64); NR</td>
<td>P=0.103</td>
<td>GA+GG carriers favored to avoid weight gain</td>
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<td>Recessive genetic model: AA vs GA+GG (Asian)</td>
<td>4</td>
<td>563</td>
<td>OR (fixed) 1.62 (1.15-2.26); NR</td>
<td>P=0.005</td>
<td>G allele favored to avoid weight gain</td>
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<td>Recessive genetic model: AA vs GA+GG (European)</td>
<td>3</td>
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<td>OR (fixed) 0.78 (0.49, 1.24); NR</td>
<td>P=0.296</td>
<td>AA carriers favored to avoid weight gain</td>
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<td>Zhang et al., 2016</td>
<td>GG vs A</td>
<td>3</td>
<td>340</td>
<td><strong>BMI or weight change &gt;7%</strong></td>
<td>P=0.43</td>
<td>A carriers favored to</td>
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<tr>
<td>Gene - Outcome Assn</td>
<td>Author, Yr</td>
<td>Comparison</td>
<td># Studies in MA</td>
<td># Pts in MA</td>
<td>Effect Size (95% CI); $^2$</td>
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<td><strong>MTHFR (rs1801131, 1298A/C) and weight gain</strong></td>
<td>Zhang et al., 2016</td>
<td>AA vs C</td>
<td>3</td>
<td>359</td>
<td><strong>BMI or weight change &gt;7%</strong> or 10%; OR 0.73 (0.33, 1.60); 5%</td>
<td>$P=0.19$</td>
<td>C carriers favored to avoid weight gain</td>
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<tr>
<td><strong>MTHFR (rs1801133, 677C/T) and weight gain</strong></td>
<td>Zhang et al., 2016</td>
<td>TT vs C</td>
<td>3</td>
<td>357</td>
<td><strong>BMI or weight change &gt;7%</strong> or 10%; OR 1.36 (0.86, 2.15); 0%</td>
<td>$P=0.74$</td>
<td>C carriers favored to avoid weight gain</td>
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<td><strong>Taq1A (rs1800497) polymorphism and antipsychotic drug response</strong></td>
<td>Zhang et al., 2010</td>
<td>A1/A1 genotype vs A2 allele carriers</td>
<td>7</td>
<td>CND</td>
<td>OR (fixed) 1.39 (0.91, 2.13); 42%</td>
<td>$P=0.13$</td>
<td>A1/A1 carriers favored as responders</td>
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<td><strong>TNFa (rs1800629) and CLZ response</strong></td>
<td>Gressier et al., 2016</td>
<td>A carriers vs GG</td>
<td>3</td>
<td>334</td>
<td>OR 0.75 (0.44, 1.27); 0%</td>
<td>$P=0.28$</td>
<td>GG carriers favored as responders</td>
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<td><strong>TNFa (rs1800629, SNP G-308A) and weight gain</strong></td>
<td>Zhang, et al., 2016</td>
<td>AA vs G</td>
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<td>500</td>
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<td>$P=0.34$</td>
<td>G carriers favored to avoid weight gain</td>
</tr>
</tbody>
</table>

1Where gene polymorphism is not specified, various polymorphisms are evaluated together.

2Patients with 2 wild-type (wt) functional alleles are considered extensive metabolizers (EM). Because few studies separately classify ultrarapid metabolizers (UM; more than 2 functional alleles), they are also classified as wt/wt. Sensitivity analysis of only prospective studies was chosen to show greatest effect size for this association.
APPENDIX II. Search Strategy

INITIAL SEARCH, SYSTEMATIC REVIEWS AND PRACTICE GUIDELINES (conducted August 16, 2016)

Initially, evidence for this report was obtained by searching for systematic reviews, meta-analyses, practice guidelines, and economic evaluations that had been published in the past 10 years. Searches were conducted in the following databases using the terms rhinosinusitis or sinusitis: Agency for Healthcare Research and Quality (AHRQ), Blue Cross Blue Shield Center for Clinical Effectiveness (CCE) Assessments, Canadian Agency for Drugs and Technology in Health (CADTH), Centre for Reviews and Dissemination (CRD) (York University), Hayes Knowledge Center, Institute for Clinical Systems Improvement (ICSI), National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (UK), National Guidelines Clearinghouse (NGC), National Institute for Health and Care Excellence (NICE), and Veterans Health Administration/Department of Defense Clinical Practice Guidelines. (NOTE: The CRD search strategy includes a search for Cochrane Reviews.)

The websites for the American Psychiatric Association, The American Academy of Child and Adolescent Psychiatry, the American College of Neuropsychopharmacology (no guidelines), and the World Psychiatric Association were also searched.

Additional systematic reviews were sought from a search of the PubMed database using filters for Practice Guidelines, Guidelines, Meta-Analyses, and Systematic Reviews, according to this search:

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SEARCH FOR PRIMARY CLINICAL STUDIES AND ECONOMIC EVALUATIONS

Since no systematic reviews were identified that addressed the Key Questions for this report, the main literature search was designed to identify all primary studies of pharmacogenomic testing that addressed the relevant indications and assessed clinical utility.
### PubMed search on August 15, 2016

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<td>Limit: Humans</td>
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**Update Searches**

Update searches will be conducted before publication of the Final Report.
APPENDIX III. Overview of Evidence Quality Assessment Methods

Clinical Studies

Tools used include internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, a checklist for judging the adequacy of systematic reviews used instead of de novo analysis, and Hayes Evidence-Grading Guides for evaluating bodies of evidence for different types of technologies. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body.

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Individual study appraisal:</th>
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<tbody>
<tr>
<td>a. Initial rating according to study design</td>
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<tr>
<td><strong>Good:</strong> Randomized Controlled Trials</td>
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<td><strong>Fair:</strong> Nonrandomized Trial (controlled, parallel-group, quasi-randomized)</td>
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<tr>
<td><strong>Poor:</strong> Observational Comparative Studies (prospective or retrospective trials involving historical controls, pretest-posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group)</td>
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<tr>
<td><strong>Very Poor:</strong> Descriptive Uncontrolled Studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data])</td>
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<tr>
<td>b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist</td>
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<tr>
<td>c. Repeat for each study</td>
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</table>

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<thead>
<tr>
<th>Step 2</th>
<th>Evaluation of each body of evidence by outcome, key question, or application:</th>
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<tbody>
<tr>
<td>a. Initial quality designation according to best study design in a body of evidence</td>
<td></td>
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<tr>
<td>b. Downgrade/upgrade</td>
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<tr>
<td><strong>Downgrade factors:</strong> Study weaknesses (Quality Checklists), small quantity of evidence, lack of applicability, inconsistency of results, publication bias</td>
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<tr>
<td><strong>Possible upgrade factors:</strong> Strong association, dose-response effect, bias favoring no effect</td>
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<tr>
<td>c. Assign final rating: High-Moderate-Low-Very Low</td>
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<tr>
<td>d. Repeat for each outcome/question/application</td>
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</table>

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<thead>
<tr>
<th>Step 3</th>
<th>Evaluation of overall evidence:</th>
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<td>a. Rank outcomes by clinical importance</td>
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<tr>
<td>b. Consider overall quality of evidence for each critical outcome</td>
<td></td>
</tr>
<tr>
<td>c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low</td>
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</table>

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<tr>
<th>Step 4</th>
<th>Evidence-based conclusion:</th>
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<tbody>
<tr>
<td>Overall quality of evidence + Balance of benefits and harms</td>
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</tbody>
</table>

Practice Guidelines (checklist taken from AGREE Tool and approach to scoring used in this report)

Rank each item on a scale of 1-7.
Decide on overall quality (1 = lowest to 7 = highest), giving strongest weight to items 7-14 (Rigor of Development Domain) and items 22-23 (Editorial Independence).

For qualitative labels:
- Very poor = 1
- Poor = 2-3
- Fair = 4-5
- Good = 6-7

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

**Economic Evaluations**

A tool developed by Hayes for internal use guides interpretation and critical appraisal of economic evaluations. The tool includes a checklist of items addressing issues such as the reliability of effectiveness assumptions, transparency of reporting, quality of analysis, generalizability/applicability, and conflicts of interest. The following publications served as sources of best practice.


**Books**


**Other**

APPENDIX IV. Excluded Studies

The following 19 key studies were excluded during full-text review.

Noncomparative studies


Not studies of pharmacogenomic testing


[Medications adjusted for other reasons in addition to pharmacogenomic test results]


Limited to assessment of physician ordering practices


Review

Muller 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.

Case report


Erratum


Economic studies narrowly focused on a single drug


Economic study focused on non-psychiatric indications


Economic study concerned with impact of physician prescribing concentration


Economic study; superseded by Olgiati 2012 (included study)

### APPENDIX Va. Evidence Tables

#### APPENDIX Va. Studies Assessing the Impact of Pharmacogenomic Testing on Clinical Decision-Making (KQ1a) and Patient Outcomes (KQ1b)

**Key:** ADHD, attention deficit/hyperactivity disorder; CGI-S, Clinical Global Impression of Severity; Ctl, control arm; CYP450, cytochrome P450; Exp, experimental arm; HAM-D, Hamilton Depression Rating Scale (21 items unless otherwise specified); MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; NS, not statistically significant; OR, odds ratio; PGx, pharmacogenomic; PHQ-9, Patient Health Questionnaire (9 items); pt(s), patient(s); PTSD, posttraumatic stress disorder; QIDS-C16, Quick Inventory of Depressive Symptomatology-Clinician Rated (16 items); RCT, randomized controlled trial; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; tx, treatment

<table>
<thead>
<tr>
<th>Authors/Study Design/Protocol</th>
<th>Patients/Setting/Treatment</th>
<th>Main Findings</th>
<th>Quality/Comments</th>
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<tbody>
<tr>
<td><strong>Depressive Disorders</strong></td>
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<tr>
<td>Winner et al. (2013)</td>
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<tr>
<td>Prospective double-blind RCT</td>
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<tr>
<td><strong>Index test:</strong> GeneSight assay (genotypes CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A-T102C; includes proprietary interpretive report and recommendations in which 26 psychiatric medications were placed in the advisory categories of “use as directed,” “use with caution,” and “use with caution and with more frequent monitoring” based on known pharmacological profile and specific pt genotype) results provided immediately</td>
<td><strong>Reference standard:</strong> Same genotyping but results not</td>
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<tr>
<td><strong>Clinical Decision-making:</strong></td>
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<td></td>
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<tr>
<td><strong>Exp vs Ctl:</strong></td>
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<tr>
<td>100% of baseline medications that genotyping indicated should be used with caution and with more frequent monitoring were changed in the Exp group; only 50% of similarly classified medications were changed or dose adjusted in the Ctl group.</td>
<td></td>
<td></td>
<td>Fair Very small study, lacking in power to discriminate outcomes between tx arms.</td>
</tr>
<tr>
<td><strong>Pt Outcomes:</strong></td>
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</tr>
<tr>
<td><strong>Exp vs Ctl:</strong></td>
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<tr>
<td>36% of genotyped pts were responders (50% reduction in HAM-D17 at 10 weeks) vs 20.8% treated as usual: OR=2.14; 95% CI, 0.59-7.69; P=NS</td>
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<tr>
<td>20% of genotyped pts achieved remission (HAM-D17 ≤7) at 10 weeks vs 8.3% treated as usual: OR=2.75; 95% CI, 0.48-15.8; P=NS</td>
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<tr>
<td>Improvements in HAM-D17, PHQ-9, and QIDS-C16 scores favored the genotyped arm at 10 weeks but were not statistically significant.</td>
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<tr>
<td>Authors/Study Design/Protocol</td>
<td>Patients/Setting/Treatment</td>
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</table>
| **Singh et al. (2015)**     | **Exp:** 74 white pts with a principal diagnosis of MDD (HAM-D17 >18) randomized to pharmacogenomic genotyping  
**Ctl:** 74 pts similarly selected, randomized to tx as usual (DNA sample obtained for blinding but not analyzed)  
**General exclusions:** Pts with other active psychiatric diagnoses, those with a principal diagnosis of a personality disorder, pregnant or breastfeeding pts, or pts with hepatic or renal impairments. Pts co-prescribed known CYP2D6, CYP2C19, or ABCB1 inducers/inhibitors; smokers; those regularly drinking grapefruit juice.  
**Setting:** Not described  
**Pharmacologic tx:** Sertraline, Escitalopram, Paroxetine, Fluoxetine, Fluvoxamine, Reboxetine, Venlafaxine, Desvenlafaxine, Duloxetine, Mirtazapine, Agomelatine, Clomipramine, Nortriptyline, Amitriptyline  
**Previous tx:** Allowed  
**Maximum follow-up:** 12 weeks | **Clinical Decision-making:**  
**Exp:** 100% of treating prescribers reviewed the pharmacogenomic interpretive report. Prescribers indicated that in 65% of cases, pharmacogenomic results let to medication dosing different from usual practice.  
**Pt outcomes:**  
**Exp vs Ctl:** Genotyped pts were 2.52 times more likely to obtain remission (HAM-D17 <7) from MDD (95% CI, 1.71-3.73; P<0.0001) than the unguided group.  
Number needed to test for remission=3 (95% CI, 1.7-3.5).  
Non-genotyped pts were 1.13 times more likely to have medication tolerability problems (95% CI, 1.01-1.25; P=0.0272) requiring either dose reduction or cessation.  
Genotyped pts had significantly less risk of taking sick leave (4% vs 15%; P=0.0272) and significantly less duration of sick leave when needed (4.3 vs 7.7 days; P=0.014). | Fair  
Randomized, appropriately blinded trial with relevant outcomes but small sample size. No description of setting, population limited to one ethnicity. |
| **Hall-Flavin et al. (2013)**  | **Exp:** 114 consecutively selected adult cases, aged 18 to 72 years, with a primary diagnosis of major depressive disorder or depressive disorder not otherwise specified (HAM-D17 ≥14), genotyped and results provided to the treating physicians  
**Ctl:** 113 similarly selected controls, also genotyped, but results not provided until the completion of 8 weeks of tx  
**General exclusions:** Subjects with a diagnosis of bipolar disorder type I, schizophrenia and schizoaffective disorders  
**Setting:** Mayo Health System hospital in Wisconsin  
**Pharmacologic tx:** Not listed | **Clinical decision-making:**  
No data.  
**Pt outcomes:**  
**Exp vs Ctl:** At 8 weeks there was a greater reduction in symptoms for cases vs controls as measured by:  
HAM-D17 (46.9% vs 29.9%; P<0.0001)  
QIDS-C16 (44.8% vs 26.4%; P<0.0001)  
PHQ-9 (40.1% vs 19.5%; P=0.0001)  
Results were similarly significant using repeated measures analysis.  
At 8 weeks, more cases responded (>50% reduction in score from baseline) vs controls as measured by:  
QIDS-C16 (OR=2.58; 95% CI, 1.33-5.03; P=0.005) | Fair  
Trial not randomized or blinded. Sample size calculated to provide 90% power to detect a 15% reduction in symptom scores over 8 weeks. Data imputation used to check results with 27% loss to follow-up. Limited to population of European ancestry. Pts had a variety of diagnoses and tx modalities and chronicity of illness for which results were not controlled. |
<table>
<thead>
<tr>
<th>Authors/Study Design/Protocol</th>
<th>Patients/Setting/Treatment</th>
<th>Main Findings</th>
<th>Quality/Comments</th>
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<tbody>
<tr>
<td>Hall-Flavin et al. (2012)</td>
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<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Prospective controlled trial</td>
<td></td>
<td></td>
<td>Trial not randomized or blinded. Small sample size. Limited to population of European ancestry. Pts had a variety of diagnoses and tx modalities and chronicity of illness for which results were not controlled.</td>
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<tr>
<td><strong>Index test:</strong> GeneSight assay (see Winner et al., 2013)</td>
<td><strong>Exp:</strong> 25 consecutively selected adult cases, aged 25 to 75 years, with a primary diagnosis of MDD (HAM-D17 ≥14), genotyped and results provided to the treating physicians</td>
<td><strong>Clinical decision-making:</strong> <strong>Exp vs Ctl:</strong> At 8 weeks, 5.9% of cases were prescribed a “use with caution” medication vs 21.4% of controls (P=0.02).</td>
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<td><strong>Ctl:</strong> 26 similarly selected controls, also genotyped, but results not provided until the completion of 8 weeks of tx</td>
<td><strong>Pt outcomes:</strong> <strong>Exp vs Ctl:</strong> At 8 weeks, repeated measures analysis of the reduction of depression rating score across the study duration found a greater reduction of symptoms in cases vs controls using the QIDS-C16 (P=0.003) and using the HAM-D17 (P=0.05).</td>
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<tr>
<td><strong>Reference Standard:</strong> No genotyping results available when tx prescribed</td>
<td><strong>General exclusions:</strong> Subjects with a diagnosis of bipolar disorder type I, schizophrenia and schizoaffective disorders</td>
<td>At 8 weeks, the QIDS-C16 score was reduced 31.2% for case scores vs a 7.2% reduction in control scores (P=0.002). Similarly the HAM-D17 was reduced 30.8% in case scores vs 18.2% in control scores (P=0.04).</td>
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<tr>
<td><strong>Setting:</strong> Nonprofit outpatient behavioral health clinic in St Paul, MN</td>
<td><strong>Pharmacologic tx:</strong> Not listed</td>
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<td><strong>Previous tx:</strong> Allowed</td>
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<tr>
<td><strong>Maximum follow-up:</strong> 8 weeks</td>
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<tr>
<td>Breitenstein et al. (2014)</td>
<td></td>
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<td>Poor</td>
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<tr>
<td><strong>Index Test:</strong> ABCB1 (codes for P-glycoprotein) genotyping (TT at rs2032583 and GG at rs2235015 [TT/GG] considered unfavorable genotype; C and T alleles [C/T] considered favorable)</td>
<td><strong>Exp:</strong> 58 pts with at least a moderate depressive episode (HAM-D ≥14) at admission; genotyping results available for tx decisions</td>
<td><strong>Clinical decision-making:</strong> <strong>Exp:</strong> Dose of antidepressants with P-glycoprotein substrate properties increased 1.63-fold in TT/GG pts (unfavorable genotype) compared with other genotypes (P=0.012). Change to a different antidepressant occurred more often in TT/GG patients than in other genotypes (P=0.011).</td>
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<td><strong>Ctl:</strong> 58 pts drawn from same setting using same criteria before genotyping available; matched for age, gender, bipolarity, and HAM-D score at admission and tx week 4</td>
<td><strong>Pt outcomes:</strong> <strong>Exp vs Ctl:</strong> Genotyped pts more likely to be in remission (HAM-D &lt;10) at</td>
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<td><strong>General exclusions:</strong> No other severe neurological disorder or severe medical conditions</td>
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<td><strong>Setting:</strong> Hospital of the Max Planck Institute of</td>
<td><strong>Clinical decision-making:</strong> <strong>Exp vs Ctl:</strong> At 8 weeks, 5.9% of cases were prescribed a “use with caution” medication vs 21.4% of controls (P=0.02).</td>
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**Pharmacogenomic testing for selected conditions: Draft report**

Page 86
<table>
<thead>
<tr>
<th>Authors/Study Design/Protocol</th>
<th>Patients/Setting/Treatment</th>
<th>Main Findings</th>
<th>Quality/Comments</th>
</tr>
</thead>
</table>
| **Reference Standard:** No genotyping | Psychiatry; pts selected from the Munich Antidepressant Response Signature project  
**Pharmacologic tx:** Any, classified into substrates and non-substrates of P-glycoprotein transporter  
**Previous tx:** Allowed  
**Maximum follow-up:** 5 weeks after genotyping for decision-making outcomes; unknown for pt outcomes | discharge compared with non-genotyped pts (83.6% vs 62.1%; P=0.005).  
Dose increases in substrate antidepressants were associated with shorter hospital stays (P=0.009). TT/GG pt hospital stay was reduced by 4.7 weeks if substrate dose increased more than 1.5. | Very poor  
Small, retrospective, “exploratory” study based on medical record review. Those who received pharmacogenomic genotyping differed significantly from those who did not making comparisons difficult. Not fully representative of consulting pt population. |
| **Rundell et al. (2011)**  
Retrospective comparative study  
**Index test:** At least one of CYP2D6, CYP2C19, CYP2C9, and/or serotonin transporter genotype 5-HTTLPR  
**Reference standard:** No genotyping ordered | Exp: 29 psychiatric outpatients who had at least 2 PHSQ-9 depression severity scores preceding and 2 following (by at least 14 days) a consultation with pharmacogenomic genotyping  
**Ctl:** 17 similarly qualified pts who did not have pharmacogenomic genotyping  
**General exclusions:** None  
**Setting:** Mayo Clinic Rochester, outpatient psychiatric consultation practices  
**Pharmacologic tx:** Antidepressants, mood stabilizers, antipsychotics  
**Previous tx:** Allowed  
**Maximum follow-up:** 8 weeks | **Clinical decision-making:**  
No data.  
**Pt outcomes:**  
**Exp vs Ctl:**  
For post-day 14 serial PHQ-9 scores, there were no significant differences over time among CYP450 genotype categories. For 5-HTTLPR categories, L/L genotype pts had significantly greater improvement in PHQ-9 scores than other genotypes at times 4 and 5 (P=0.02 to P=0.05).  
There were no significant differences between genotyped and non-genotyped groups with regard to adjusted PHQ-9 scale slopes post-day 14.  
The differences in pre-baseline to post-baseline PHQ-9 depression severity scale score slopes, were not significant. | Small, retrospective, “exploratory” study based on medical record review. Those who received pharmacogenomic genotyping differed significantly from those who did not making comparisons difficult. Not fully representative of consulting pt population. |
| **Any Psychiatric Diagnosis**  
**Espadaler et al. (2016)**  
Retrospective comparative study  
**Index Test:** Neuropharmagen (Spain) recommendations used to direct tx (genotypes for CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP2B6, EPHX1, BDNF, 5-HTTLPR, ABCB1, GRIK4, | Exp: 89 pts aged ≥18 years, who failed a previous tx regimen due to lack of efficacy and/or poor tolerability, and whose tx followed genotyping recommendations  
**Ctl:** 93 pts drawn from same source group but whose tx did not follow genotyping recommendations  
**General exclusions:** CGI-S score <3; no restrictions on diagnoses (primarily major depression, psychotic disorder, bipolar disorder), other medical conditions (49%), or prescribed treatments | **Clinical decision-making:**  
No data.  
**Pt outcomes:**  
**Exp vs Ctl:**  
At 3 months, 93% (Exp) vs 82% (Ctl) had CGI-S scores lower than baseline (adjusted OR controlling for comorbidities = 3.86 (95% CI, 1.36-10.95; P=0.011)).  
The magnitude of change in CGI-S score was -1.43 (Exp) vs +1.25 (Ctl); adjusted mean score difference 0.24 (P=0.034). | Poor  
<table>
<thead>
<tr>
<th>Authors/Study Design/Protocol</th>
<th>Patients/Setting/Treatment</th>
<th>Main Findings</th>
<th>Quality/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR2C, DRD2-related, GRIK2, GRIA3 and others; total of 26 genes, 96 variants; summary and recommendations regarding drug and dose choices based on pt genotype provided)</td>
<td><strong>Setting:</strong> Private psychiatry clinics in Madrid  <strong>Pharmacologic tx:</strong> Top-prescribed medications were escitalopram, paroxetine, clomipramine, fluvoxamine, mirtazapine, venlafaxine, sertraline, and duloxetine among antidepressants; quetiapine, aripiprazole, clozapine, and haloperidol among antipsychotics; lorazepam, clonazepam, bromazepam, and pinazepam among anxiolytics; and lithium and lamotrigine among mood stabilizers.  <strong>Previous tx:</strong> Allowed  <strong>Maximum follow-up:</strong> 3 months from baseline</td>
<td>At 3 months, 77% (Exp) achieved a CGI-S score of ≤3 (considered condition “stabilization”) vs 62% (Ctl) (P=0.033). An equal number of adverse events were reported in each group.</td>
<td></td>
</tr>
<tr>
<td>Fagerness et al. (2014)</td>
<td><strong>Exp:</strong> 111 cases with a psychiatric diagnosis (primarily ADHD, anxiety disorder, depression, mood disorder) and psych-related drug activity in pharmacy claims whose treating clinicians ordered genetic testing during specified date range  <strong>Ctl:</strong> 222 propensity score-matched (age, sex, payer type, US Census region, all psychiatric conditions, all medication types, comorbidity index, treating physician specialty) controls whose treating clinicians did not have access to genetic information, treating pts as usual</td>
<td><strong>Clinical decision-making:</strong> No data.  <strong>Pt outcomes:</strong>  <strong>Exp vs Ctl:</strong> Cases showed an average increase in drug tx adherence of 6.3% compared with 0.3% in controls (P=0.0016)</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td><strong>General exclusions:</strong> None specified  <strong>Setting:</strong> Claims database  <strong>Pharmacologic tx:</strong> Mood stabilizers, anxiolytics, TCAs, MAOIs, SSRIs, SNRIs, mirtazapine, bupropion, serotonin modulators, stimulants, atomoxetine, alpha-2a agonist, antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Use</td>
<td><strong>Exp:</strong> 38 alcohol-dependent pts randomized to naltrexone and 44 randomized to placebo were genotyped as asp40 (predicted to improve tx response)  <strong>Ctl:</strong> 73 pts randomized to naltrexone and 66</td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Oslin et al. (2015)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors/Study Design/Protocol</td>
<td>Patients/Setting/Treatment</td>
<td>Main Findings</td>
<td>Quality/Comments</td>
</tr>
<tr>
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<tr>
<td><strong>Index test:</strong> OPRM1 (asn40asp) genotyping administered to all pts</td>
<td>randomized to placebo were genotyped as asn40</td>
<td>In the asp40 genotyped stratum, the OR for heavy drinking in the naltrexone group was 1.10 (95% CI, 0.52-2.31; ( P=0.80 )) compared with the placebo group. <strong>Ctl:</strong> In the asn40 genotyped stratum, the OR for heavy drinking in the naltrexone group was 0.69 (95% CI, 0.41-1.18; ( P=0.17 )) compared with the placebo group. Adherence (at least 80% of 12 wks of tx days): • asn40: naltrexone 72.6%; placebo 66.7% • asp40: naltrexone 50.0%; placebo 79.6% Serious and severe adverse events were infrequent and unrelated to group assignment.</td>
<td>enrolled for clear results</td>
</tr>
</tbody>
</table>

**General exclusions:** Psychoactive dependence other than alcohol or nicotine; urine sample positive for cocaine or opioids; taking psychotropic medications or have a current diagnosis of psychosis, mania, posttraumatic stress disorder, or enrolled in an addiction treatment program

**Setting:** Medical centers

**Pharmacologic tx:** Naltrexone

**Previous tx:** Allowed

**Maximum follow-up:** 12 weeks
**APPENDIX Vb. Summary of Subgroup Results for Clinical Utility Studies of Pharmacogenomic Testing (KQ3)**

Key: CGI-S, Clinical Global Impression of Severity; Ctl, control group for which genotyping results were available at the end of the treatment period or not available at all, depending on study design; Exp, experimental or genotyped treatment group for which results were immediately available to prescribing physicians; HAM-D, Hamilton Depression Rating Scale (21 items unless otherwise specified); hx, history; MDD, major depressive disorder; med, medication; PGx, pharmacogenomic; PHQ-9, Patient Health Questionnaire (9 items); Prev, previous; psych, psychiatric; pts, patients; QIDS-C16, Quick Inventory of Depressive Symptomatology-Clinician Rated (16 items); tx, treatment

<table>
<thead>
<tr>
<th>Author/Study Design/Protocol</th>
<th>Patient Qualifications</th>
<th>Exp vs Ctl (see Key and APPENDIX Table IVa) Statistically Significant Differences at Baseline</th>
<th>Subgroup Results by Clinical History</th>
<th>Subgroup Results by Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive disorders</strong></td>
<td></td>
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</tr>
<tr>
<td>Winner et al. (2013)</td>
<td>Pts with a diagnosis of a depressive disorder, minimum HAM-D17 score; bipolar disorder, schizophrenia, or schizoaffective disorders excluded</td>
<td>31% vs 8% male; ( P = 0.04 )</td>
<td>No subgroup results</td>
<td>No subgroup results</td>
</tr>
<tr>
<td>Singh (2015)</td>
<td>Pts of white ethnicity with a principal diagnosis of MDD, minimum HAM-D17 score, numerous exclusions (see APPENDIX Table IVa)</td>
<td>None</td>
<td>No subgroup results</td>
<td>No subgroup results</td>
</tr>
<tr>
<td>Hall-Flavin et al. (2013)</td>
<td>Consecutively selected adult cases with a primary diagnosis of a depressive disorder, minimum HAM-D17 score; bipolar disorder type I, schizophrenia and schizoaffective disorder diagnoses excluded; mostly European ancestry</td>
<td>QIDS-C16 Score ( (P=0.003) ) Previous med trials ( (P=0.021) ) Previous panel med trials ( (P=0.026) )</td>
<td>No subgroup results</td>
<td>No subgroup results</td>
</tr>
<tr>
<td>Hall-Flavin et al. (2012)</td>
<td>Primary diagnosis major depressive disorder, minimum HAM-D17 score; bipolar, schizophrenia, schizoaffective</td>
<td>None</td>
<td>No subgroup results</td>
<td>No subgroup results</td>
</tr>
<tr>
<td>Author/Study Design/Protocol</td>
<td>Patient Qualifications</td>
<td>Exp vs Ctl (see Key and APPENDIX Table IVa) Statistically Significant Differences at Baseline</td>
<td>Subgroup Results by Clinical History</td>
<td>Subgroup Results by Patient Characteristics</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>all genotyped, see Key)</td>
<td>disorders excluded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breitenstein et al. (2014)</td>
<td>All white ethnicity; cases had at least a moderate depressive episode and no other severe medical conditions; controls were matched for age, gender, bipolarity, HAM-D score at admission and tx week 4</td>
<td>None</td>
<td>No subgroup results</td>
<td></td>
</tr>
</tbody>
</table>
| Rundell et al. (2011)       | Psychiatric outpatients with PHQ-9 depression severity scores (Mayo Clinic [Rochester]) | Baseline PHQ-9 scale score: P<0.001
Prev antidepressant trials: P<0.001
Prev mood stabilizer trials: P<0.001
Prev antipsychotic trials: P<0.001
MDD diagnosis: P=0.008
Family hx mood disorders: P=0.002
Psych hospitalization hx: P<0.001
Prev antidepressant trials: P<0.001
Prev mood stabilizer trials: P<0.001
Prev antipsychotic trials: P<0.001 | PGx testing was statistically significantly more often ordered for pts with greater degrees of psychiatric predisposition and depression severity.
PHQ-9 depression severity score outcomes were not statistically significantly different among genotypes after adjustment for diagnosis of major depressive disorder, family hx of mood disorder and numbers of previous antidepressant, mood stabilizer and antipsychotic trials, and psychiatric hospitalization hx | No subgroup results |

Any Psychiatric Diagnosis

| Espadaler et al. (2016) | All pts with a psychiatric diagnosis and failed previous tx and/or poor tolerability admitted to Madrid psychiatric clinics, baseline CGI <3 excluded | Psychotic disorder: 13.8% vs 27.8%
Concurrent non-psychiatric disease: 48.9% vs 33.0% | Duration of current disorder, diagnosis of depression or psychosis, hospitalization, substance use, concurrent physical illness were not significant predictors of the magnitude of change in CGI-S scores | Age, sex were not significant predictors of the magnitude of change in CGI-S scores |
<p>| Fagerness et al. (2014) | Exp cases were selected from claims data if physician ordered PGx, had psychiatric | None after matching | Propensity score matching used a logistic model adjusted for age, sex, payer type, U.S. census region, | Propensity score matching used a logistic model adjusted for age, sex payer type, U.S. |</p>
<table>
<thead>
<tr>
<th>Author/Study Design/Protocol</th>
<th>Patient Qualifications</th>
<th>Exp vs Ctl (see Key and APPENDIX Table IVa) Statistically Significant Differences at Baseline</th>
<th>Subgroup Results by Clinical History</th>
<th>Subgroup Results by Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Comparative, poor Exp n=111 vs Ctl n=222, see Key)</td>
<td>diagnosis listed, and, psychotropic drugs dispensed; Ctls were matched for birth year, sex, psychiatric condition</td>
<td>psychiatric conditions, all meds, comorbidity index, practitioner specialty No subgroup results</td>
<td>census region, psychiatric conditions, all meds, comorbidity index, practitioner specialty No subgroup results</td>
<td></td>
</tr>
</tbody>
</table>

**Alcohol use**

| Oslin et al. (2015) | Alcohol-dependent pts randomized to naltrexone or placebo and genotyped as OPRM1 gene asp40 or asn40 sequence variant; numerous exclusions, see APPENDIX Table IVa; most were male and of white race | Minor differences in baseline variables across the 4 study groups | No subgroup results | No subgroup results |
## APPENDIX VI. Summary of Practice Guidelines

### APPENDIX VIa. Detailed Summary of Practice Guidelines that Mention Pharmacogenomic Testing

**Key:** AGNP, Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie; APA, American Psychiatric Association; BAP, British Association for Psychopharmacology; CPIC, Clinical Pharmacogenetics Implementation Consortium; CV, clinical validity; DoD, Department of Defense; ECT, electroconvulsive therapy; EPA, European Psychiatric Association; ICSI, Institute for Clinical Systems Improvement; NR, not reported; PGx, pharmacogenomics; TDM, therapeutic drug monitoring; VA, Department of Veterans Affairs; WFSBP, World Federation of Societies for Biological Psychiatry

<table>
<thead>
<tr>
<th>Sponsor, Year</th>
<th>Guideline Title</th>
<th>Relevant Recommendations</th>
<th>Repeat Testing</th>
<th>Quality/Main Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive Disorders</strong></td>
<td></td>
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<tr>
<td>beyondblue (2010)</td>
<td>Clinical practice guidelines: Depression in adolescents and young adults</td>
<td>No formal recommendations for use of PGx testing. Guidelines state that PGx testing may specify treatment effectiveness in individuals with varying genotypes.</td>
<td>No recommendations</td>
<td>6.9 – Good (specific search terms and search strategy not reported)</td>
</tr>
<tr>
<td>EPA (Möller et al., 2011)</td>
<td>Position statement of the European Psychiatric Association on the value of antidepressants in the treatment of unipolar depression</td>
<td>No formal recommendations for use of PGx testing. Authors state that PGx testing is gaining increasing attention for the prediction of response to antidepressants in terms of individual pharmacokinetic and pharmacodynamics particularities; however, further research is required to determine the respective significance of PGx testing. In addition, PGx testing may be specifically beneficial for the treatment of poor responders by making use of different treatment strategies (e.g., specific antidepressants, higher dosage, combination therapy, ECT, etc.) from the very beginning of treatment.</td>
<td>No recommendations</td>
<td>3.1 – Poor (systematic search methods and criteria for selecting evidence not described, methods for formulating consensus recommendations not described; guideline not reviewed by external experts; procedure for update of guideline NR)</td>
</tr>
<tr>
<td>ICSI (Trangle et al., 2016)</td>
<td>Adult Depression in Primary Care</td>
<td>No formal recommendations for use of PGx testing. The guideline states that cytochrome P450 testing can be used to determine genetic differences in the metabolism of particular medications, including antidepressants, and may help identify patients that are more sensitive to serious adverse reactions or medications with narrow therapeutic windows; however, the clinical significance and</td>
<td>No recommendations</td>
<td>6.7 – Good (methods for evaluation of bias and interpretation not described)</td>
</tr>
</tbody>
</table>
applicability of PGx testing to daily clinical practice has not yet been established.

| VA/DoD (2016) | VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder | No formal recommendations for use of PGx testing. The guideline states a need for a better understanding of the value and use of measurement-based care, including the place of PGx testing in the treatment of major depressive disorder. Currently there is insufficient evidence to support the routine use of genetic testing for the selection of antidepressant medication and further research is required in the use of genetic testing to aid in the selection of the most appropriate medication for a specific patient. | No recommendations | 5.9 – Fair (guideline update process not described; source of funding NR) |

| WFSBP (Bauer et al., 2013) | World Federation of Societies for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on acute and continuation treatment of unipolar depressive disorders | Clinical Consensus Recommendation: In possibly non-adherent patients (e.g., low drug plasma levels despite high doses of the antidepressant), a combination of TDM and genotyping may be informative. Such analyses can aid in identifying those individuals who are slow or rapid metabolizers of certain antidepressants. | No recommendations | 5.0 – Fair (search terms and dates literature covered NR; criteria for selecting evidence and how the body of evidence was evaluated for bias not described) |

**Schizophrenia Spectrum Disorders**

No guidelines addressing PGx testing specific to schizophrenia spectrum disorders were identified.

**Bipolar Disorder and Related Disorders**

No guidelines addressing PGx testing specific to bipolar disorder and related disorders were identified.

**Anxiety Disorders**

| APA (Stein et al., 2009) | Practice Guideline for the Treatment of Patients with Panic Disorder | No formal recommendations for use of PGx testing. The guideline states that as our understanding of how genetic polymorphisms (e.g., cytochrome P450 isoenzymes) influence a patient’s biological response to a medication (e.g., metabolism, sensitivity to side effects, etc.) expands, it will aid in the selection of individualized treatment. | No recommendations | 5.7 – Fair (methods for evaluation of bias not described; procedure for update of guideline NR; pharmaceutical companies funded consensus meeting) |

**Attention Deficit/Hyperactivity Disorder**

No guidelines addressing PGx testing specific to attention deficit/hyperactivity disorder were identified.

**Substance Use Disorders**

<p>| APA (Kleber et al., 2006) | Practice Guideline for the Treatment of Patients with | No formal recommendations for use of PGx testing. | No recommendations | 5.3 – Fair (methods for |</p>
<table>
<thead>
<tr>
<th>Source</th>
<th>Description</th>
<th>Recommendations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance Use Disorders Second Edition</td>
<td>The guideline states that cessation of substance use may be associated with changes in metabolism of medication (e.g., altered antipsychotic metabolism via cytochrome P450 1A2 with smoking cessation). Further research on the PGx approach to optimizing the choice of pharmacotherapy based on the gene or genes involved in the etiology or treatment responsiveness of substance use disorders may help guide identification of patient populations that will benefit from specific therapeutic options.</td>
<td>formulating consensus recommendations and evaluation of bias not described)</td>
<td></td>
</tr>
<tr>
<td>BAP (Lingford-Hughes et al., 2012)</td>
<td>BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP</td>
<td>No formal recommendations for use of PGx testing. Guidelines state that a functional polymorphism, Asp40 allele, of the mu opioid receptor gene has been shown to predict naltrexone treatment response in alcohol-dependent individuals; however, this association may be moderated by other efficacious treatment or patient variables (e.g., motivation) (Evidence category Ib: Evidence from at least 1 RCT).</td>
<td>2.9 – Poor (systematic review not conducted; criteria for selecting evidence and how the body of evidence was evaluated for bias not described; guideline review and update process not described; competing interests of group members not declared)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| Other AGNP (Baumann et al., 2005)           | The AGNP-TDM Expert Group Consensus Guidelines: focus on therapeutic monitoring of antidepressants | No formal recommendations for use of PGx testing. Guidelines state that PGx testing alone has limited value, as environmental factors also regulate drug metabolism; however, PGx testing in combination with TDM may be beneficial and indicated in the following circumstances:  
  - Metabolism of a medication is governed to a significant extent by the enzyme which is considered to be phenotyped or genotyped.  
  - A medication’s metabolism shows a wide interindividual variability as demonstrated by TDM.  
  - A drug is characterized by a low therapeutic index.  
  - The patient presents unusual plasma | 2.0 – Poor (systematic search methods and criteria for selecting evidence not described; methods for formulating recommendations not described; guideline not reviewed by external experts; guideline review and update process not described; competing interests of group members not declared; source of funding NR) |
concentrations of the drug or its metabolites, and genetic factors are suspected to be responsible.
- The patient suffers from a chronic illness that requires life-long treatment.

<table>
<thead>
<tr>
<th>BAP</th>
<th>BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No formal recommendations for use of PGx testing. Guidelines state that genetic factors associated with drug-induced weight gain and its metabolic consequences provide clues about the underlying mechanisms, and in the future may provide opportunities for personalized medicine in the predictive assessment of metabolic risk with antipsychotic drug treatment.</td>
</tr>
<tr>
<td></td>
<td>No recommendations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPLIC</th>
<th>Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants</th>
</tr>
</thead>
</table>
|       | Dosing recommendations for amitriptyline and nortriptyline based on CYP2D6 phenotype: CYP2D6 ultrarapid metabolizer:  
- For increased metabolism of tricyclics to less active compounds as compared with extensive metabolizers, avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. (Strong)  
- If tricyclic is warranted, consider increasing the starting dose. Use therapeutic drug monitoring to guide dose adjustments. (Strong)  
CYP2D6 extensive metabolizer:  
- For normal metabolism of tricyclics, initiate therapy with recommended starting dose. (Strong)  
CYP2D6 intermediate metabolizer:  
- For reduced metabolism of tricyclics to less active compounds as compared with extensive metabolizers, consider a 25% reduction in starting dose. (Strong) |
|       | No recommendations |

3.3 – Poor (systematic review not conducted; criteria for selecting evidence and how the body of evidence was evaluated for bias not described; guideline not reviewed by external experts; guideline review and update process not described; competing interests of group members not declared)

4.9 – Fair (recommendations based on CV evidence and consensus; methods evaluation of bias and interpretation not described; guideline not reviewed by external experts)
reduction of recommended starting dose. Use TDM to guide dose adjustments. (Moderate)

**CYP2D6 poor metabolizer:**
- For greatly reduced metabolism of tricyclics to less active compounds as compared with extensive metabolizers, avoid tricyclic use due to potential side effects. Consider alternative drug not metabolized by CYP2D6. (Strong)
- If a tricyclic is warranted, consider a 50% reduction of recommended starting dose. Use TDM to guide dose adjustments. (Strong)

Dosing recommendations for amitriptyline based on CYP2C19 phenotype:

**CYP2C19 ultrarapid metabolizer:**
- For increased metabolism of amitriptyline as compared with extensive metabolizers, consider alternative drug not metabolized by CYP2C19. If tricyclic is warranted, use therapeutic drug monitoring to guide dose adjustments. (Optional)

**CYP2C19 extensive metabolizer:**
- For normal metabolism of amitriptyline, initiate therapy with recommended starting dose. (Strong)

**CYP2C19 intermediate metabolizer:**
- For reduced metabolism of amitriptyline as compared with extensive metabolizers, initiate therapy with recommended starting dose. (Strong)

**CYP2C19 poor metabolizer:**
- For greatly reduced metabolism of amitriptyline as compared with extensive metabolizers, consider a 50% reduction of recommended starting dose. Use TDM to guide dose adjustments. (Moderate)

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**CPIC**
(Hicks et al., 2015)

_Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake_
Inhibitors

compounds when compared with extensive metabolizers, select an alternative drug not predominantly metabolized by CYP2D6. (Strong)

CYP2D6 extensive metabolizer:
- For normal metabolism, initiate therapy with recommended starting dose. (Strong)

CYP2D6 intermediate metabolizer:
- For reduced metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. (Moderate)

CYP2D6 poor metabolizer:
- For greatly reduced metabolism when compared with extensive metabolizers, select an alternative drug not predominantly metabolized by CYP2D6 or if paroxetine is warranted, consider a 50% reduction of recommended starting dose and titrate to response. (Optional)

Dosing recommendations for fluvoxamine based on CYP2D6 phenotype:

CYP2D6 ultrarapid metabolizer:
- No recommendation due to lack of evidence.

CYP2D6 extensive metabolizer:
- For normal metabolism, initiate therapy with recommended starting dose. (Strong)

CYP2D6 intermediate metabolizer:
- For reduced metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. (Moderate)

CYP2D6 poor metabolizer:
- For greatly reduced metabolism when compared with extensive metabolizers, consider a 25%-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6. (Optional)

Dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype:

of bias and interpretation not described; guideline not reviewed by external experts)
CYP2C19 ultrarapid metabolizer:
- For increased metabolism when compared with extensive metabolizers, consider an alternative drug not predominantly metabolized by CYP2C19. (Moderate)

CYP2C19 extensive metabolizer:
- For normal metabolism, initiate therapy with recommended starting dose. (Strong)

CYP2C19 intermediate metabolizer:
- For reduced metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. (Strong)

CYP2C19 poor metabolizer:
- For greatly reduced metabolism when compared with extensive metabolizers, consider a 50% reduction of recommended starting dose and titrate to response or select an alternative drug not predominantly metabolized by CYP2C19. (Moderate)

Dosing recommendations for sertraline based on CYP2C19 phenotype:

CYP2C19 ultrarapid metabolizer:
- For increased metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19. (Optional)

CYP2C19 extensive metabolizer:
- For normal metabolism, initiate therapy with recommended starting dose. (Strong)

CYP2C19 intermediate metabolizer:
- For reduced metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. (Strong)

CYP2C19 poor metabolizer:
- For greatly reduced metabolism when compared with extensive metabolizers,
*According to the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors. Guidelines were scored on scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).

**APPENDIX VIb. Listing of Reviewed Practice Guidelines that Do not Mention Pharmacogenomic Testing**

**Key:** AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; APA, American Psychiatric Association; APS, American Pain Society; CADTH, Canadian Agency for Drugs and Technologies in Health; CAMH, Centre for Addiction and Mental Health; DOD, Department of Defense; MOH, Ministry of Health; NICE, National Institute for Health and Care Excellence; PGx, pharmacogenomics; SIGN, Scottish Intercollegiate Guidelines Network; VA, Department of Veterans Affairs

<table>
<thead>
<tr>
<th>Sponsor, Year</th>
<th>Title</th>
<th>Pharmacologic Prescribing Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICE 2009</td>
<td>Depression in adults: recognition and management</td>
<td>No PGx</td>
</tr>
<tr>
<td>APA Reaffirmed 2015</td>
<td>Practice guideline for the treatment of patients with major depressive disorder, third edition.</td>
<td>No PGx; only interactions discussed</td>
</tr>
<tr>
<td><strong>Schizophrenia Spectrum and Other Psychotic Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AACAP McClellan et al., 2013</td>
<td>Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia</td>
<td>No PGx</td>
</tr>
<tr>
<td>CADTH 2011</td>
<td>Optimal Use Recommendations for Atypical Antipsychotics: Combination and High-Dose Treatment Strategies in Adolescents and Adults with Schizophrenia</td>
<td>No PGx</td>
</tr>
<tr>
<td>NICE 2013a</td>
<td>Psychosis and schizophrenia in children and young people: recognition and management</td>
<td>No PGx</td>
</tr>
<tr>
<td>NICE 2014a</td>
<td>Psychosis and schizophrenia in adults: prevention and management</td>
<td>No PGx</td>
</tr>
<tr>
<td>SIGN 2013</td>
<td>Management of schizophrenia: A national clinical guideline</td>
<td>No PGx</td>
</tr>
<tr>
<td><strong>Bipolar Disorder and Related Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICE 2014b</td>
<td>Bipolar disorder: assessment and management</td>
<td>No PGx</td>
</tr>
<tr>
<td>VA/DOD 2010</td>
<td>Management of Bipolar Disorder in Adults (BD)</td>
<td>No PGx; Pharmacotherapy adjusted based on therapeutic concentration if known, or empiric adjustment if not known</td>
</tr>
<tr>
<td><strong>Anxiety Disorders</strong></td>
<td></td>
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</tr>
<tr>
<td>Sponsor, Year</td>
<td>Title</td>
<td>Pharmacologic Prescribing Method</td>
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<td>--------------</td>
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<tr>
<td>MOH Singapore 2015</td>
<td>Clinical Practice Guidelines: Anxiety Disorders</td>
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<tr>
<td>NICE 2011a</td>
<td>Generalized anxiety disorder and panic disorder in adults: management</td>
<td>No PGx</td>
</tr>
<tr>
<td>NICE 2013b</td>
<td>Social anxiety disorder: recognition, assessment and treatment</td>
<td>No PGx</td>
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<tr>
<td>NICE 2013b</td>
<td>Social anxiety disorder: recognition, assessment and treatment</td>
<td>No PGx</td>
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</tbody>
</table>

**Attention Deficit/Hyperactivity Disorder**

| AAP 2011    | ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents | No PGx; describes % response, trial z error approach |
| NICE 2008   | Attention deficit hyperactivity disorder: diagnosis and management     | No PGx                            |

**Substance Use Disorders**

| APS Chou et al., 2014 | Methadone Safety: A Clinical Practice Guideline From the American Pain Society and College on Problems of Drug Dependence, in Collaboration With the Heart Rhythm Society | No PGx; only interactions discussed |
| CAMH Handford et al., 2012 | Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline | No PGx                            |
| NICE 2011b | Alcohol-Use Disorders: Diagnosis, Assessment, and Management of Harmful Drinking and Alcohol Dependence | Does not address pharmacological interventions |
| VA/DoD 2015 | VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders | No PGx; all treatments by recommended or empiric dosing |

**Other**

| AACAP 2011 | Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents | No PGx                            |