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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Pharmacogenomic Testing for Psychotropic Medication Selection: A Systematic Review of the Assurex GeneSight Psychotropic Test

KEY MESSAGES

Many people in Ontario live with mental illness, including major depressive disorder, bipolar disorder, schizophrenia, or anxiety. Medications are commonly used to treat mental illnesses, but choosing the right medication for each patient is a challenge. The GeneSight Psychotropic test uses a patient's unique genetic profile to guide doctors in choosing medications.

Patients with depressive symptoms who had the GeneSight test to help guide the choice of their medication responded better to treatment and their mood improved compared with patients who did not have the test. However, GeneSight-guided care did not lead to better rates of complete relief of depressive symptoms. Overall, these findings were based on evidence of low to very low quality and because of this, the effect of the GeneSight test on patient outcomes is uncertain.

HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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ABSTRACT

Background

A large proportion of the Ontario population lives with a diagnosed mental illness. Nearly 5% of Ontarians have major depressive disorder, and another 5% have another type of depressive disorder, bipolar disorder, schizophrenia, anxiety, or some other disorder not otherwise specified. Medications are commonly used to treat mental illness, but choosing the right medication for each patient is challenging, and more than 40% of patients discontinue their medication within 90 days because of adverse effects or lack of response. The Assurex GeneSight Psychotropic test is a pharmacogenomic panel that provides clinicians with a report to guide medication selection that is unique to each patient based on their individual genetic profile. However, it is uncertain whether guided treatment using GeneSight is effective compared with unguided treatment (usual care).

Methods

We performed a systematic review to identify English-language studies published before February 22, 2016, that compared GeneSight-guided care and usual care among people with mood disorders, anxiety, or schizophrenia. Primary outcomes of interest were prevention of suicide, remission of depression symptoms, response to depression therapy, depression score, and quality of life. Secondary outcomes of interest were impact on therapeutic decisions and patient and clinician satisfaction. Risk of bias was evaluated, and the quality of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group criteria.

Results

Four studies met the inclusion criteria. These studies used a version of GeneSight that included the *CYP2D6*, *CYP2C19*, *CYP1A2*, *SLC6A4*, and *HTR2A* genes; one of the studies also included *CYP2C9*. Patients who received the GeneSight test to guide psychotropic medication selection had improved response to depression treatment, greater improvements in measures of depression, and greater patient and clinician satisfaction compared with patients who received treatment as usual. We observed no differences in rates of complete remission from depression. The findings were based on GRADE assessment of low to very low quality evidence, and the body of evidence had several limitations: the included studies used an older version of GeneSight and were limited to a population with major depression, so results may not be generalizable to other versions of the test or different populations such as patients with anxiety or schizophrenia.

Conclusions

There is uncertainty about the use of GeneSight Psychotropic pharmacogenomic genetic panel to guide medication selection. It was associated with improvements in some patient outcomes, but not others. As well, our confidence in these findings is low because of limitations in the body of evidence.

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BACKGROUND

Health Condition

Mental illness, specifically mood disorders, anxiety, and schizophrenia, can affect daily living and may be accompanied by fatigue, insomnia, sudden weight loss, and an overall depressed mood, among other symptoms.¹ Approximately 10% of Ontarians live with mental illness, and 4.8% live with major depression.² Of people who contact the emergency department about a mental illness, a third (34%) do so because of anxiety, and another 18% because of other mental illnesses.² Of people admitted to hospital because of mental illness, 12.4% have bipolar disorder and 28.4% have major depressive disorder.² People with one form of mental illness often experience other forms as well. For example, as many as 70% of people who have generalized anxiety disorder also have another mental illness, and 45% of people with anxiety also live with depression at some point in their lifetime.³

There are some differences in equity related to rates of mental illnesses and people's experience of them. For example, major depression affects 5.8% of women and only 3.8% of men.² Bipolar disorder is more commonly seen among younger people (2.4% of people aged 15 to 24 years vs. 1.7% of people older than 45 years).² As well, people from low-income areas are at greater risk of developing a mental illness than people from high-income areas.²

Variation in access to care is another equity consideration. At present, Toronto Central Local Health Integration Network (LHIN) has 63 full-time psychiatrists per 100,000 people, about three times more than Champlain, the next most concentrated LHIN, which has 24 psychiatrists per 100,000, and in great contrast to the Central West LHIN, which has only 4.7 psychiatrists per 100,000 people.² As well, laboratory and genetic testing is not standardized across Ontario; people in one region may have access to different tests than people in another.

Treating mental illness is challenging, because people who have mental illness often avoid asking for professional help due to the stigma associated with a mental disorder. When they do seek treatment, they often need a combination of therapies, including psychotherapy (such as cognitive behavioural therapy), one or more medications (such as antidepressants), or both.⁴ Antidepressants are among the most commonly prescribed medications in young Canadians, used by 3.6% of males and 13% of females aged 6 to 24 years.⁵ They are also the most commonly prescribed medication for Canadian women, used by 13.7% of women aged 25 to 79 years.⁵ Antidepressant use is less common among Canadian men, but is still within the top five prescriptions, at 8.2% of those aged 44 to 64 years.⁵

The Canadian Network for Mood and Anxiety Treatments Clinical guidelines lists 17 different antidepressants as potential first-line medications for major depressive disorder, grouped by mechanism of action, including tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs).⁶ However, choosing the right medication is a challenge. For example, even though SSRIs are listed as first-line treatments, they are effective in only a third of the patients treated with them; patients may need four or more different medications, plus dosage augmentations, to manage the symptoms of major depressive disorder.⁷

Of those who are treated, many do not respond sufficiently to treatment or experience a return of their symptoms.⁸ More than 40% of patients discontinue their medications within the first 90 days of therapy because of a lack of response, side effects, or both.⁶ Some of the more common side effects include drowsiness, headache, dry mouth, nausea, anxiety, and sexual dysfunction.⁶ There is also a risk of uncommon side effects such as seizures, bleeding in the upper gastrointestinal tract, and osteoporosis and fractures in the elderly.⁶

Clinical Need and Target Population

Individual variations in people's genetic code may cause them to respond differently to medications. They may experience differences in metabolism (how the drug is broken down and used in the body), differences in mechanism of action (how the drug works), and individual adverse effects. For example, a person classified as a poor metabolizer because of differences in their genetic coding may have a lower enzyme response rate and metabolize a medication more slowly.^{9,10} This would lead to higher concentrations of the medication in their system than a typical metabolizer would have, and thus, potential adverse effects. Ultra (or fast) metabolizers are less likely to experience side effects that lead to discontinuing the medication, but they may need a higher dosage to achieve a noticeable benefit.⁶

Genome-wide association studies have attributed as much as 42% of the variation in response to antidepressants to individual genetic differences, and other studies have demonstrated correlations with ethnicity and ancestral variations.¹⁰⁻¹² It is believed that prescribing clinicians who know a patient's genetic predisposition could better target therapies, reduce the risk of adverse effects, and minimize the use of the health care system, services, and costs.¹³

More and more medications include pharmacogenomic biomarker information in their product labelling.¹⁴ The most common information related to psychotropic medications is a warning about dosage for poor metabolizers known to be associated with the CYP2D6 and CYP2C19 enzymes; for example, patients classified as poor metabolizers for CYP2C19 should receive a starting dose of citalopram at 60% of the dose for a typical metabolizer.¹⁴

As research in this area continues to evolve, the evidence is improving around some single genes to predict how effective a drug will be for an individual. According to one review, the best evidence for specific genes that can predict response to antidepressant efficacy are *CYP2D6*, *CYP2C19*, *SLC6A4*, *HTR2A*, *BDNF*, *GNB3*, *FKBP5*, and *ABCB1*.⁹ However, another review concluded that while there was some good evidence for certain individual candidate genes, there was no major effect of any single gene variant on antidepressant efficacy.¹⁵

Evaluating the usefulness of a combination of genes in a panel may be a more effective way to identify individual variations than assessing single genes alone¹⁶; this is believed to be due to the complex metabolic pathways that cause interactions between enzymes.¹⁶ Further adding to the complexity is growing evidence of the effects of environment on gene expression, biological variations in depression based on ancestry, and changes in enzyme metabolism with age.^{11,12,17-19} Using genetic testing to support health care decision-making is still a relatively new idea; it is still uncertain whether such tests can affect important patient outcomes.

Technology

GeneSight Psychotropic is a multi-gene, multivariant genetic test that combines genotype (a person's genetic profile), phenotype (a person's physical characteristics), and drug metabolism information in an algorithm to categorize included medications for each patient using a system of green, yellow, and red bins. "Green" medications are supported for use as usual, "yellow" for use with caution, and "red" for use with increased caution and more frequent monitoring by the prescribing clinician.²⁰

The test can be ordered by any prescribing clinician, and the results of the test integrate a person's genetic information with each medication into an easy-to-read report that is proprietary to Assurex Health.²⁰ The test is noninvasive and easy to administer: it requires only a cheek

swab to collect a sample of a person's DNA. Results are provided within 36 hours, but rush service is available if needed.²⁰

At present, the test is sent via courier to the Assurex Health laboratory. Samples are analyzed using primers developed by Assurex and existing DNA testing technology: the Luminex xTAG Multiplex Technology (Luminex, Austin, TX) and the Lonza FlashGel system (Lonza, Basel, Switzerland).²⁰ The test has 100% sensitivity and specificity at concentrations of 20 ng/μL for all genes except *SLC6A4*, for which it is valid at 10 ng/μL.²¹ The test is also valid at concentrations of 5 ng/μL to determine *CYP2D6* copy number variation.²¹

Eight genes were included in the version of the GeneSight Psychotropic test requested for review (Appendix 1). Of these, six were pharmacokinetic—members of the cytochrome P450 family of liver enzymes, which play an important role in overall drug metabolism. The other two were pharmacodynamic—associated with the serotonergic transporter and receptor genes, where variations can affect the mechanism of action of SSRIs. Although the requested version of GeneSight includes eight genes, the Assurex website currently lists a version that includes 12.²⁰

Potential Value of GeneSight Psychotropic Testing

In a retrospective study conducted in 79 psychiatric patients with depressive disorder or anxiety, patients were classified using the GeneSight test and their health services utilization was analyzed, looking back 1 year into administrative data.¹³ Patients who took red-bin medications had more total health care visits and disability claims than patients who took yellow- or green-bin medications (Table 1). Patients who took red-bin medications also had significantly more medical absence days than patients who took green-bin medications alone ($P = .043$).¹³ The authors found significant correlations between the number of weeks a patient spent on a red-bin medication and higher numbers of health care visits ($P = .05$), as well as the total number of drugs taken and medical or other health care visits ($P < .001$).¹³ Taken together, these findings may demonstrate the potential for the GeneSight test to predict which treatment medication would be optimal for a person and support the avoidance of red-bin medications to minimize health care utilization, improve the benefit from selected therapies, and enhance patients' overall quality of life.¹³

Table 1: Health Care Utilization by GeneSight Patient Classification

Outcome Measure	Results by Patient Classification			Significance (Red-Bin Patients vs. Green- and Yellow-Bin Patients)
	Red Bin (n = 9)	Yellow Bin (n = 28)	Green Bin (n = 39)	
Total health care visits	21.9	12.3	13.7	$P = .014$
Nonpsychiatric medical visits	12.8	7.1	8.4	$P = .039$
Outpatient psychiatric visits	8.9	5	5.1	$P = .145^a$
Number of disability claims	0.56	0.11	0.15	$P = .013$
Medical absence days	20.8	8.4	4.6	$P = .126$
Hospitalizations (days admitted)	NR	NR	NR	NS ^b
Emergency department visits	NR	NR	NR	NS ^b

Abbreviations: NR, not reported; NS, not significant.

^aCalculated based on F statistic provided in the publication.

^bReported as not statistically significant using a threshold of $P > .05$

Source: Winner et al.¹³

Another study compared the relative effectiveness of combinatorial genomics (evaluating the effects of several genes together) with single-gene phenotyping (evaluating the effects of one gene at a time). Altar et al¹⁶ used a cohort of patients who received usual care but also underwent genotyping with GeneSight. Patients were categorized as ultra-rapid, extensive, intermediate, or poor metabolizers based on single-gene phenotyping. Within those groups, patients were further categorized using combinatorial genomics and the GeneSight Psychotropic red-, yellow-, and green- bin algorithm. Overall, there was no significant difference in 17-item Hamilton Rating Scale for Depression (HAMD-17) scores between metabolizer categories based on single-gene phenotyping. Based on the GeneSight categories, however, yellow- and green-bin patients had significantly greater improvement in depression scores than red-bin patients. The authors observed similar trends for total health care visits, medical visits, and disability claims. Results are summarized in Appendix 1.

While these studies provide examples of how GeneSight may be able to predict patient outcomes and health care utilization, it remains uncertain whether using GeneSight to guide medication selection leads to better patient outcomes.

Regulatory Information

The focus of this systematic review was the Assurex GeneSight Psychotropic test. This test is currently not available through the Ontario government. It does not require Health Canada approval; most laboratory tests are subject to approvals at the provincial level.

In the United States, GeneSight Psychotropic is covered by some health insurance plans, including Medicare and Medicaid. According to guidelines from the Centers for Medicare & Medicaid Services, GeneSight may be ordered only by psychiatrists for patients diagnosed with major depressive disorder whose symptoms are refractory after at least one prior neuropsychiatric medication and who continue to experience moderate to severe depression as defined by the Hamilton Rating Scale for Depression.²²

Context

The clinical guideline put out by the Clinical Pharmacogenetic Implementation Consortium (CPIC) lists guidance for assessing two of the genes included in the GeneSight test to support the dosing of SSRIs.²³ As well, some jurisdictions include information about pharmacogenomics on drug labelling requirements,¹⁴ including Health Canada/Santé Canada, the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceutical and Medical Devices Agency, Japan (PMDA). PharmGKB summarizes these labels on its website, organized by medication and available at <https://www.pharmgkb.org/view/drug-labels.do>. In Ontario, there is no standard method for pharmacogenomic testing at present.

Research Questions

Compared with usual care, what is the effect on depression outcomes of using the GeneSight Psychotropic test to guide the selection of psychotropic medications for patients with mood disorders, anxiety, or schizophrenia?

CLINICAL EVIDENCE REVIEW

Objective

The objective of this study was to assess the effect of the GeneSight Psychotropic test compared with usual care in supporting the selection of psychotropic medications for patients with mood disorders, anxiety, or schizophrenia, within the context of the Ontario Ministry of Health and Long-Term Care.

Methods

Research questions are developed by Health Quality Ontario in consultation with experts, end users, and/or applicants in the topic area.

Sources

We performed a literature search on February 22, 2016, using all Ovid MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database, for studies published from inception to February 22, 2016.

Search strategies were developed by medical librarians using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist (McGowan, 2016). Database auto-alerts were created in MEDLINE, Embase, and PsycINFO, and monitored for the duration of the HTA review. See Appendix 2 for full details, including all search terms. We supplemented searches by conducting general web searches (e.g., Google Scholar), hand-searching bibliographies of identified publications, and by consulting experts.

Literature Screening

A single reviewer reviewed the abstracts and, for those studies meeting the eligibility criteria, we obtained full-text articles.

Inclusion Criteria

- English-language full-text publications
- Studies published up to February 22, 2016
- Studies examining the use of Assurex GeneSight Psychotropic to guide psychotropic medication prescribing among patients with mood disorders, anxiety, or schizophrenia compared with usual (unguided) care

Exclusion Criteria

- Studies examining genetic panels other than the GeneSight Psychotropic test
- Studies examining the predictive value of a single gene associated with a disorder (e.g., studies looking at candidate genes for association with a phenotype)
- Studies examining panels developed for general medication metabolism assessment, not specific to psychotropic medication selection
- Animal and in vitro studies

- Editorials, case reports, commentaries, or conference abstracts

Outcomes of Interest

- Primary outcomes (patient outcomes)
 - Prevention of suicide
 - Remission of depression symptoms
 - Response to depression therapy
 - Depression score
 - Quality of life
- Secondary outcomes
 - Impact on therapeutic decisions
 - Patient and clinician satisfaction

Data Extraction

We extracted relevant data on study characteristics, risk of bias items, and population, intervention, comparison, outcome, and time (PICOT), collecting information about:

- Source (i.e., citation information, contact details, study type)
- Methods (i.e., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, and whether or not the study compared two or more groups)
- Outcomes (i.e., outcomes measured, number of participants for each outcome, outcome definition, and source of information)

Statistical Analysis

We conducted analyses to compare the intervention group (GeneSight Psychotropic) and control groups using Review Manager version 5.3.²⁴ We assumed statistical significance when $P < .05$. We expressed pooled results as mean differences for continuous data and odds ratios for categorical data. We used a fixed-effects model where there was low between-study heterogeneity based on the interventions and populations described, an $I^2 \leq 30\%$, or both.²⁵ Where fixed-effects models were inappropriate, we applied a random-effects model. Where pooling of data was not appropriate after considering study design, inclusion criteria, and other sources of heterogeneity between individual studies, we summarized data narratively in evidence tables.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.²⁶ The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology. Details of the GRADE analysis are provided in Appendix 3.

Expert Consultation

In the spring of 2016, we solicited expert consultation on the appropriate use of pharmacogenomic testing to support psychotropic medication selection. Members of the consultation included physicians in the specialty areas of psychiatry and pharmacogenomics. The role of the expert advisors was to provide insight during the development of the research

question and contextualize the evidence, providing advice on the potential use of a pharmacogenomic test to support psychotropic medication selection in Ontario. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Literature Search

The database search yielded 1,807 citations published up to February 22, 2016. After removing duplicates, we reviewed titles and abstracts to identify potentially relevant articles. We obtained the full texts of these articles for further assessment. Four studies met the inclusion criteria.²⁷⁻³¹ One was identified through hand-searching of the reference lists of the included studies, along with health technology assessment websites and other sources, to identify additional relevant studies.³⁰

Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

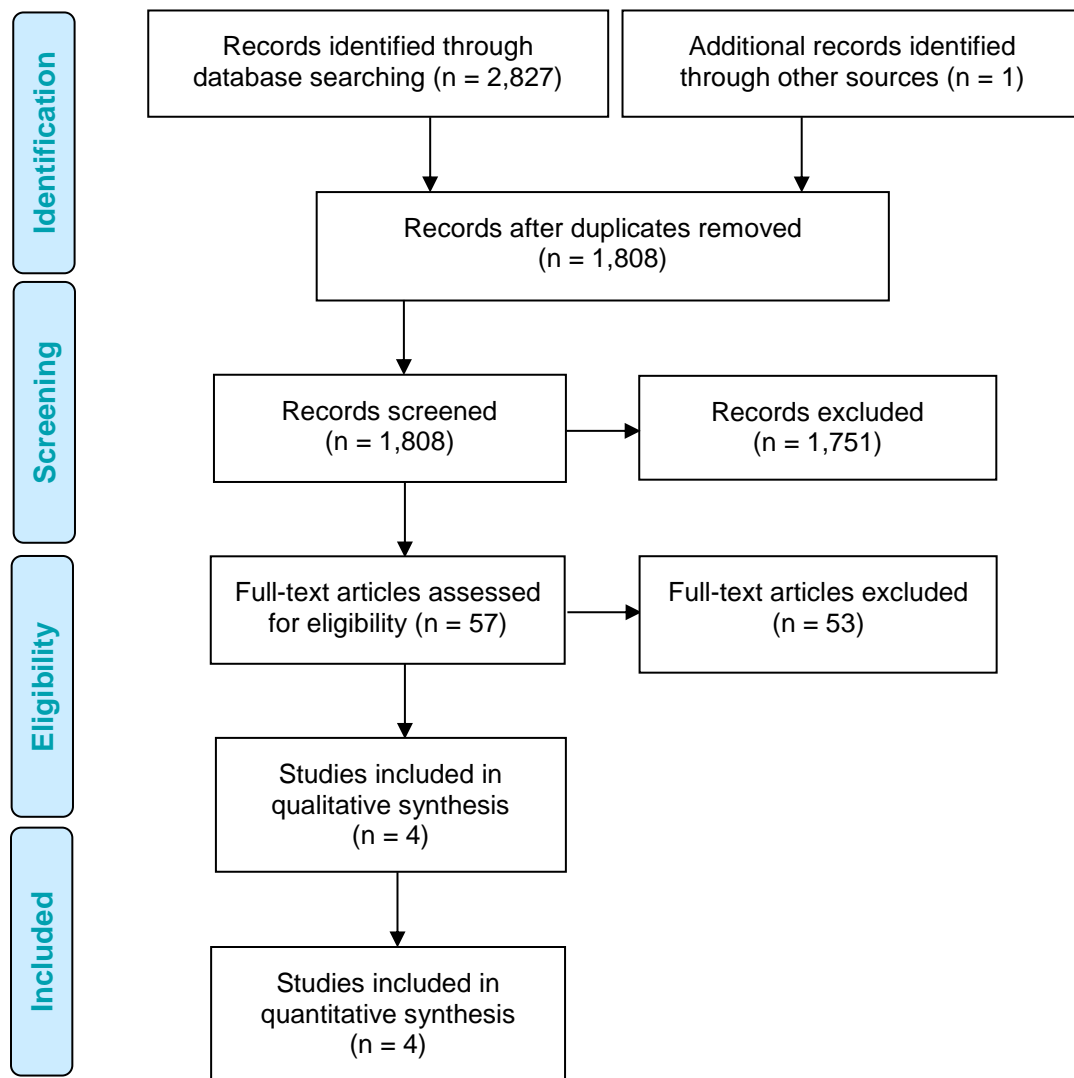


Figure 1: PRISMA Flow Diagram

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
 Source: Adapted from Moher et al.³²

Summary of Included Studies

Four studies met the inclusion criteria. Table 2 summarizes the study designs and conclusions of the included studies.

Table 2: Summary of Studies Examining GeneSight Pharmacogenomic Testing

Author, Year	Study Design	Study Conclusion
Hall-Flavin et al, 2012 ²⁸	Nonrandomized, open-label, consecutive comparative cohort study comparing unguided treatment as usual and guided care with combinatorial genomic testing using GeneSight	Patients in the group guided by GeneSight had greater reduction in depression scores than patients who received unguided treatment
Hall-Flavin et al, 2013 ²⁷	Nonrandomized, open-label, consecutive comparative cohort study comparing unguided treatment as usual and guided care with combinatorial genomic testing using GeneSight	Patients had improved depression outcomes when GeneSight was used for pharmacogenomic testing
Winner et al, 2013 ²⁹	Double-blind randomized controlled trial comparing unguided treatment as usual and guided care with combinatorial genomic testing using GeneSight	Patients who received treatment guided by GeneSight were more likely to respond to therapy, and patients with severe gene-drug interactions who were switched to a more gene-suitable medication had the greatest improvement in depressive symptoms
Winner et al, 2015 ³⁰	Controlled, propensity-matched, prospective cohort study evaluating medication regimens between patients who received guided care with GeneSight vs. usual care, with a focus on cost comparison	Combinatorial testing improved adherence and led to cost savings

Table 3 outlines the details of the included study populations and interventions. All studies were conducted in the United States, and all studies had a conflict of interest, with authors employed by Assurex, the manufacturer of GeneSight.

Three of the studies limited the populations to patients with a diagnosis of major depressive disorder or depressive disorder not otherwise specified (treated by psychiatrists), and they excluded patients with other diagnoses such as bipolar type I, schizophrenia, or schizoaffective disorder.²⁷⁻²⁹ One study was broader in its inclusion criteria and included all psychiatric patients diagnosed with depressive disorder, anxiety, bipolar disorder, or other psychiatric disorders. As well, this study did not explicitly limit the ordering of GeneSight to psychiatrists.³⁰

All studies used the same protocol to identify polymorphisms. Genotyping for *CYP2D6*, *CYP2C19*, and *CYP1A2* (plus *CYP2C9* in Winner et al 2013b¹³) was done using the Luminex xTAG Multiplex Technology (Luminex, Austin, TX) with polymerase chain reaction (PCR) amplification of the relevant regions and using Exonuclease I and Shrimp Alkaline Phosphatase to clarify. Serotonin transporter and receptor genes *SLC6A4* and *HTR2A* were amplified using PCR. The restriction enzyme MSPO (*Moraxella* species) was used on *HTR2A*, and both *SLC6A4* and *HTR2A* were run on a 2% gel to genotype.

Table 3: Design and Methodology of Studies Examining GeneSight Pharmacogenomic Testing

Author, Year	Setting	Population	Guided/ Unguided, N	Method	Intervention ^a (Genes Examined)	Length of Follow-up
Hall-Flavin et al, 2012 ²⁶	Outpatient behavioural health clinic in St. Paul, MN	Psychiatric patients with a primary diagnosis of major depressive disorder, a HAMD-17 score ≥ 14 , 25–75 years old, and taking at least one of the medications listed by the GeneSight panel. Excluded patients with bipolar disorder (any type), schizophrenia, or schizoaffective disorder	26/25	Patients were consecutively screened by their treating physician for eligibility, and allocated in a nonrandomized fashion to the treatment group (results from the GeneSight test were provided to their treating clinician before the start of their therapy to support medication selection) or the unguided control group (treatment as usual)	5 genes: <i>CYP2D6</i> , <i>CYP2C19</i> , <i>CYP1A2</i> , <i>SLC6A4</i> , <i>5HTR2A</i>	8 weeks
Hall-Flavin et al, 2013 ²⁷	Outpatient psychiatry unit at a hospital in La Crosse, WI	Psychiatric patients with a primary diagnosis of major depressive disorder or depressive disorder not otherwise specified, a HAMD-17 score ≥ 14 , and 18–72 years old. Excluded patients with bipolar disorder type I, schizophrenia, or schizoaffective disorder	114/113	The first of the two consecutive groups received treatment as usual. The second group's treating clinicians were given GeneSight results to support medication selection. Physicians were not given additional education or training on pharmacogenomics or GeneSight	5 genes: <i>CYP2D6</i> , <i>CYP2C19</i> , <i>CYP1A2</i> , <i>SLC6A4</i> , <i>5HTR2A</i>	8 weeks
Winner et al, 2013 ²⁹	Outpatient clinic at a mental health services clinic in Grand Rapids, MI	Patients with a diagnosis of major depressive disorder or depressive disorder not otherwise specified, and a HAMD-17 score ≥ 14 . Excluded patients with bipolar disorder (any type), schizophrenia, schizoaffective disorder, or substance abuse or dependence	26/25	Patients were randomized to the intervention group (treating psychiatrist or psychiatric nurse practitioner received the GeneSight test results within 2 days of enrolment) or the control group (treatment as usual). Analysts and patients were blinded to their treatment group allocation	6 genes: <i>CYP2D6</i> , <i>CYP2C19</i> , <i>CYP2C9</i> , <i>CYP1A2</i> , <i>SLC6A4</i> , <i>5HTR2A</i>	10 weeks
Winner et al, 2015 ³⁰	Various, United States	Psychiatric patients diagnosed with anxiety, depressive disorders, bipolar disorders, or other psychotic disorders, and prescribed one of the 26 antidepressant or antipsychotic medications covered by GeneSight at the time. Patients were eligible if they had no prescriptions in the 180 days prior to the eligible GeneSight medication prescription, maintained continuous pharmaceutical support in the previous 180 days, or experienced an augmentation in prescribed medication or dosage in the previous 90 days	2,168/10,880	Clinicians of eligible patients were contacted and asked if they authorized GeneSight testing. Patients were then propensity-matched 1:5 on date of project enrolment, age, sex, psychotropic medication, and primary diagnosis against controls from a large administrative data set of 65 million individuals from the participating health insurance plan who did not receive testing. Patients were then followed for 1 year using administrative data	Specific version not reported ^b	1 year

Abbreviations: HAMD-17, 17-item Hamilton Rating Scale for Depression.

^aSee Appendix 1 for more details about the specific alleles.

^bWhile the specific version of GeneSight was not reported in the study, the reported enrolment period was from September 2011 to December 2013. Winner et al¹³ published a paper that reported the six-gene version of GeneSight was used in April 2011, and we found a press release dated July 2013 announcing a new version of GeneSight that included a new variant,³³ leading us to believe that the six-gene version was used for the majority of this study.

Results for Primary Outcomes

The primary outcomes of interest were patient outcomes: prevention of suicide, remission of depression symptoms, response to depression therapy, depression score, and quality of life.

Three depression scores were used across the included studies. The HAMD-17 is administered by health care professionals to patients who have already been diagnosed with depression to assess severity; a higher score indicates increased severity of depression.³⁴ The 16-item Quick Inventory of Depressive Symptomatology is also a depression severity scale with a clinician-rated component (QIDS-C16) and a patient self-rated component (QIDS-SR), both of which have demonstrated internal consistency and are commonly used in practice as valid measures of depression.³⁵ The 9-item Patient Health Questionnaire (PHQ-9) is a validated survey completed by patients to diagnose major depressive disorder or other depressive syndromes; a higher score indicates increased severity of depressive symptoms.³⁶

Prevention of Suicide

When managing patients with depression, prevention of suicide is the most important outcome, as advised by experts consulted for this review. However, none of the included studies reported on suicide.

Remission of Depression Symptoms

Total remission is the primary goal when treating patients with depression, as advised by the experts consulted for this review. Figure 2 summarizes results from the two studies that reported on patient remission. In both studies, patients were considered to be in remission when they achieved HAMD-17 scores <8, QIDS-C16 scores <5, and PHQ-9 scores <5.^{27,29}

One study, Hall-Flavin et al,²⁷ also conducted sensitivity analyses using the intention-to-treat analytical strategies of expected maximum and last observation carried forward; they found results to be consistent and/or stronger in favour of guided therapy than those reported here. There was a statistically significant benefit in depression remission for GeneSight compared with usual treatment when depressive symptoms were assessed using QIDS-C16, but no significant difference when using HAMD-17 or PHQ-9. This was based on very low quality evidence (Table 4), as the findings were inconsistent with respect to the effectiveness of GeneSight to improve remission from depression, and they depended on the scale used to measure depression (Figure 2).

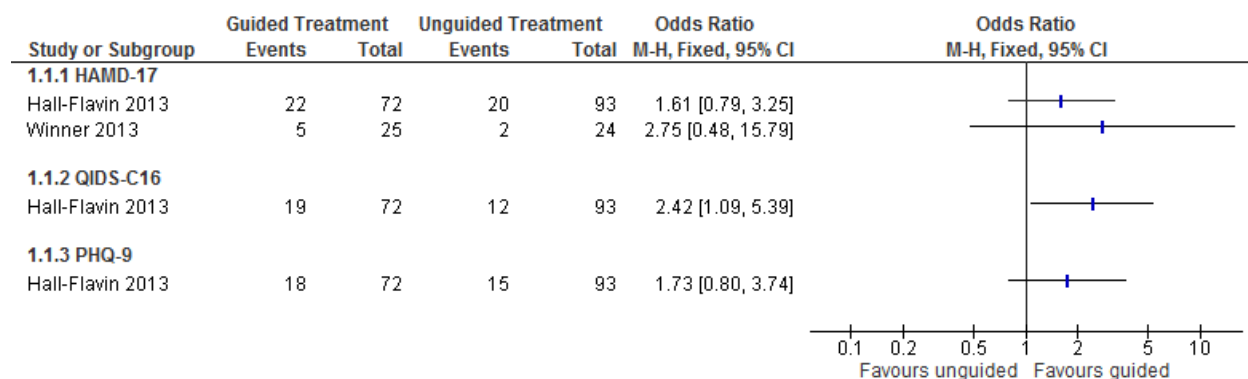


Figure 2: Proportion of Patients With Remission of Depression Symptoms^{a,b}

Abbreviations: CI, confidence interval; HAMD-17, 17-item Hamilton Rating Scale for Depression; M-H, Mantel-Haenszel; PHQ-9, 9-item Patient Health Questionnaire; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating.

^aHall-Flavin et al reported nonsignificant results for HAMD-17 and PHQ-9, but calculations were estimates based on raw data presented in the original report. For HAMD-17, there were some rounding differences in the data presented here compared with the original study.²⁷

^bHall-Flavin et al had a follow-up period of 8 weeks; Winner et al had a follow-up period of 10 weeks.^{27,29}

Table 4: GRADE Evidence Profile for Remission of Depression Symptoms

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
HAMD-17							
1 (RCT)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
1 (observational)							
QIDS-C16							
1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
PHQ-9							
1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAMD-17, 17-item Hamilton Rating Scale for Depression; PHQ-9, 9-item Patient Health Questionnaire; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating; RCT, randomized controlled trial.

^aRisk of bias assessment details are available in Appendix 3.

^bWide confidence intervals impacted our confidence in the estimate. Given the small number of events, the findings may not be as robust, which leads us to have some uncertainty about the results observed. In particular, the relatively large treatment effect given the small sample size of the RCT may be due to prognostic imbalance and warrants caution in interpretation of the results.

Response to Depression Therapy

Three studies reported the proportion of patients who responded to depression therapy.^{27-29,31} In these studies, responders were defined as having achieved at least a 50% reduction in depression scores.^{27-29,31}

Figure 3 analyzes the results for response rate. Hall-Flavin et al²⁸ did not report response rates in their publication, but data for that population were available from a cost-effectiveness analysis published by Hornberger et al.³¹

One study, Hall-Flavin et al²⁷ conducted sensitivity analyses using the intention-to-treat analytical strategies of expected maximum and last observation carried forward and found that results were consistent and/or stronger in favour of guided therapy than those reported here. A significantly greater proportion of patients had a response to depression therapy with GeneSight-guided care than those who received usual care (Figure 3), based on low to very low quality evidence (Table 5).

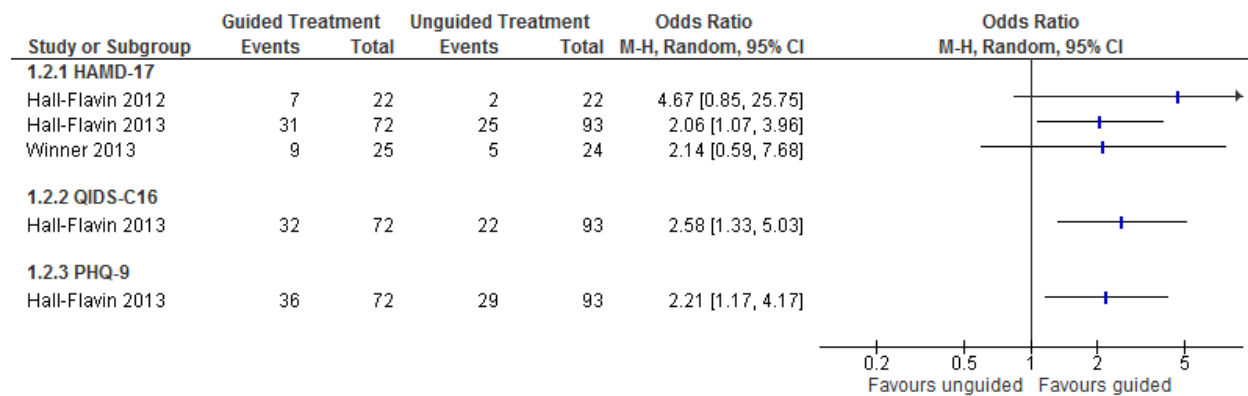


Figure 3: Proportion of Patients With Response to Depression Therapy^{a,b,c}

Abbreviations: CI, confidence interval; HAMD-17, 17-item Hamilton Rating Scale for Depression; M-H, Mantel-Haenszel; PHQ-9, 9-item Patient Health Questionnaire; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating.

^aFor Hall-Flavin et al, the numbers presented here present some rounding differences from the study, which reported an odds ratio for the HAMD-17 score of 2.06 (95% CI, 1.07–3.95).²⁷

^bThe response rate for Hall-Flavin et al²⁸ was not reported in the original study, but data were available from a cost-effectiveness analysis published by Hornberger et al.³¹

^cHall-Flavin et al had a follow-up period of 8 weeks; Winner et al 2013 had a follow-up period of 10 weeks.^{27,29}

Table 5: GRADE Evidence Profile for Response to Depression Therapy

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
HAMD-17							
1 (RCT) 2 (observational)	Serious limitations ^a	No limitations	No limitations	No limitations	None detected	None	⊕⊕ Low
QIDS-C16							
1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
PHQ-9							
1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAMD-17, 17-item Hamilton Rating Scale for Depression; PHQ-9, 9-item Patient Health Questionnaire; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating; RCT, randomized controlled trial.

^aRisk of bias assessment details are available in Appendix 3.

^bWide confidence intervals impacted our confidence in the estimate of effect.

Depression Score

Across the studies that reported on changes in depression scores, patients in the guided and unguided study groups were considered to be similar at baseline.²⁷⁻²⁹

Table 6 summarizes the effect on measures of depression among patients who received guided care compared with those who did not (at end-of-study follow-up). Overall, patients who received guided care with GeneSight had a greater reduction in depression than those who had treatment as usual.

Table 6: Depression Score at End of Study

Author, Year	Length of Follow-up	% Reduction in Score (Improvement in Depression)		Significance ^a
		Guided	Unguided	
HAMD-17				
Hall-Flavin et al, 2012 ²⁸	8 weeks	30.8%	18.2%	$P = .04$; adjusted $P = .05$
Hall-Flavin et al, 2013 ²⁷	8 weeks	46.9%	29.9%	$P < .0001$; adjusted $P < .0001$
Winner et al, 2013 ²⁹	10 weeks	30.8%	20.7%	$P = .28$
QIDS-C16				
Hall-Flavin et al, 2012 ²⁸	8 weeks	31.2%	7.2%	$P = .002$; adjusted $P = .003$
Hall-Flavin et al, 2013 ²⁷	8 weeks	44.8%	26.4%	$P < .0001$; adjusted $P < .0001$
Winner et al, 2013 ²⁹	10 weeks	27.6%	22.1%	NS
PHQ-9				
Hall-Flavin et al, 2013 ²⁷	8 weeks	40.1%	19.5%	$P < .0001$; adjusted $P = .002$
Winner et al, 2013 ²⁹	10 weeks	35.4%	21.3%	$P = .18$

Abbreviations: ANOVA, analysis of variance; HAMD-17, 17-item Hamilton Rating Scale for Depression; NS, not significant; PHQ-9, 9-item Patient Health Questionnaire; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating.

^aA repeated-measures ANOVA mixed-model approach was used, adjusting for time (in weeks) and treatment group.

No statistically significant differences were observed between groups at 2 weeks except for Hall-Flavin et al,²⁷ who observed a significantly greater depression score with the QIDS-C16 measure at baseline in the guided group than in the unguided group (17.5 vs. 16.0, $P = .003$). At 4 weeks, Hall-Flavin et al²⁷ found a significantly greater improvement in the guided group on the HAMD-17 ($P = .0002$) and QIDS-C16 ($P = .0002$), but not on the PHQ-9 ($P = \text{NS}$). At 6 weeks, Winner et al²⁹ saw similarly greater improvement on the HAMD-17 score in the guided group (35.4% improvement vs. 18.5% improvement in the unguided group, $P = .04$). Sensitivity analyses conducted by the studies using expected maximum and last observation carried forward to account for missing data demonstrated that results were robust and conclusions remained aligned to the primary analyses summarized in Table 6.

Based on very low quality evidence (Table 7), improvements in depression score were greater among patients who received GeneSight-guided care than those who received usual care.

Table 7: GRADE Evidence Profile for Depression Score

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
HAMD-17							
1 (RCT)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
2 (observational)							
QIDS-C16							
2 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
PHQ-9							
2 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAMD-17, 17-item Hamilton Rating Scale for Depression; PHQ-9, 9-item Patient Health Questionnaire; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating.

^aRisk of bias assessment details are available in Appendix 3.

^bWide confidence intervals impacted our confidence in the estimate of effect; experts advised that a clinically meaningful difference in HAMD-17 was two to three points.

Subgroup Analyses

Some studies conducted subgroup analyses based on patients' bin status. Table 8 summarizes the results comparing the end-of-study reduction in depression score among those who received guided versus unguided care in patients who took red-bin medications at the start of each study.

Table 8: Depression Score Among Patients Who Took Red-Bin Medications

Author, Year	Measure	% Reduction in Score (Improvement in Depression)		Significance
		Guided	Unguided	
Hall-Flavin et al, 2013 ²⁷	HAMD-17	42.5%	16.6%	$P = .01$
	QIDS-C16	41.9%	11.0%	$P = .004$
Winner et al, 2013 ²⁹	HAMD-17	32% ^a	0.8%	$P = .06$

Abbreviations: HAMD-17, 17-item Hamilton Rating Scale for Depression; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating.

^aPercentage reduction is an estimate based on Figure 4 published in the study.²⁹

The authors also observed a difference among patients in the unguided care group who were prescribed red-bin medications compared with those who received yellow- or green-bin medications. Patients who were prescribed red-bin medications but received unguided care demonstrated an improvement in HAMD-17 and QIDS-C16 scores of 0.8% to 16.6%; patients on yellow- and green-bin medications improved significantly more, from 26.5% to 36.1% ($P = .007$).^{27,29}

Quality of Life

None of the studies reported on quality of life.

Results for Secondary Outcomes

Impact on Therapeutic Decisions

We considered changes to medication regimens as a measure of therapeutic decisions, presuming that modifications indicated that patients were not responding to depression therapy or had had adverse reactions that prompted decisions to change the regimen. All included studies reported some measure of medication change (Table 9).

Table 9: Impact on Therapeutic Decisions—Modifications to Medication Regimens, Adherence to Medication Regimens, and Polypharmacy

Author, Year	Measure	Results		Significance
		Guided	Unguided	
Modifications				
Hall-Flavin et al, 2013 ²⁷	Proportion of patients who had a change ^a in their medication from baseline	76.8%	44.1%	$P < .0001$
Winner et al, 2013 ²⁹	Proportion of patients who had a change ^a in their medication from baseline to end of study	53%	58%	$P = .66$
Adherence				
Winner et al, 2015 ³⁰	Adherence ^b at end of follow-up	0.74	0.79	$P < .0001$
	Change from baseline in adherence ^b	0.111	-0.01	$P < .0001$
	Differences between rates of medication discontinuation before and after the start of study	-7.6%	+0.3%	$P < .0001$
	Mean time to discontinuation of the initial medication from the start of study	103 days	134 days	$P < .0001$
Polypharmacy				
Hall-Flavin et al, 2012 ²⁸	Difference in mean number of medications per patient at the end of the study compared with the beginning	-2.7 (SD 3.5) ^c	-2.2 (SD 3.4) ^c	Difference of the means: 0.5 (SD 6.7) ^c
Winner et al, 2013 ²⁹	Mean number of psychiatric medications per patient at end of study	1.9	1.7	$P = .27$
Winner et al, 2015 ³⁰	Increase in average number of medications taken from baseline to end of follow-up	0.88	1.07	$P < .0001$

Abbreviation: SD, standard deviation.

^aChange included a switch of medication or augmentation in dosage.

^bAdherence was the ratio of the proportion of days on a medication over the total covered days from the index prescription, with discontinuation defined as ≥ 45 days between refills.

^cCalculated based on data provided in the original study; estimate around the variance is conservative given that within-study correlation was not accounted for. Reported mean medications at baseline in the guided and unguided groups were 4.4 (SD 3.4) and 4.4 (SD 3.13), respectively. Reported mean medications at the end of the study in the guided and unguided groups were 1.7 (SD 0.84) and 2.2 (SD 1.4), respectively.²⁸

One study found a significant difference in the proportion of patients who discontinued the medication prescribed at the start of the study between the guided group (60.9%) and the unguided group (40.9%; $P < .001$).³⁰ However, patients who received guided care were also more likely to discontinue their medication during the study period (53.3%) than those who received treatment as usual (41.2%; $P < .001$).³⁰ The guided group also had a slightly shorter but statistically significant ($P < .001$) time before discontinuing the initial medication, at 150 days after the start of the study compared with 152 days for the unguided group.³⁰

Based on very low quality evidence (Table 10), the findings were inconsistent as to whether GeneSight-guided care improved therapeutic decisions compared with usual care (Table 9).

Table 10: GRADE Evidence Profile for Impact on Therapeutic Decisions

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 (RCT) 3 (observational)	Serious limitations ^a	Serious limitations ^b	Very serious limitations ^c	No limitations	None detected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

^aRisk of bias assessment details are available in Appendix 3.

^bResults were inconsistent between the studies: some demonstrated an increase in the mean number of medications per patient by end of study, and others a decrease.

^cOutcomes were indirect measures of the outcome of interest (the impact of guided therapy on therapeutic decision-making).

Subgroup Analyses

Table 11 summarizes the subgroup analyses conducted by studies that assessed results based on whether patients were prescribed green-bin, yellow-bin, or red-bin medications according to the GeneSight test.

Table 11: Modifications to Medication Regimens by Subgroup Based on GeneSight Results

Author, Year	Measure	Results		
		Guided	Unguided	Significance
Hall-Flavin et al, 2012 ²⁸	Proportion of patients taking a green-bin medication at end of study	71% ^a	21% ^a	NR
	Proportion of patients taking a yellow-bin medication at end of study	23% ^a	57% ^a	NR
	Proportion of patients taking a red-bin medication at end of study	5.9%	21.4%	$P = .02$
Hall-Flavin et al, 2013 ²⁷	Proportion of patients taking a green-bin medication at end of study	40%	27.6%	NS ^b
	Absolute increase in percentage points of the proportion of patients taking a green-bin medication compared with baseline	13.4	1.7	NS ^b
	Proportion of patients taking a red-bin medication who changed their medication by end of study	93.8%	55.6%	$P = .01$
Winner et al, 2013 ²⁹	Proportion of patients taking a red-bin medication at baseline	100%	50%	$P = .02$
Winner et al, 2015 ³⁰	Change in proportion of patients taking a green-bin medication from start of study to end of study ^c	+13.3%	NR	NR
	Change in proportion of patients taking a yellow-bin medication from start of study to end of study ^c	-4.8%	NR	NR
	Change in proportion of patients taking a red-bin medication from start of study to end of study ^c	-8.5%	NR	NR

Abbreviation: NR, not reported.

^aEstimates based on visual inspection of a graph reported in the study.

^bStudy reported as not significant, but did not provide detailed statistics.

^cWithin the previous 90 days.

By the end of the studies, most patients were taking green-bin or yellow-bin medications, and few were taking red-bin medications.

Patient and Clinician Satisfaction

One study reported on satisfaction. The authors asked clinicians to rate their level of satisfaction, and to estimate their patients' level of satisfaction (Table 12).

Table 12: Satisfaction

Author, Year	Measure	Intervention/Control, N	Results		Significance
			Guided	Unguided	
Patient Satisfaction					
Hall-Flavin et al, 2013 ²⁷	Physician perception of patient satisfaction; proportion rated as having very high perceived satisfaction	37/88	40.5%	14.8%	<i>P</i> = .008
Clinician Satisfaction					
Hall-Flavin et al, 2013 ²⁷	Physician satisfaction with care	37/88	94.6%	61.8%	<i>P</i> = .0007
	Physician confidence in choice of medication	37/88	91.9%	61.8%	<i>P</i> = .003

Based on very low quality evidence (Table 13), there was significantly greater patient satisfaction among those who received GeneSight-guided care than among those who received usual care (Table 12). Similarly, based on low quality evidence (Table 13), there was greater clinician satisfaction with GeneSight-guided care than with usual care (Table 12).

Table 13: GRADE Evidence Profile for Satisfaction

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Patient Satisfaction							
1 (observational)	Serious limitations ^a	No serious limitations	Very serious limitations ^b	No serious limitations	None detected	None	⊕ Very low
Clinician Satisfaction							
1 (observational)	Serious limitations ^a	No serious limitations	No serious limitations	No serious limitations	None detected	None	⊕⊕ Low

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

^aRisk of bias assessment details are available in Appendix 3.

^bMeasure of patient satisfaction was based on clinician perception of their patients' satisfaction.

Discussion

We identified one systematic review on this topic. It was published by authors affiliated with the manufacturer, and it identified the same studies included in this review and drew similar conclusions to this report.³⁷

Limitations

There are multiple versions of the GeneSight Psychotropic test. The results from the studies were based on an algorithm that used a combination of five or six genes and may not be generalizable to a version of GeneSight containing eight, 12, or more genes. As well, the three studies that reported our primary outcomes of interest limited their design to psychiatrists; we cannot draw conclusions about the effectiveness of the test when used by other clinicians. One study by the manufacturers found that non-psychiatrist primary care physicians followed the recommendations of GeneSight more closely than psychiatrists, but this study did not demonstrate whether this difference had an impact on patient outcomes, so it did not meet the inclusion criteria for this review.³⁰ Similarly, GeneSight has been proposed for use in patients with mood disorders, anxiety, or schizophrenia, but the three studies that reported results for our primary outcomes of interest limited their populations to patients with major depressive disorder, excluding patients with anxiety alone without depression, patients with bipolar disorder, or schizophrenia. Taken together, these factors limit the generalizability of the body of evidence. Looking to other jurisdictions, at the time of writing this report, the United States Centers for Medicare & Medicaid Services covered GeneSight only if it was ordered by psychiatrists for patients with major depressive disorder whose symptoms were refractory after at least one prior neuropsychiatric medication and who continued to have moderate to severe depression as defined by the Hamilton Rating Scale for Depression.²²

A second limitation was the uncertainty around the level of evidence supporting each medication included in the GeneSight report. Each medication has its own evidence profile, but the quality of the evidence supporting green-, yellow-, or red-bin classifications in GeneSight is not clear in the current version of the GeneSight report as clinicians would not know the strength of the evidence behind what moves a medication from green bin- to another status. Assurex has indicated that a revised version of the report, expected in early 2017, will be more transparent. The updated version is expected list which genes are related to which medications.

Comparable Tests

This review focused on the Ontario context, which at the time of review did not cover pharmacogenomic testing for patients with mood disorders. However, this test, and others similar to GeneSight are available if paid for by the patient. The list in Table 14 is not exhaustive or comprehensive—simply a summary of known tests similar in purpose to GeneSight Psychotropic providing a pharmacogenomic panel to support psychotropic medication selection.

Table 14: Comparable Pharmacogenomic Panels to Support Psychotropic Medication Selection

Company	Assurex	CNSdose	CRL Corp	Genele X	Genomind	MDL-Labs
Test	GeneSight	CNSDose	SureGene	You Script psychotropic plus	Genecept	Psychiatric pharmacogenetic
Website ^a	https://genesight.com/	https://www.cnsdose.com/	http://www.crlcorp.com/services/personalized-medicine/tests/	http://genelex.com/	https://genomind.com/	http://www.mdl-labs.com/providers/tests/psychiatric-pharmacogenetic-test-panel
Number of genes	8 ^b	3 ^c	19	12	19	4
List of genes		ABC transporters ^c				
				ADRA2A	ADRA2A	
					ANK3	
					BDNF	
					CACNA1C	
			COMT	COMT	COMT	
	CYP1A2		CYP1A2	CYP1A2	CYP1A2	
	CYP2B6		CYP2B6	CYP2B6	CYP2B6	
	CYP2C19		CYP2C19	CYP2C19	CYP2C19	CYP2C19
	CYP2C9		CYP2C9		CYP2C9	CYP2C9
	CYP2D6		CYP2D6	CYP2D6	CYP2D6	CYP2D6
	CYP3A4		CYP3A4	CYP3A4	CYP3A4	CYP3A4
			CYP3A5		CYP3A5	
		CYP450 ^c				
					DRD2	
			FOLH1			
			GLP1R			
				GRIK4	GRIK1	
			HLA-A			
			HLA-B			
	HTR2A		5HTR2A	HTR2A		
			5HTR2C	HTR2C	5HT2C	
					MC4R	
			MTHFR	MTHFR	MTHFR	
			OPRM1		OPRM1	
	SLC6A4		SLC6A4	SLC6A4/5-HTT	SLC6A4	
			SULT4A1			
		UGT1A1				
			VKORC1			

^aAll websites were accessed on May 2, 2016.

^bIncluded genes were based on the application received from Assurex for review.

^cSpecific genes in these gene groups were not identified on the company website, or in the academic paper by Singh et al.³⁸ We are aware of two other similar tests, but we were unable to locate specific details about these tests at the time of this review. These tests are psynome2 by psynomics and PsychINDx by curidium medica.

Conclusions

Patients who received guided medication selection with the GeneSight Psychotropic test demonstrated improved response to depression therapy and greater improvement in measures of depression and patient and clinician satisfaction than patients who received treatment as usual. However, there were no observed differences in rates of complete remission from depression. These findings are uncertain because they are supported by low to very low confidence in the evidence (Table 15).

Table 15: Summary of Results for Review of GeneSight to Support Psychotropic Medication Selection Among Patients With Mood Disorders

Outcome	Measure	Results	GRADE
Patient Outcomes			
Suicide	Mortality	None reported	NA
Remission of depression symptoms	Depression below a predefined threshold: HAMD-17 <8, QIDS-C16 <5 or PHQ-9 <5	No significant difference between groups ^a	Very low
Response to depression therapy	At least 50% reduction in depression scores based on HAMD-17, QIDS-C16, or PHQ-9	Favoured guided therapy	Low to very low
Measures of depression	% reduction in score (improvement in depression)	HAMD-17	Favoured guided therapy
		QIDS-C16	Favoured guided therapy
		PHQ-9	Favoured guided therapy
Quality of life	Validated measures of quality of life	None reported	NA
Secondary Outcomes			
Impact on therapeutic decisions	Changes to medications	Inconsistent measurement outcome resulted in either no significant difference or observed difference in favour of guided therapy	Very low
Satisfaction	Patient satisfaction	Favoured guided therapy	Very low
	Clinician satisfaction	Favoured guided therapy	Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAMD-17, 17-item Hamilton Rating Scale for Depression; NA, not applicable; NS, not significant; PHQ-9, 9-item Patient Health Questionnaire; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating.

^aNo significant difference when using the HAMD-17 or PHQ-9 measures; a significant result was observed with the QIDS-C16 in favour of guided care.

ABBREVIATIONS

CPIC	Clinical Pharmacogenetic Consortium
EMA	European Medicines Agency
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAMD-17	17-item Hamilton Rating Scale for Depression
LHIN	Local Health Integration Network
PHQ-9	9-item Patient Health Questionnaire
PICOT	Population, intervention, comparison, outcome and time
PMDA	Pharmaceutical and Medical Devices Agency, Japan
QIDS-C16	16-item Quick Inventory of Depression Symptomatology, clinician rating
SSRI	Selective serotonin reuptake inhibitor

GLOSSARY

Fixed effects	A meta-analysis method (a study of studies) that takes into account only the variation in effects among the individual participants across all studies. It does not look at the variation in results among the studies. This analysis assumes differences in study methods do not affect the overall outcome.
Gene	A specific segment of a chromosome (a DNA strand) that is responsible for passing on a specific trait through inheritance.
Genome	The entire genetic makeup (all DNA) that includes the genes and non-gene segments of a chromosome.
Genomics	The field of study that focuses on the genome of an organism (as distinct from genetics, which focuses on the effects of a single gene). It includes how the expression of genes is affected by environmental factors, such as a person's lifestyle.
Genotype	The genome of a specific person. Genotype may also be used to refer to a segment of a person's genome (usually a gene).
Pharmacogenomics	A field of study that looks at how a person's genotype may affect their response to a drug.
Phenotype	The physical characteristics resulting from a person's genetic profile (their genotype).

APPENDICES

Appendix 1: Additional Clinical Evidence

Table A1: Genes Included in the GeneSight Psychotropic Test

Gene	Location	Variants Detected by the Test	Mechanism of Action
<i>CYP1A2</i>	15q24.1	15 SNPs: -163C>A, -246delT, -3860 G>A, -729C>T, -739 T>G, 125C>G, 2116 G>A, 2473 G>A, 2499 A>T, 349 G>A, 3533 G>A, 5090C>T, 5166 G>A, 5347C>T, 558C>A	A member of the cytochrome P450 family of liver enzymes, which plays an important role in drug metabolism
<i>CYP2B6</i>	19q13.2	2 SNPs: A785G (*4) and G516T (*6)	A member of the cytochrome P450 family of liver enzymes, which plays an important role in drug metabolism
<i>CYP2C19</i>	10q23.33	Detection of *1, *2, *3, *4, *5, *6, *7, *8 and *17 alleles	A member of the cytochrome P450 family of liver enzymes, which plays an important role in drug metabolism
<i>CYP2C9</i>	10q23.33	Detection of *1, *2, *3, *4, *5, and *6 alleles	A member of the cytochrome P450 family of liver enzymes, which plays an important role in drug metabolism
<i>CYP2D6</i>	22q13.2	Detection of *1, *2, *2 A, *3, *4, *5 (deletion of allele), *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, and *41 alleles. Multiple copies of the allele	A member of the cytochrome P450 family of liver enzymes, which plays an important role in drug metabolism
<i>CYP3A4</i>	7q22.1	Detection of *1, *13, *15A, and *22 alleles	A member of the cytochrome P450 family of liver enzymes, which plays an important role in drug metabolism
<i>HTR2A</i>	13q14.2	3 genotypes: A/A, A/G, and G/G	A serotonergic gene where variations affect the mechanism of action for the transporter activity of certain SSRIs (e.g., adverse drug effects)
<i>SLC6A4</i>	17q11.2	Detection of three genotypes of two alleles: homozygous for the long allele, homozygous for the short allele, and heterozygous for long and short The long allele is characterized by a 44 base-pair insertion in the promoter region and a 419 base-pair fragment of DNA vs. 375 in the short allele, a visible difference on gel electrophoresis	A serotonergic gene where variations affect the mechanism of action for the receptor activity of certain SSRIs (e.g., reduced response rate and increased time to response)

Abbreviation: SNP, single nucleotide polymorphism; SSRI, selective serotonin reuptake inhibitor.

Table A2: Results for Differences Across Patient Phenotypes Identified With Single Genotyping vs. Combinatorial Genomic Testing (GeneSight)^a

Outcome	Patient Gene Group	Unguided Patients, N	Results	
			Combinatorial Genomics (GeneSight)	Single-Gene Phenotyping
HAM-D-17 improvement	<i>CYP2D6</i>	117	<i>P</i> = .003 ^b	<i>P</i> = .96
	<i>CYP2C19</i>	80	<i>P</i> = .04 ^b	<i>P</i> = .52
	<i>CYP1A2</i>	35	<i>P</i> = .03 ^b	<i>P</i> = .33
	<i>SLC6A4</i>	66	<i>P</i> = .27	<i>P</i> = .43
	<i>HTR2A</i>	5	<i>P</i> = .16	<i>P</i> = .16
Total health care visits	<i>CYP2D6</i>	79	<i>P</i> = .04 ^b	<i>P</i> = .11
	<i>CYP2C19</i>	59	<i>P</i> = .04 ^b	<i>P</i> = .02 ^b
	<i>CYP1A2</i>	32	<i>P</i> = .01 ^b	<i>P</i> = .83
	<i>CYP2C9</i>	10	<i>P</i> = .55	<i>P</i> = .32
	<i>SLC6A4</i>	60	<i>P</i> = .77	<i>P</i> = .63
	<i>HTR2A</i>	15	<i>P</i> = .78	<i>P</i> = .26
Medical visits	<i>CYP2D6</i>	79	<i>P</i> = .06	<i>P</i> = .26
	<i>CYP2C19</i>	59	<i>P</i> = .14	<i>P</i> = .05 ^b
	<i>CYP1A2</i>	32	<i>P</i> = .02 ^b	<i>P</i> = .61
	<i>CYP2C9</i>	10	<i>P</i> = .17	<i>P</i> = .44
	<i>SLC6A4</i>	60	<i>P</i> = .51	<i>P</i> = .58
	<i>HTR2A</i>	15	<i>P</i> = .61	<i>P</i> = .18
Disability claims	<i>CYP2D6</i>	79	<i>P</i> = .002 ^b	<i>P</i> = .55
	<i>CYP2C19</i>	59	<i>P</i> = .001 ^b	<i>P</i> = .62
	<i>CYP1A2</i>	32	<i>P</i> = .14	<i>P</i> = .35
	<i>CYP2C9</i>	10	<i>P</i> = .65	<i>P</i> = .44
	<i>SLC6A4</i>	60	<i>P</i> = .44	<i>P</i> = .26
	<i>HTR2A</i>	15	<i>P</i> = .80	<i>P</i> = .51

Abbreviations: HAM-D-17, 17-item Hamilton Rating Scale for Depression.

^aResults from Altar et al.¹⁶

^bStatistically significant.

Appendix 2: Literature Search Strategies

Search date: Feb 22, 2016

Librarians: Corinne Holubowich

Databases searched: All Ovid MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2016>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 19, 2016>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Health Technology Assessment <1st Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2016 Week 08>, All Ovid MEDLINE(R) <1946 to Present>, PsycINFO <1967 to February Week 2 2016>

Search Strategy:

-
- 1 Depressive Disorder, Major/ (26865)
 - 2 ((depression* or depressive* or melancholia* or paraphrenia* or psychos?s) adj2 (major or disorder* or involution* or unipolar*)).tw. (187247)
 - 3 Mood Disorders/ (29497)
 - 4 ((affective or mood) adj disorder*).tw. (90895)
 - 5 Anxiety Disorders/ (48451)
 - 6 Bipolar Disorder/ (97611)
 - 7 ((anxiety adj (disorder* or neuros?s)) or ((bipolar or manic) adj (psychos?s or disorder* or depression* or depressive*))).tw. (165660)
 - 8 or/1-7 (432557)
 - 9 Pharmacogenetics/ (25576)
 - 10 (pharmacogenetic* or pharmacogenomic*).tw. (29773)
 - 11 Genetic Testing/ (59139)
 - 12 Genotyping Techniques/ (6016)
 - 13 (((genetic* or gene or genes) adj2 (test or tests or testing or panel* or assess* or screen* or profil* or algorithm* or combinatorial)) or psychotropic panel*).tw. (204909)
 - 14 (genotype adj (assignment* or method* or technique*)).tw. (948)
 - 15 (genesight or assurex).tw. (25)
 - 16 or/9-15 (287465)
 - 17 8 and 16 (3171)
 - 18 Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. or Congresses.pt. (4518636)
 - 19 17 not 18 (3096)
 - 20 exp Animals/ not (exp Animals/ and Humans/) (13325189)
 - 21 19 not 20 (2251)
 - 22 limit 21 to english language [Limit not valid in CDSR,DARE; records were retained] (2150)
 - 23 22 use pmoz,cctr,coch,dare,clhta,cleed (974)
 - 24 major depression/ (141961)
 - 25 ((depression* or depressive* or melancholia* or paraphrenia* or psychos?s) adj2 (major or disorder* or involution* or unipolar*)).tw. (187247)
 - 26 mood disorder/ (56353)
 - 27 ((affective or mood) adj disorder*).tw. (90895)
 - 28 anxiety disorder/ (92738)
 - 29 bipolar disorder/ (97611)
 - 30 ((anxiety adj (disorder* or neuros?s)) or ((bipolar or manic) adj (psychos?s or disorder* or depression* or depressive*))).tw. (165660)
 - 31 or/24-30 (519047)
 - 32 pharmacogenomics/ (17736)
 - 33 (pharmacogenetic* or pharmacogenomic*).tw. (29773)

- 34 genetic screening/ (85784)
- 35 genotyping technique/ (7207)
- 36 (((genetic* or gene or genes) adj2 (test or tests or testing or panel* or assess* or screen* or profil* or algorithm* or combinatorial)) or psychotropic panel*).tw. (204909)
- 37 (genotype adj (assignment* or method* or technique*)).tw. (948)
- 38 (genesight or assurex).tw. (25)
- 39 or/32-38 (299732)
- 40 31 and 39 (3541)
- 41 Case Report/ or Comment/ or Editorial/ or Letter/ or conference abstract.pt. (8411318)
- 42 40 not 41 (3032)
- 43 (exp animal/ or nonhuman/) not exp human/ (9612770)
- 44 42 not 43 (2919)
- 45 limit 44 to english language [Limit not valid in CDSR,DARE; records were retained] (2804)
- 46 45 use emez (1249)
- 47 major depression/ (141961)
- 48 ((depression* or depressive* or melancholia* or paraphrenia* or psychos?s) adj2 (major or disorder* or involution* or unipolar*)).tw. (187247)
- 49 affective disorders/ (56371)
- 50 ((affective or mood) adj disorder*).tw. (90895)
- 51 anxiety disorders/ (48451)
- 52 bipolar disorder/ (97611)
- 53 ((anxiety adj (disorder* or neuros?s)) or ((bipolar or manic) adj (psychos?s or disorder* or depression* or depressive*))).tw. (165660)
- 54 or/47-53 (497656)
- 55 pharmacodynamics/ (22342)
- 56 (pharmacogenetic* or pharmacogenomic*).tw. (29773)
- 57 genetic testing/ (59139)
- 58 (((genetic* or gene or genes) adj2 (test or tests or testing or panel* or assess* or screen* or profil* or algorithm* or combinatorial)) or psychotropic panel*).tw. (204909)
- 59 (genotype adj (assignment* or method* or technique*)).tw. (948)
- 60 (genesight or assurex).tw. (25)
- 61 or/55-60 (292630)
- 62 54 and 61 (3364)
- 63 case report/ or editorial.dt. or comment reply.dt. or letter.dt. (3980795)
- 64 62 not 63 (3245)
- 65 limit 64 to english language [Limit not valid in CDSR,DARE; records were retained] (3106)
- 66 65 use psyb (604)
- 67 23 or 46 or 66 (2827)
- 68 67 use pmoz (884)
- 69 67 use emez (1249)
- 70 67 use psyb (604)
- 71 67 use coch (10)
- 72 67 use cctr (71)
- 73 67 use clhta (0)
- 74 67 use cleed (3)
- 75 67 use dare (6)
- 76 remove duplicates from 67 (1890)

Appendix 3: Evidence Quality Assessment

Our first consideration was study design; we started with the assumption that randomized controlled trials are high quality, whereas observational studies are low quality. We then took into account five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias. Limitations in these areas resulted in downgrading the quality of evidence. Finally, we considered three main factors that may raise the quality of evidence: the large magnitude of effect, the dose-response gradient, and any residual confounding factors.²⁶ For more detailed information, please refer to the latest series of GRADE articles.²⁶

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	We are very confident that the true prognosis (probability of future events) lies close to that of the estimate
Moderate	We are moderately confident that the true prognosis (probability of future events) is likely to be close to the estimate, but there is a possibility that it is substantially different
Low	Our confidence in the estimate is limited: the true prognosis (probability of future events) may be substantially different from the estimate
Very Low	We have very little confidence in the estimate: the true prognosis (probability of future events) is likely to be substantially different from the estimate

Table A3: GRADE Evidence Profile for Comparison of GeneSight-Guided Care and Usual Care

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Remission of Depression Symptoms							
HAMD-17							
1 (RCT) 1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
QIDS-C16							
1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
PHQ-9							
1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
Response to Depression Therapy							
HAMD-17							
1 (RCT) 2 (observational)	Serious limitations ^a	No limitations	No limitations	No limitations	None detected	None	⊕⊕ Low
QIDS-C16							
1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
PHQ-9							
1 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
Depression Score							
HAMD-17							
1 (RCT) 2 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
QIDS-C16							
2 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
PHQ-9							
2 (observational)	Serious limitations ^a	No limitations	No limitations	Serious limitations ^b	None detected	None	⊕ Very low
Impact on Therapeutic Decisions							
1 (RCT) 3 (observational)	Serious limitations ^a	Serious limitations ^c	Very serious limitations ^d	No limitations	None detected	None	⊕ Very low
Patient Satisfaction							
1 (observational)	Serious limitations ^a	No serious limitations	Very serious limitations ^e	No serious limitations	None detected	None	⊕ Very low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Clinician Satisfaction							
1 (observational)	Serious limitations ^a	No serious limitations	No serious limitations	No serious limitations	None detected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAMD-17, 17-item Hamilton Rating Scale for Depression; PHQ-9, 9-item Patient Health Questionnaire; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, clinician rating; RCT, randomized controlled trial.

^aRisk of bias assessment details are available in Tables A2 and A3.

^bWide confidence intervals impacted our confidence in the estimate of effect; experts advised that a clinically meaningful difference in HAMD-17 was two to three points.

^cResults were inconsistent between the studies: some demonstrated an increase in the mean number of medications per patient by end of study, and others a decrease.

^dOutcomes were indirect measures of the outcome of interest (the impact of guided therapy on therapeutic decision-making).

^eMeasure of patient satisfaction was based on clinician perception of their patients' satisfaction.

Table A4: Risk of Bias Among Randomized Controlled Trials Evaluating Pharmacogenomic Testing With GeneSight

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Winner et al, 2013 ²⁹	No limitations ^a	Limitations ^b	No limitations ^c	None detected	Limitations ^d

^aSpecific method of allocation was not reported, but study reported randomized allocation.

^bPatients and assessors were blinded to treatment allocation, but clinicians could not be blinded to whether or not they received the GeneSight Psychotropic test results and may have introduced bias during their interaction with patients. There was potential uncertainty around subjective outcomes such as patient-reported feelings of depression.

^cOne patient in each study arm was lost to follow-up.

^dStudy included authors with conflicts of interest related to Assurex, the manufacturer of the GeneSight Psychotropic test.

Table A5: Risk of Bias Among Observational Studies Evaluating Pharmacogenomic Testing With GeneSight

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up	Other Limitations
Hall-Flavin et al, 2012 ²⁸	No limitations ^a	No limitations	Limitations ^b	Limitations ^c	No limitations ^d	Limitations ^e
Hall-Flavin et al, 2013 ²⁷	No limitations ^a	No limitations	Limitations ^b	No limitations ^f	Serious limitations ^g	Limitations ^e
Winner et al, 2015 ³⁰	No limitations	No limitations	Limitations ^b	No limitations ^h	Serious limitations ^g	Limitations ^e

^aStudy included only patients with certain psychiatric disorders. This may have limited the generalizability of the results to other populations.

^bOutcomes that were subjective in nature, such as measurements of feelings of depression, could be at risk for sources of bias due to lack of blinding of patients and clinicians.

^cBaseline criteria were significantly different for patients in the guided and unguided groups for number of medications previously tried. Patients in the guided group had more attempts with different medications than those in the unguided group, and results were not adjusted for potential sources of confounding.

^dOnly 72% of enrolled patients completed the study, but the authors conducted sensitivity analyses accounting for participant attrition using expectation maximization and last observation carried forward algorithms.

^eStudy included authors with conflicts of interest related to Assurex, the manufacturer of the GeneSight Psychotropic test.

^fStudy demonstrated balance in clinically meaningful criteria such as baseline depression score between treatment and control study arms.

^gPatients were dropped out after enrolment if they were prescribed a medication other than one covered by the GeneSight test, introducing a bias in effectiveness for the disease population as a whole.

^hStudy conducted 5:1 propensity matching of unguided to guided patients and demonstrated no statistically significant difference in clinically meaningful baseline characteristics between the groups.

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

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