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

May 2016

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APPENDIX A: EXISTING GUIDELINES

MDD GUIDELINES

Guideline	Reference to genetic testing?	Specific reference	Notes
VA/DoD: "Management of Major Depressive Disorder"[1]	Yes – Noted as a knowledge gap and area for future research	“There also needs to be a better understanding of the value and use of measurement-based care, including the place of pharmacogenetics in the treatment of MDD. Additional research is required in the use of genetic testing to aid in the selection of the most appropriate medication for a specific patient. Currently, there is insufficient evidence to support the routine use of genetic testing for the selection of one antidepressant over another.”	Updated version released in 2016
APA Practice Guideline for the Treatment of Patients With Major Depressive Disorder[2]	Yes – Noted as focus of future research as state that there is insufficient evidence about optimizing and individualizing treatment and cost-effectiveness	"In time, genetic testing may help guide selection or dosing of antidepressants, but data are currently insufficient to justify the cost of such tests." "...there are still many unanswered questions about optimizing and individualizing treatment." "Potential causes of depression or moderators of treatment response may be found through genomics, proteomics, physiological markers, personality traits, personal experiences, co-occurring conditions, or clusters of specific depressive symptoms."	Published in 2010
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders. Part 2: Maintenance Treatment of Major Depressive Disorder[3]	No	N/A	Published in 2015
NICE Guidelines for Depression in adults: recognition and management[4]	No	N/A	Published in 2009

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders. Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders[5]	Yes -- More referenced as a *future* effective tool *eg* "may" be informative and mentioned as having the potential to contribute to effective individualized treatment	"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." "Individualized (personalized) treatment approaches aim at selecting among different treatment options based on individual response predictors. **Although (particularly for antidepressant treatments) there have been a wide array of genetic studies which have described possible response predictors, their results are still not fully transferable to clinical practice**." "We can expect that results from genome-wide assays will broaden our knowledge and foster the validity of our findings regarding genetic predictors. **Successful integration of genetic predictors as well as further biomarkers and neuroimaging data into a combined model could open the door to an effective and clinically applicable personalized treatment of depression**."	Guidelines will be updated in 2018 and will review recommendations in light of new evidence from ongoing trials

GENETIC TESTING GUIDELINES

Guideline	***Recommendations for CYP450 genotype testing***	***Mention of others markers? (Examples: ABCB1, serotonin, dopamine)***
Clinical Pharmacogenomics Implementation Consortium guideline[6]	Provides information to allow the interpretation of existing CYP2D6 and/or CYP2C19 genotype tests to guide SSRI dosing, particularly focusing on fluvoxamine, paroxetine, citalopram, escitalopram and sertraline. Rates supporting evidence as moderate to high quality based on a systematic review. Patients on a stable and effective dose of an SSRI most likely will not benefit from additional dose modifications based on CYP2D6 or CYP2C19 genotype results. Similar to all diagnostic tests, genetic tests are one of several pieces of clinical information that should be considered before initiating drug therapy.	None
National Academy of Clinical Biochemistry (NACB)[7]	No recommendations specific to antidepressant medications.	None

AGNP (Germany) [8]	PGx represents "trait marker" not influenced by environmental factors. States that PGx is applicable to all situations and lifetime value. No evidence provided in ECRI summary.	Unknown
International Society of Psychiatric Genetics[9]	For already available genotype data, ISPG generally concurs with available dosing guidance, such as CPIC 2015. But ISPG does not recommend global genetic testing: “Evidence remains inconclusive as to the possible clinical utility of CYP450 genetic testing, but more research is needed. Expanded research efforts are needed to clarify the role of genetic testing in psychiatry.”	None
Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19[10]	CYP2D6 and CYP2C19 testing may help some patients taking some antidepressants. Extreme CYP2D6 and/or CYP2C19 genetic profiles should encourage clinicians to explore different treatment options. It is crucial to have a detailed pharmacological history. Clinical diagnosis is a Bayesian process of progressive accumulation of data, in which each piece makes the diagnosis “somewhat more or less suggestive.” Therapeutic drug monitoring (TDM) of drug levels may be particularly helpful when one suspects unusual genetic profiles of CYP2D6 and CYP2C19. Pharmacogenetic testing may be a new addition to psychiatric treatment, but, to use it properly, one needs to take into account basic pharmacological knowledge and common sense. CYP2D6 and CYP2C19 testing provides information only on one aspect [of drug response]: genetic pharmacokinetic factors. Information from Appendix 3: Clinical Guidelines for Selecting a Laboratory to Send Sample for CYP Genotyping: Remember that the **clinical applications of pharmacogenetics are very limited, and many of the gene tests have very limited evidence supporting their use**.	There are no clear reasons to consider genotyping other genes besides CYP2D6 and CYP2C19 in a typical psychiatric patient at this time.
Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and carbamazepine dosing	Detailed guidelines regarding the selection of alternative therapies, the use of phenotypic tests, when to conduct genotype testing, and costeffectiveness analyses are beyond the scope of this document.	N/A
CPIC drug-specific guidelines[11,12]	Dosing guidelines. In regards to testing, each drug-specific guideline states: "Guidelines regarding the use of pharmacogenomic tests in dosing of selective serotonin reuptake inhibitors have been published in Clinical Pharmacology and Therapeutics by the Clinical Pharmacogenetics Implementation Consortium (CPIC)."	N/A

APPENDIX B: SEARCH STRATEGIES

Database: Ovid MEDLINE

Database: Ovid MEDLINE(R) <1946 to February Week 4 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 03, 2016>
Search Strategy:

1. pharmacogenetic.mp. or exp Pharmacogenetics/ (12208)
2. pharmacogenomic.mp. (1946)
3. 1 or 2 (13046)
4. antidepressant.mp. or exp Antidepressive Agents/ (137858)
5. exp Depression/ or depression.mp. (302917)
6. major depressive disorder.mp. or exp Depressive Disorder, Major/ (28690)
7. 5 or 6 (311056)
8. 3 and 4 and 7 (335)
9. limit 8 to (english language and humans) (296)

Database: Ovid MEDLINE(R) without Revisions <1996 to February Week 4 2016>
Search Strategy:

1. pharmacogenomic.mp. or Pharmacogenetics/ (9631)
2. systematic review.mp. (53368)
3. Depression/ or depression.mp. (178021)
4. meta analysis.mp. or Meta-Analysis/ (83682)
5. 2 or 4 (115800)
6. 1 and 3 and 5 (7)

Database: Cochrane Central Register of Controlled Trials (February 2016)

1. pharmacogenetic.mp. or exp Pharmacogenetics/ (544)
2. pharmacogenomic.mp. (122)
3. 1 or 2 (637)
4. antidepressant.mp. or exp Antidepressive Agents/ (13539)
5. exp Depression/ or depression.mp. (35805)
6. major depressive disorder.mp. or exp Depressive Disorder, Major/ (4502)
7. 5 or 6 (36737)
8. 3 and 4 and 7 (51)
9. limit 8 to (english language and humans) [Limit not valid; records were retained] (46)

Database: PsychINFO (March 2016)

1. pharmacogenetic.mp. or exp Pharmacogenetics/ (694)
2. pharmacogenomic.mp. (140)
3. 1 or 2 (801)
4. antidepressant.mp. or exp Antidepressive Agents/ (28844)
5. exp Depression/ or depression.mp. (250924)
6. major depressive disorder.mp. or exp Depressive Disorder, Major/ (14871)
7. 5 or 6 (252352)

8. 3 and 4 and 7 (114)
9. limit 8 to (english language and humans) [Limit not valid in PsycINFO; records were retained] (108)

APPENDIX C: LIST OF EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type 8=Outdated or ineligible systematic review

#	Citation	Exclude reason
1	Gvozdic K, Brandl EJ, Taylor DL, Muller DJ. Genetics and personalized medicine in antidepressant treatment. *Curr Pharm Des.* 2012;18(36):5853-5878.	7
2	Hall-Flavin DK, Schneekloth TD, Allen JD. Translational Psychiatry: Bringing Pharmacogenomic Testing into Clinical Practice. *Primary Psychiatry.* 2010;17(5).	7
3	Horstmann S, Binder EB. Pharmacogenomics of antidepressant drugs. *Pharmacol Ther.* Oct 2009;124(1):57-73.	7
4	Kirchheiner J, Bertilsson L, Bruus H, Wolff A, Roots I, Bauer M. Individualized medicine-implementation of pharmacogenetic diagnostics in antidepressant drug treatment of major depressive disorders. *Pharmacopsychiatry.* 2003;36:S235-S243.	7
5	Licinio J, Wong ML. Pharmacogenomics of antidepressant treatment effects. *Dialogues Clin Neurosci.* 2011;13(1):63-71.	7
6	Miller DB, O'Callaghan JP. Personalized medicine in major depressive disorder -- opportunities and pitfalls. *Metabolism.* Jan 2013;62 Suppl 1:S34-39.	7
7	Mrazek D. Incorporating pharmacogenetics into clinical practice: reality of a new tool in psychiatry. The context of genetic testing in clinical psychiatric practice. *CNS Spectr.* 2006;11(3 Suppl 3):3.	7
8	Niitsu T, Fabbri C, Bentini F, Serretti A. Pharmacogenetics in major depression: a comprehensive meta-analysis.[Erratum appears in Prog Neuropsychopharmacol Biol Psychiatry. 2013 Dec 2;47:118-9]. *Prog Neuropsychopharmacol Biol Psychiatry.* Aug 1 2013;45:183-194.	7
9	Perlis RH. Pharmacogenomic testing and personalized treatment of depression. *Clin Chem.* Jan 2014;60(1):53-59.	7
10	Salloum NC, McCarthy MJ, Leckband SG, Kelsoe JR. Towards the clinical implementation of pharmacogenetics in bipolar disorder. *BMC Med.* 2014;12:90.	1
11	Singh AB, Bousman CA, Ng C, Berk M. Antidepressant pharmacogenetics. *Curr Opin Psychiatry.* Jan 2014;27(1):43-51.	7

APPENDIX D: EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED PRIMARY STUDIES

Data Abstraction of RCTs

Author Year Setting N	Diagnosis; Previous AD courses	Pharmacogenomic test platform; treatment regimen, duration, follow-up	Patient demographics	Remission and response (Guided vs usual care)	Quality of life; Precision	Harms
Singh 2015[13] Setting NR 152	MDD, DSM-5	CNSDose polygene panel and interpretive report: CYP450, UGT1A1 and ABC transporter variants; not yet commercially available; 12 weeks	41% male 44 years Race NR	Remission (HAM-D ≤ 7): 72% vs 28%; RR 2.52 (95% CI 1.71 to 3.73) Response NR	Proportion taking sick leave: Usual care=15% vs guided=4%; RR 1.13 (95% CI 1.01 to1.25)	Intolerability (having an event where patient needed to reduce the dose or stop their antidepressant): Usual care=15% vs guided=4%; RR 1.13 (95% CI 1.01 to 1.25)
Winner 2013[14] Outpatient clinic 51	MDD, DDNOS; Mean # previous psychiatric medication trials = 4.4; Mean # psychiatric medications at baseline = 2.8	GeneSight five gene test and interpretive report: CYP2D6, CYP2C10, CYP1A2, SLC6A4, HTR2A; 10 weeks	19.7% male 49.2 years 95% white	Remission (HAM-D≤7 at 10 weeks): 20.0% vs 8.3% (OR=2.75; 95% CI 0.48 to 15.8) Response (50% reduction in HAM-D at 10 weeks): 36.0% vs 20.8% (OR=2.14; 95% CI 0.59 to 7.69)	NR	NR

MDD=Major Depressive Disorder; DDNOS=Depressive Disorder Not Otherwise Specified; HAM-D=Hamilton Rating Scale for Depression; NR=Not reported; RR=Risk Ratio; OR=Odds Ratio

Data Abstraction of Observational Studies

Author Year Setting N	Diagnosis; Previous AD courses	Pharmacogenomic test platform; treatment regimen, duration, follow-up	Patient demographics	Remission and response (Guided vs usual care)	Quality of life; Precision	Harms
Breitenstein 2014[15] Hospital 116	MDD (HAM-D ≥ 14); NR	ABCB1 genotyping; Duration of hospital stay (varied by patient, average NR), genotype results received at 4th week	44.8% male 47.6 years 100% white	Remission (HAM-D <10) at discharge: 83.6% vs 62.1% (P=0.005)	NR	NR
Hall-Flavin 2012[16] Outpatient behavioral health clinic 44	MDD (HAM-D>=14); Average # previous antidepressant trials = 4.4	GeneSight; 8 wk follow-up	45% male 42.35 years 100% white	QIDS-C16: Overall reduction in depression scores: 31.2% vs 7.2% (P=.002) HAM-D: Overall reduction in depression scores: 30.8% vs 18.2% (P=.04)	NR	NR
Hall-Flavin 2013[17] Hospital 227	MDD (HAM-D>=14), DDNOS; Average # previous panel medication trials =3.45	GeneSight; 8 wk follow-up	26.9% male 42.5 years 100% white	Significant response = 50% reduction in QIDS-C16 score: 44.4% vs 23.7% (OR=2.58; 95% CI 1.33 to 5.03; P=0.05)	NR	NR

MDD=Major Depressive Disorder; AD=Antidepressant; HAM-D=Hamilton Rating Scale for Depression; QIDS-C16: Quick Inventory of Depressive Symptomatology, Clinician Rated; DDNOS=Depressive Disorder Not Otherwise Specified; NR=Not reported; OR=Odds Ratio

Data Abstraction of Controlled Cohort Studies of Cost-effectiveness

Author Year N	Diagnosis; Previous AD courses	Pharmacogenomic test platform; Data source; Timeframe	Patient demographics	Adherence	Cost-effectiveness	Harms
Fagerness 2014[18] 333	Any psychiatric diagnosis; NR	Genecept Assay; Claims data; 2010-2012	31.2% male 44.9 years Race NR	Guided = increase in adherence (MPR) of 6.0% (P=.00156)	Mean baseline difference in Medical cost utilization (case vs control): -$562 (9.2%)	NR
Winner 2015[19] 13,048	Any diagnosis requiring antidepressant or antipsychotic medication	GeneSight; Pharmacy benefits claims data; 2011-2013	30.76% male 51 years Race NR	Adherence = proportion of days covered Adherence improvement of 0.123 for Guided vs usual care (P<0.0001)	Guided saved $1035.60 in total annual medication costs compared to usual care (P=0.0007)	NR

MPR=Medication Possession Ratio; NR=Not Reported

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Quality Assessment of RCTs

Author Year	Randomization adequate?	Adequate allocation concealment?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Outcome measurement equal, reliable and valid?	Intention-to-treat (ITT) analysis?	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating (Good, Fair, Poor)
Singh 2015[13]	Yes; computer	Unclear; not described	Yes	Yes	No; prescriber knew whether or not they were using test to guide care	Yes	Yes	Yes; excluded 2.6%	Crossovers: NR Adherence: Yes - 100% of prescribers reviewed the interpretive report Contamination: N/A	Yes	Good
Winner 2013[14]	Unclear; not described	Unclear; not described	Unclear, more males in genesight group, TAU group had 4 subjects who did not receive genesight testing.	Yes	No; prescriber knew whether or not they were using test to guide care	Yes	Yes	Unclear, numbers analyzed not reported	Crossovers: NR Adherence: NR Contamination: N/A	Yes	Fair

TAU=Treatment as Usual; NR=Not Reported; N/A=Not Applicable

Quality Assessment of Observational Studies

Author Year	Risk of selection bias? (High, medium, low)	Risk of performance bias? (High, medium, low)	Risk of detection bias? (High, medium, low)	Risk of bias due to confounding? (yes, no, unclear)	Risk of attrition bias? (High, medium, low)	Risk of reporting bias? (High, medium, low)	Overall risk of bias (High, medium, low)
Breitenstein 2014[15]	Unclear; different time frames for each cohort.	Unclear; no mention of other treatments that may have influenced outcome ie psychotherapy or other somatic treatments	Unclear; no mention of who assessed outcome presumably clinicians. Outcomes were rater assessed ie HAM-D.	Unclear; no control for greater proportion of recurrent depression in the ABCB1 group (60% vs 45%) and the longer current episode in the control group (39 vs 25 months); no information about smoking, antidepressant medications	Unclear; don't tell us about drop outs although we can infer there are some drop-outs based on some of the data presented	Unclear; no reporting of whether outcomes were prespecified	Fair
Fagerness 2014[18]	No	Unclear; no mention of other treatments that may have influenced outcome ie psychotherapy	No	Unclear; propensity-matched based on gender, age, number of medication trials, number of drug classes, psychiatric diagnosis group, Charlson comorbidity index, physician specialty and physician gender, no information about severity and type of	No	Unclear; no reporting of whether outcomes were prespecified	Fair

Author Year	Risk of selection bias? (High, medium, low)	Risk of performance bias? (High, medium, low)	Risk of detection bias? (High, medium, low)	Risk of bias due to confounding? (yes, no, unclear)	Risk of attrition bias? (High, medium, low)	Risk of reporting bias? (High, medium, low)	Overall risk of bias (High, medium, low)
				depression			
Hall Flavin 2012[16]	Unclear; consecutive enrollment into guided then usual care	Unclear; no mention of other treatments that may have influenced outcome ie psychotherapy	Unclear; no mention of who assessed outcome, presumably clinicians	Unclear; no information about comorbidities, gender, no statistical adjustment	No; low attrition (4 missing in usual care group, 3 missing in guided group)	Unclear; no reporting of whether outcomes were prespecified	Fair
Hall-Flavin 2013[17]	Unclear; 2 consecutive cohorts. Wonder about a priming (practitioners) effect	Yes; no explanation of differences in other treatments accessed ie psychotherapy, which might affect outcome	Unclear; outcome assessors were not blinded to condition (although most outcomes were self-report). Nonstandard remission definition of HAM-D < 8 instead of 7	Unclear; insufficient information about presence and balance of comorbidities, no adjustment for fewer previous psychiatric medication trials in the guided group, which could have led to a better chance of success	Unclear; large differential in drop out between groups. Did do sensitivity analyses using EM and LOCF approaches to evaluate consistency with completers-analysis	Unclear; no reporting of whether outcomes were prespecified	Fair
Winner 2015[19]	No	Unclear; no information about critical co-interventions	No	Unclear; propensity-matched based on gender, age, index CNS medication, primary CNS diagnosis and date of project enrollment, but	Unclear; analysis excluded 23% with no sensitivity analysis	Unclear; protocol not cited	Fair

Author Year	Risk of selection bias? (High, medium, low)	Risk of performance bias? (High, medium, low)	Risk of detection bias? (High, medium, low)	Risk of bias due to confounding? (yes, no, unclear)	Risk of attrition bias? (High, medium, low)	Risk of reporting bias? (High, medium, low)	Overall risk of bias (High, medium, low)
				no information about severity and type of depression or other important confounders			

HAM-D=Hamilton Rating Scale for Depression; LOCF=Last Observation Carried Forward; EM=Expected Maximization; CNS=Central Nervous System

STRENGTH OF EVIDENCE FOR INCLUDED STUDIES

SOE Grade	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Findings
CNSDose								
Remission: Moderate	1 RCT, N=148[13]	Low	Direct	Unknown	Precise	None	None	Improved remission (HAM-D ≤ 7): 72% guided vs 28% usual care; RR 2.52 (95% CI 1.71 to 3.73)
Proportion taking sick leave: Low	1 RCT, N=148[13]	Low	Direct	Unknown	Imprecise	None	None	Proportion taking sick leave: Usual care=15% vs guided=4%; RR 1.13 (95% CI 1.01 to 1.25)
Intolerability: Low	1 RCT, N=148[13]	Low	Direct	Unknown	Imprecise	None	None	Intolerability (having an event where patient needed to reduce the dose or stop their antidepressant): Usual care=15% vs guided=4%; RR 1.13 (95% CI 1.01 to 1.25)
ABCB1 Genotyping								
Remission: Moderate	1 Observational N=116 [15]	Medium	Direct	Unknown	Precise	Suspected (selective analysis reporting bias) (no report on harms/adverse events)	None	Improved remission (HAM-D<10): 83.6% vs 62.1%; X^2 (1)=6.596, P=0.005
GeneSight								
Remission: Low	1 RCT, N=51[14]	Medium	Direct	Unknown	Imprecise	None	None	No difference in remission (HAM-D ≤ 7): 20% vs 8%; RR 2.40 (95% CI 0.51 to 11.21)
Response	1 RCT, N=51[14]	Medium	Direct	Unknown	Imprecise	None	None	No difference in response (≥ 50% HAM-D improvement): 36% vs 21%; RR 2.14 (95% CI 0.56 to 7.69)

HAM-D=Hamilton Rating Scale for Depression; RR=Risk Ratio; OR=Odds Ratio

APPENDIX E: ONGOING CLINICAL TRIALS

Trial title	*NCT#*	*Comparison*	*Status*	*Additional information*
		IDgenetix		
Clinical Study to Evaluate Patient Outcomes Following Pharmacogenetic Testing of Subjects Exhibiting Neuropsychiatric Disorders	NCT02411123	IDgenetix Neuropsychiatric vs Treatment as Usual	Completed in October 2015; No results posted & listed publications are prior to study completion	Primary outcomes = Comparison of change in neuropsychiatric state between the two treatment arms measured by Neuropsychiatric Questionnaire (NPQ); Comparison of change in responsiveness between the two treatment arms measured by Symbol Digit Coding (SDC) test Secondary outcomes = Reduction in adverse events; hospitalization rates; hospital length of stay; ER visits; death; serious drug side effects
		Genecept		
Genecept Assay™ vs Treatment-as-Usual to Evaluate Efficacy of Assay-Guided Treatment in Adults With MDD	NCT02634177	Genecept assay vs Treatment as Usual	Recruiting participants (estimated data collection September 2016)	Primary outcome = Mean change from Baseline in SIGH-D-17 (Hamilton Depression Rating Scale) score at 8 Weeks
An Open Label Study of Clinical Utility and Patient Outcomes of the Genecept Assay (COM-1)	NCT01507155	None (Single group assignment)	Completed in May 2014; No results or publications posted	Using Genecept Assay to analyze seven pharmacodynamic and three pharmacokinetic genes important in psychiatric disorders Non-randomized retrospective study to determine the efficacy of assay-guided treatment (AGT) in terms of illness severity as measured by change from baseline in Clinical Global Impressions (CGI) scale at 3 months.
An Open Label Study of the Genecept™ Assay in Treatment Resistant Depression	NCT01438242	None (Single group assignment)	Study withdrawn prior to enrollment	
Pharmacogenomics for	NCT01426516	PGx testing guided	Terminated due to invalid	

Trial title	*NCT#*	*Comparison*	*Status*	*Additional information*
Antidepressant Guidance and Education 1		treatment (Genecept TM assay) vs Treatment as Usual	data collection	
		YouScript®		
Drug & Gene Interaction Risk Analysis With & Without Genetic Testing Among Patients Undergoing MTM	NCT02428660	(1) Pharmacogenetic testing+ Software-based drug & gene interaction risk analysis + Treatment as Usual (TAU) (2) Software-based drug & gene interaction risk analysis + TAU (3) TAU only	Recruiting participants (estimated data collection September 2016)	Using YouScript ® Personalized Prescribing System Primary outcome = Number of Drug Therapy Problems Secondary outcomes = Number of adverse drug reactions; Quality of Life; Acceptance of recommendations by pharmacists; Major event risk reduction; Acceptance of recommendations by clinician providers
		Genesight (AssureRx)		
Pharmacokinetic/Pharmaco-dynamic Genetic Variation Treatment Algorithm Versus Treatment As Usual for Management Of Depression (MOD)	NCT02189057	AssureRx GeneSight genotyping results vs Treatment as Usual	Recruiting participants (estimated data collection to begin in June 2016)	Primary outcome = baseline to endpoint change (8 weeks) in the Quick Inventory of Depressive Symptomatology
Pharmacogenomic Decision Support With GeneSight Psychotropic to Guide the Treatment of Major Depressive Disorder	NCT02466477	Three-arm comparison—GeneSight Psychotropic (GEN) vs Enhanced GEN vs Treatment as Usual	Recruiting participants (estimated completion June 2018)	Primary outcome = Change in depressive symptoms as assessed by the 17-item Hamilton Depression (HAM-D) score
Impact of GeneSight Psychotropic on Response to Psychotropic Treatment in Outpatients Suffering	NCT02109939	GeneSight Psychotropic Tested vs Treatment as Usual	Recruiting participants	Purpose = Evaluate the impact of GeneSight Psychotropic on response to psychotropic treatment as judged by the mean change in the 17-item Hamilton Depression (HAM-D) score from baseline to end of

Trial title	*NCT#*	*Comparison*	*Status*	*Additional information*
From a Major Depressive Disorder (MDD) and Having Had an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic (RCT)				Week 8 of the study
		CNSDose		
Do adults with major depression whose antidepressant treatment is guided by a pharmacogenetic algorithm generated report have better clinical outcomes compared to care as usual?	ACTRN12613001135707	Pharmacogenetic treatment algorithm vs Care as Usual	Recruitment closed; Data currently in analysis	Ajeet Singh (corresponded with Kim) principal investigator; Primary outcome = Remission from major depression, a score of 7 or less on the 17-item Hamilton Depression Rating Scale; Secondary outcome = Medication Tolerability
		Non-specific test		
Clinical Impact of the Antidepressant Pharmacogenomic Algorithm in an Outpatient Therapy-based Clinical Setting (HAMM)	NCT02479464	Genotyping results (no specific test given; referred to as pharmacogenomics algorithm) vs Treatment as Usual	Completed in 2015; No results or publications noted	Pilot study
A Pilot Study for the Evaluation of the Clinic-wide Impact of the Antidepressant Pharmacogenomic Algorithm in an Outpatient Clinical Setting	NCT01610063	Genetic test results through algorithm for guided prescribing vs no algorithm	Completed; No results or publications posted	Primary outcome: Proportion of time physician prescribed medication Secondary outcome: Physician and patient satisfaction (eg remission of symptoms)
Pharmacogenomics for Antidepressant Guidance and Education	NCT01555021	Genotyping assay guided treatment vs Treatment as Usual	Recruiting participants	Outcome measures: To determine the efficacy of assay-guided treatment (AGT) versus treatment-as-usual (TAU), in terms of depression severity as measured by change in the Quick Inventory of

Trial title	*NCT#*	*Comparison*	*Status*	*Additional information*
				Depressive Symptoms (QIDS-SR)15, adjusted for baseline severity, weekly, upon discharge, and at 1, 3, and 6 months post discharge from inpatient treatment
		Other pharmacogenomic trials		
Pharmacogenetic Testing on an Outpatient Population With a Depression Diagnosis (PGX-AMG)	NCT02443584	Genetic testing released to physician at 4 weeks vs released at 12 weeks	Recruiting participants (estimated completion January 2017)	Primary outcome = Clinical outcomes (response to medication following medication recommendation guided by pharmacogenetic testing) Secondary outcome = Clinical utility (Utilization by physicians in following medication recommendations guided by pharmacogenetic testing)
Development of Pharmacogenomic Method to Predict Antidepressant Responsiveness (PG)	NCT00817011	SSRI treated group vs non-SSRI treated group	Recruiting participants (estimated completion December 2016)	Primary outcome = all pharmacogenetic and biological marker variables cause drug response
Pharmacogenomic Study to Predict Antidepressant Responsiveness in Depressed Patients	NCT00817375	SSRI (fluoxetine, paroxetine, or sertraline) vs non-SSRI (milnacipran, venlafaxine, nortriptyline, or mirtazapine) treatment	Recruiting participants; First received in 2009	The purpose of this study is (1) to determine whether genomic effects on antidepressant response differed by class of drug, (2) whether genomic differences between drug responders and nonresponders predict the response of antidepressant and (3) to construct the prediction model for antidepressant treatment in order to aid to select the their genetically matching drugs. Primary outcome = Antidepressant Response at 2,4,6 weeks A/E monitoring at 1,2,4,6 weeks; Based in South Korea
Antidepressant Treatment of Mexican-Americans: UCLA Pharmacogenetics and Pharmacogenomics Research Group	NCT00265291	Fluoxetine or desipramine (Prozac) vs placebo	Completed 2008 (2 publications in 2004)	"Our goal is to study pharmacogenetics in Mexican-Americans, using depression treatments as a proof of the concept that pharmacogenetic approaches can be used to optimize treatment strategies for common and complex disorders in this population."
Retrospective Analysis of Outcomes With a	NCT01632267	Unclear	Completed; Follow-up rates posted but not	The present one year retrospective study seeks to evaluate the indirect and direct healthcare costs for 96

Trial title	*NCT#*	*Comparison*	*Status*	*Additional information*
Pharmacogenomic Algorithm (UHS)			outcome information	patients with a DSM-IV-TR depressive or anxiety disorder, in relation to an interpretive reporting system designed to predict antidepressant responses based on DNA variations in cytochrome P450 genes (CYP2D6, CYP2C19, CYP1A2), the serotonin transporter gene (SLC6A4), and the serotonin 2A receptor (5HTR2A) genes.
Pharmacogenetic Testing in an Outpatient Population of Patients With Depression (PGx-UPA)	NCT02497027	Genetic testing released to physician at 4 weeks vs released at 12 weeks	Recruiting participants	Outcome = depression score
Evaluation of Pharmacogenetic Testing In a Mental Health Population and Economic Outcomes (PGx-TIME)	NCT02474680	None	Recruiting participants	Non-randomized, single-case design of pharmacogenetic implementation in a mental health patient population of subjects taking antipsychotics and/or antidepressants
Genetic Testing Decision Analysis Model for Antidepressant Treatment	SHP 08-195	Initiate paroxetine vs gene testing	Completed 2008; 2 publications	Findings: When the clinical decision was simplified to two treatment strategies, initiate paroxetine or the gene testing strategy, the gene testing strategy dominated the no gene testing strategy up until the cost of genetic testing exceeded $100/patient.
Measuring the quality of genomic health services in the VA: A pilot	PPO 10-114	None	Completed 2012; 5 publications	Findings: This pilot suggests that the delivery and accessibility of VA-based genomic services could benefit from having more genomic experts on staff, standardizing the genomic testing approval and ordering process, and clarification regarding what services can be provided to non-veteran family members.

APPENDIX F: SYSTEMATIC REVIEW SEARCHES

Search for current systematic reviews of markers other than CYP450

Date Searched: 04/05/2016-04/06/2016

Search terms: "Genetic" "Markers" "Variants" "Depression" "Testing" "Pharmacogenomics" "Review"

Sources:	Evidence:
Drozda article sources	Yip VL, Marson AG, Jorgensen AL, Pirmohamed M, Alfirevic A. HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review. Clin Pharmacol Ther 2012;6:757–65. · https://www.researchgate.net/profile/Vincent_Yip2/publication/232969477_HLA_Genotype_and_Carbamazepine-Induced_Cutaneous_Adverse_Drug_Reactions_A_Systematic_Review/links/00b7d5229d5bfc663a000000.pdf Schosser A, Serretti A, Souery D, et al. European Group for the Study of Resistant Depression (GSRD)–where have we gone so far: review of clinical and genetic findings. Eur Neuropsychopharmacol 2012;7:453–68. · http://www.sciencedirect.com.liboff.ohsu.edu/science/article/pii/S0924977X12000521 Seretti 2007: "Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients" · http://www.nature.com.liboff.ohsu.edu/mp/journal/v12/n3/full/4001926a.html
Niitzu 2013	**Searched who cited this review in Web of Science Breitenstein 2015: "ABCB1 Gene variants and antidepressant treatment outcome: A meta-analysis" http://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.32309/abstract?userIsAuthenticated=false&deniedAccessCustomisedMessage= Hu 2015: "Influence of GNB3 C825T polymorphism on the efficacy of antidepressants in the treatment of major depressive disorder: A meta-analysis" · http://www.sciencedirect.com/science/article/pii/S016503271400593X Zhao 2015: "Association between the TPH1 A218C polymorphism and antidepressant response: evidence from an updated ethnicity, antidepressant-specific, and ethnicity-antidepressant interaction meta-analysis" http://journals.lww.com/psychgenetics/Abstract/2015/02000/Association_between_the_TPH1_A218C_polymorphism.1.aspx Lin 2014: "Influence of 5-HTR2A genetic polymorphisms on the efficacy of antidepressants in the treatment of major depressive disorder: A meta-analysis" · http://www.sciencedirect.com/science/article/pii/S0165032714003735

Google Scholar	**Also searched for specific markers in comment above in combination with depression Dunn 2015: "Genetic determinant of depression: recent findings and future directions." (Reviews other markers beside CYP450) · http://europepmc.org/articles/pmc4309382 Flint 2014: "The Genetics of Major Depression" · http://www.sciencedirect.com/science/article/pii/S0896627314000580 *((Prior to 2013))* Gyekis 2012: "No association of genetic variants in BDNF with major depression: A meta and gene-based analysis" · http://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.32122/abstract;jsessionid=EFE40349E058E8F6FEB336636BA69AB6.f01t04?userIsAuthenticated=false&deniedAccessCustomisedMessage= Kato and Serretti 2008: "Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder" · http://www.nature.com/mp/journal/v15/n5/abs/mp2008116a.html Lopez-Leon 2008 "Meta-analyses of genetic studies on major depressive disorder" · http://www.nature.com/mp/journal/v13/n8/abs/4002088a.html Levinson 2005 "The Genetics of Depression: A review" · http://depressiongenetics.stanford.edu/researchfiles/Levinson_GeneticsDepression.pdf
AHRQ	http://www.ahrq.gov/research/findings/evidence-based-reports/search.html **None found**
CADTH	https://www.cadth.ca **None found**
Cochrane Database of Systematic Reviews: Protocols & Reviews	http://www.ohsu.edu/xd/education/library/ **None found (only trials)**
ECRI Institute	https://www.ecri.org/Pages/default.aspx Potentially relevant review, but cannot access: · Pharmacogenetic Testing to Guide Treatment of Behavioral and Mental Health Disorders (Rapid Review) o Many psychotropic medications are available to treat behavioral and mental health disorders, but response is highly variable. Genetic testing is gaining attention as a way to help predict treatment response and individualize medication prescribing.
NHS Evidence	http://www.evidence.nhs.uk/default.aspx · Influence of SERTPR STin2 in the serotonin transporter gene on the effect of selective serotonin reuptake inhibitors in depression: a systematic review http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=12004009882 o To examine the relationship between clinical response to selective serotonin re-uptake inhibitors (SSRIs) in patients with depression and genetic polymorphisms (SERTPR and STin2) in the serotonin transporter gene.
NLM	http://www.ncbi.nlm.nih.gov/pubmedhealth/ **None found**
Campbell Collaboration	http://www.campbellcollaboration.org/lib/?go=browse **None found**

Hayes	http://www.hayesinc.com/hayes/ **None found**
Institute for Clinical Evaluative Sciences	http://www.ices.on.ca/Publications/Atlases-and-Reports **None found**
IOM	http://www.iom.edu/Reports.aspx **None found**
Robert Wood Johnson	http://www.rwjf.org/en/research-publications.html **None found**
WHO Health Evidence Network	http://www.euro.who.int/en/what-we-do/data-and-evidence/health-evidence-network-hen/publications/by-keyword **None found**

APPENDIX G: PEER REVIEW COMMENTS

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	None
2	2	Yes	None
3	3	Yes	None
Is there any indication of bias in our synthesis of the evidence?			
4	1	No	None
5	2	Yes - Missed important details about the unmet need. Poorly documented statements.	To the Executive Summary, we added more details about rationale for strength of evidence ratings and descriptions of the sample populations. We also specifically raise the issue of unmet need.
6	3	No	None
Are there any published or unpublished studies that we may have overlooked?			
7	1	Yes - Include current Assurex study in Canada (http://impact.camhx.ca/en/sample-report) and the ongoing study in San Diego (John Kelsoe, PI) on Pathway's genomic testing- Steve Schictman at VA Little Rock would also be a good resource for additional studies	Canadian Assurex study already included in ongoing study appendix (NCT02466477). We reached out to the individuals suggested, but this did not result in identification of any additional studies.
8	2	Yes - Bousman. Commercial pharmacogenetic-based decision-support tools in psychiatry. 2016	Added Bousman 2016 to Characteristics and Regulation of Antidepressant Pharmacogenetics Testing Resources section of Background to supplement existing information on test characteristics

9	3	Yes - When considering CYP2D6 and CYP2C19 only, well over 26 papers were evaluated for clinical utility regarding the TCAs and SSRIs. It is very unclear how the entire field of psychiatric pharmacogenomics was narrowed down to 26 papers (with 11 finally excluded). 15 included articles for synthesis most likely does not adequately cover the entire field of depression pharmacogenomics. It appears that most of the papers cited are reviews and guidelines along with many papers focusing on Genesight (AssureRx). Primary literature is needed....the papers that supported the reviews and guidelines.	As outlined in the Scope section, among the entire field of depression pharmacogenomics, (Analytic validity, Clinical validity, Clinical utility, and Ethical, legal, and social implications - ACCE Model, National Office of Public Health Genomics), this review focused only on clinical utility and, specifically, studies that compared guided to unguided treatment. The reviews and guidelines this reviewer is referring to are focused on clinical validity, which were included as key background for this review. A complete accounting of the primary literature on clinical validity is outside of the scope of this review. As has been confirmed by other recent articles, such as Bousman 2016 in Lancet Psychiatry, compared to the literature on clinical validity, there is yet very limited evidence on clinical utility.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
10	1	Outstanding report: In the Executive summary, pages 4, 8, Implications (e.g., lines 16/56, page 23, page 24, line 46, page 25, lines 24 and 37) and throughout; please omit the term "pilot" after study	Removed
11	1	Page 4, line 10, delete “association” study since the review seems to suggest limitations in this method of design and the term itself might imply a unique genetic test (genome-wide association study). This would pigeonhole the type of limit of study.	Changed to: “undertaking new primary research to evaluate the potential association between genes and variants and antidepressant medication benefits and harms”
12	1	Page 4, line 12: delete "using data from the Million Veteran Program" MVP does not do CLIA-certified testing and to ensure timeliness of research and clinical utility, studies should require CLIA lab certification since they involve return of results	Deleted
13	1	Page 4, line 15: add patient behavioral factors”	Changed item #5 from “patient populations…” to “accounting for key patient characteristics to encompass behavioral factors as well as all others specified in Key Question 5 and elaborated on in Implications for Future Research.
14	1	Page 4, line 47 – spelling (Neurotransmitter) – Neurotransmitter.	Corrected.
15	1	Page 6, line 40: add “patient health behaviors such as food intake”	Added
16	1	Page 5, line 16-17 – “This pilot will build on the Million …” should be changed to “This trial will supplement MVP’s capabilities to…”	Changed as suggested
17	1	Page 5, line 17 “(1) understand the genomics” – change to – (1) understand the lifestyle, genomic and…”	Changed as suggested

18	1	Page 6, lines 19-23: The concept is difficult to relay, but CYPs with variants that reduce enzyme function might will lead to higher drug level or reduced prodrug levels; rapid/ultrarapid metabolizers will decrease drug levels of increase prodrug levels. (The spirit here is that if it is a prodrug, it needs to get activated – that process depend on the activity of the CYP. In contrast, an active drug is just that, and the CYP will move it to the next level (intermediate or post phase I).	Changed to: CYP450 variants that *reduce* enzyme function may cause poor or intermediate metabolism levels, which may lead to higher than expected active drug levels or reduced prodrug levels. CYP450 variants that *increase* enzyme function may cause ultra-rapid metabolism, which may lead to lower than expected active drug levels or increased prodrug levels."
19	1	Page 7, line 3, define 510(k) process and what it entails. And line 12, clarify whether FDA regulation includes same CLIA certification step	For 510(k) process, added "The 510(k) is "a premarket submission made to the FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device." For how new FDA regulation relates to CLIA certification added: "LDTs have historically not been assessed before being offered for clinical use and have only been regulated by the Centers for Medicare and Medicaid Services (CMS) with regard to whether laboratories' practices for using them are in compliance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA). However, in 2010, the FDA proposed initiating premarket evaluation of pharmacogenomics LDTs' analytical and clinical validity as well."
20	1	Page 9, line 4, should it be 6 key questions?	No, ORD's original nomination only included 4 key questions. Then, the ESP Coordinating Center worked with ORD to refine those and added 2 more.
21	1	Page 9, line 48 – I'm not sure if I'm correct, but, wouldn't effectiveness "delay or eliminate" the time to remission?	Changed Key Questions to list specific outcomes each address: 1) What is the impact of using pharmacogenomic-guided antidepressant treatment on remission, response, quality of life, and functional capacity in patients with MDD? 2) What is the impact of using pharmacogenomic-guided antidepressant treatment on reducing *time to* remission, response, improved functional capacity or reducing treatment switches in patients with MDD?

22	1	Page 14, line 27, omit sentence starting “Despite their methodological . . .” this is a design issue not a review issue. Non-randomized studies also do not address historical trends or issues of response bias, as pointed out below. The paragraph also seems to suggest that more RCTs are needed	Deleted sentence as requested, which broadly commented on inherent limitations of observational studies in general. Paragraph now focuses on specific limitations of the actual included studies. The paragraph was not meant to suggest that more RCTs are needed. Our intent was to outline the potential advantages of nonrandomized trials *in general* (e.g., address gaps in RCTs such as evaluating more applicable patient populations and/or providing longer-term follow-up and/or adding data on missing outcomes), but to clarify that these specific nonrandomized studies did not offer such advantages over the available RCT.
23	1	Page 14, line 34, how was response defined (spell out)	Added: “defined as a 50% or greater decreased from baseline in HAM-D17 score”
24	1	Page 22, line 12, add "due to sample characteristics" before “likely to have low”	Changed to: “But these studies were short-term, ranging in duration from 5-12 weeks, and sample characteristics likely have low applicability to Veterans”
25	1	Page 22, second bullet – Just an question but is there a metric that would be associated with “overall improvement?” If not, what does this mean?	The “overall” was in reference to the entire guided group and meant as a contrast to the subgroup of patients who were switched to more genetically-suitable medication. Changed to: “In establishing the clinical utility of pharmacogenomic-guided treatment, a first step is to demonstrate an improvement in the key outcomes of remission, response, and tolerability for the guided group overall versus usual care.”
26	1	Page 23, line 16 – “… a pilot built on the MVP” might be better rephrased as “A clinical trial that could augment MVP’s capabilities”	Changed as suggested.
27	1	Page 23, line 47 – “… to conduct new research ….association between genetic polymorphisms” – suggested adding “and other lifestyle confounders” at the end of the quoted segment.	Changed to “…to better examine the association between genetic polymorphisms, patient behavioral and environmental factors, and antidepressant effectiveness”
28	1	Page 23, line 47, add after "conduct new research . . ."either through a more comprehensive systematic review of test validity or through a prospective study...."	Added: “This first step may be in the form of conducting an updated evidence review that emphasizes Veteran relevancy prior to or in addition to undertaking new primary research to evaluate the potential association between genes and variants and antidepressant medication benefits and harms.”

29	1	Page 23, line 58, take out "using MVP participants" since the test would need to be conducted via CLIA labs, which MVP does not do; and that will be a research design decision that is not part of the review	Removed.
30	1	Page 24, lines 48-58 (Ethical) – Just a note – the Genetic Information Nondiscrimination Act (GINA) covers much of the concerns noted when it comes to the general US population. VA has its own policy to protect from such issues as well (we have note from GC about this very issue).	Added: The Genetic Information Nondiscrimination Act of 2008 (GINA) and VHA privacy laws were created to address fears about and prevent genetic discrimination by health insurers or employers. However, uncertainty remains about the actual impact of genetic nondiscrimination laws on medical practice, participation in genetic testing and associated ethical, legal, and social considerations, which may warrant exploration.
31	2	This paper in Lancet is a good summary of many of the types of tools being developed, and may be of interest to call out to readers.	Added Bousman 2016 from Lancet Psychiatry to Characteristics and Regulation of Antidepressant Pharmacogenetics Testing Resources section of Background to supplement existing information on test characteristics
32	3	It should be noted that Genesight (AssureRx) does not follow CPIC guidelines regarding CYP2D6 interpretation. Additionally, Genesight uses proprietary algorithms to make dosing recommendations. In other words, their recommendations in many instances is a 'black box'.	Please see response to related comment #33 below.
33	3	There was a lack of discussion on how the reviewed papers assigned phenotype, which variants were tested, and what guided dosing recommendations. For example, the CYP2C19 ultra-rapid phenotype was not defined until 2007. Any papers prior to 2007 would not include this phenotype. Without knowing this information, it is difficult to compare studies, or interpret findings.	All included studies that compared guided versus usual care were published subsequent to 2007. Added specific variants for CNSDose. Specific variants already provided for others. To page 17 we added: "Although methods used to predict phenotype (e.g., poor metabolizer) from genotype may vary across laboratories,[6] they were not specified in any of the studies. Studies of polygene panels also did not describe the algorithms they used to combine phenotype information across multiple variants to make drug selection and dosing recommendations or what guidelines they based their recommendations on. The lack of this information limits interpretation of findings and comparison of panels."

34	3	It is unclear if this review is supposed to identify goals and strategies for a clinical study. Some of the genes mentioned (e.g., ABCB1, CACNA1C, MTHFR) are probably not ready for clinical implementation. Furthermore, it not clear as to what recommendations will accompany such genes.	The purpose of this review is to determine the need for a clinical study. To identify specific goals and strategies for a clinical study – such as which genes and variants to focus on – we recommend more work is needed, such as a new systematic review and/or primary research to evaluate the potential association between genes and variants and antidepressant medication benefits and harms
35	3	It is unclear what the difference is between Key Questions 1 and 2 (effectiveness vs. precision).	Changed Key Questions to list specific outcomes each address: 1) What is the impact of using pharmacogenomic-guided antidepressant treatment on remission, response, quality of life, and functional capacity in patients with MDD? 2) What is the impact of using pharmacogenomic-guided antidepressant treatment on reducing *time to* remission, response, improved functional capacity or reducing treatment switches in patients with MDD?
36	3	On page 10, the purpose of this guideline was stated to address clinical utility. Many more papers than 15 should be evaluated to determine clinical utility. Which genes are of clinical utility? Which drugs should be considered for clinical utility?	Respectfully, this is an evidence review, not a guideline. Yes, per page 10, the purpose of this review was to evaluate studies that directly assessed clinical utility, defined by many sources as the likelihood that actually using a pharmacogenomic test to guide antidepressant choice will improve patient outcomes *as compared to* the usual trial and error process. As has been confirmed by other recent articles, such as Bousman 2016 in Lancet Psychiatry (http://www.sciencedirect.com/science/article/pii/S2215036616000171) , compared to the literature on clinical validity, there is yet very limited evidence on clinical utility. Although the much larger body of evidence on *clinical validity* (the association between genes and variants and patient outcomes) is key component in the overall framework of depression pharmacogenomics, a complete accounting of the primary literature on clinical validity was outside of the scope of this review.

37	3	If the intent of this work is to support the need for a clinical trial at the VA, then this goal was accomplished. If the intent of this work is to guide a clinical trial, then additional work is needed to define which genes to focus on, which variants, and how to translate results into clinical recommendations.	Agree

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