

Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing

Zane Zeier, Ph.D., Linda L. Carpenter, M.D., Ned H. Kalin, M.D., Carolyn I. Rodriguez, M.D., Ph.D., William M. McDonald, M.D., Alik S. Widge, M.D., Ph.D., Charles B. Nemeroff, M.D., Ph.D.

The accrual and analysis of genomic sequencing data have identified specific genetic variants that are associated with major depressive disorder. Moreover, substantial investigations have been devoted to identifying gene-drug interactions that affect the response to antidepressant medications by modulating their pharmacokinetic or pharmacodynamic properties. Despite these advances, individual responses to antidepressants, as well as the unpredictability of adverse side effects, leave clinicians with an imprecise prescribing strategy that often relies on trial and error. These limitations have spawned several combinatorial pharmacogenetic testing products that are marketed to physicians. Typically, combinatorial pharmacogenetic decision support tools use

algorithms to integrate multiple genetic variants and assemble the results into an easily interpretable report to guide prescribing of antidepressants and other psychotropic medications. The authors review the evidence base for several combinatorial pharmacogenetic decision support tools whose potential utility has been evaluated in clinical settings. They find that, at present, there are insufficient data to support the widespread use of combinatorial pharmacogenetic testing in clinical practice, although there are clinical situations in which the technology may be informative, particularly in predicting side effects.

Am J Psychiatry 2018; 175:873–886; doi: 10.1176/appi.ajp.2018.17111282

The demand for more effective antidepressant medications and optimized treatment strategies for major depressive disorder has intensified with the need for better treatment strategies as the burden of disease is projected to climb (1, 2). With major depression a leading cause of disability worldwide (www.who.int/topics/depression/en), antidepressant medications remain among the most frequently prescribed medications in the United States and other countries (3–6). The development of a standardized pharmacotherapeutic approach has been limited by various factors, including 1) heterogeneous and poorly defined major depression endophenotypes; 2) lack of reliable biomarkers to predict individual response to specific interventions; 3) variability among patients with regard to biological determinants of drug metabolism (7), including sex and hormonal modulation of liver metabolism (8); and 4) adverse drug effects, which are higher in women than in men (9). Clinicians deciding which medication to prescribe for a given patient with major depression typically collect and integrate multiple types of clinically relevant information, including the patients' symptoms, past and recent clinical history, family history, comorbidities, and personal preference. This step, in part, reflects an attempt to understand the patient's unique genetic background and biological "substrate." The clinician must then apply rigid treatment algorithms that are not truly

customized for any specific endophenotype and draw on his or her past experience and clinical intuition to navigate pharmacotherapy through a trial-and-error process that may actually prolong or complicate the clinical course before a positive outcome is achieved.

Currently, treatment guidelines for major depression are informed by only a few of the myriad elements of clinically relevant data that the clinician considers. For example, selective serotonin reuptake inhibitors (SSRIs) are widely recommended as the first-line monotherapy for depression, but lack of response to or intolerable side effects from an initial SSRI trial are common (10). In the majority of cases, the clinician will be faced with a decision regarding alternative strategies to treat the patient's depression. Evidence-based next steps include optimizing the dosage of the current SSRI (assuming that it is adequately tolerated), switching to a different antidepressant, augmenting the initial agent with a medication from a different pharmacological class, or providing a trial of combination therapy with two or more antidepressants. Each subsequent change in the treatment regimen must generally be maintained for an extended period, usually 3 to 6 weeks, before effects can be suitably evaluated (11). Information about whether the patient is likely to benefit or suffer intolerable side effects in relation to dosing strategies is not available to the clinician, so finding the most

See related feature: **Video** by Dr. Pine (online)

effective and best-tolerated pharmacotherapy relies on the clinician's application of a stepwise strategy that is largely guided by "educated guessing" and the "process of elimination" rather than by personalized prognostic data. This approach often leads to patient attrition, prolonged suffering, and other adverse sequelae.

Initiatives are under way to identify behavioral, physiological, neuroimaging, and genetic biomarkers that could successfully predict selection of effective antidepressant treatments at the outset of a course of therapy, thereby providing a more rational and customized approach for individual patients. These initiatives include the iSPOT-D (12), EMBARC (13), and TRANSFORM (14) studies. The goal of such efforts is, in part, to identify biological substrates of major depression and their roles in response to antidepressant medications. Genome-wide association studies (GWAS) have revealed genetic variants linked to major depression, but the effects of individual gene variants appear to be very small. Furthermore, GWAS data do not fully account for the observed heritability of major depression, which is estimated to be in the range of 40%–70% (15). Not only is major depression susceptibility heritable, but so too is the response to antidepressant treatment (16). Genome-wide pharmacogenetic studies have been undertaken to systematically investigate gene-by-drug interactions. Among the largest are the Genome-Based Therapeutic Drugs for Depression (GENDEP) project, the Munich Antidepressant Response Signature (MARS) project, and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D). Unfortunately, a meta-analysis of data from all three initiatives did not reveal reliable predictors of treatment outcomes (17). Several recent reviews address both the promise and the challenge of using pharmacogenetic data to improve precision in treating major depression (18–23). Few actionable drug-gene interactions have been identified, with an exception being the human leukocyte antigen (HLA) *B-1502 allele, which strongly associates with carbamazepine-induced Stevens-Johnson syndrome among Han Chinese (24). Instead, it has been generally concluded that despite laudable efforts, no studies have led to actionable pharmacogenetic data that provide a more comprehensive framework for selection of initial antidepressant medications or to guide subsequent steps in the treatment of major depression. Because most prescribers of antidepressants are not experts in pharmacogenomics or genomics, the APA Task Force for Biomarkers and Novel Treatments conducted a detailed analysis of the literature to provide prescribers with a readily understandable summary of the field, especially in view of efforts to market these tests to psychiatrists, primary care physicians, and the general public.

Several companies (reviewed in detail below) have developed commercially available combinatorial pharmacogenetic tests for application to psychopharmacology. Unlike genome-wide profiling, combinatorial pharmacogenetic testing is more focused in that only a limited number of genetic variants are assessed. By reducing the scope of genetic testing, associated time and costs are minimized. However,

the methodology of testing and the manner in which results are conveyed to the user vary widely across combinatorial pharmacogenetic products. Many combinatorial pharmacogenetic tests developed as aids for psychiatric practice include genetic variation of hepatic cytochrome P450 (CYP450) enzymes that largely determine the activity levels of the enzymes and hence the pharmacokinetics of many antidepressants. Human pharmacokinetic testing, through measurement of plasma levels after administration of a fixed dose, has demonstrated that the observed range for many antidepressants is wide and reflects, in part, individual differences in drug metabolism. Multiple phenotype categories have been identified, namely, "poor metabolizer," "intermediate metabolizer," "extensive (normal) metabolizer," and "ultrarapid metabolizer." The AmpliChip CYP450 test (Roche, Basel, Switzerland) was the first combinatorial pharmacogenetic test to be approved by the U.S. Food and Drug Administration (FDA), and it is used in many instances for prescribing antidepressants that include CYP450 information in drug labeling. Specific genomic variants for CYP450 enzymes can be assayed in the individual patient to generate a customized patient profile for each candidate psychotropic medication. Genotyping results must be linked to phenotype categories on the basis of knowledge about the known metabolic pathways of the drugs and the available scientific evidence base linking genotypes with observed biological effects. For example, a patient whose DNA expresses multiple copies of the CYP2D6 gene is likely to be associated with ultrarapid metabolism of certain drugs, such as aripiprazole, whose blood concentration is largely determined by the CYP2D6 enzyme pathway. Theoretically, knowledge that a patient's genotype predicts ultrarapid metabolism of the antidepressant selected for a treatment trial might prompt the prescriber to increase the dosage beyond the FDA-recommended range before concluding that there was a failure of clinical response. Conversely, knowledge that a patient's genotype predicted poor metabolism by the enzymes regulating pharmacokinetics of a candidate medication might portend tolerability problems even at low dosages and perhaps prompt a prescriber to use a very low dosage or to avoid that agent altogether. At present, FDA drug labeling for 28 psychiatric medications includes CYP450 pharmacogenetic information; 10 of these include specific guidelines for "dosage and administration" (25). Enhanced prediction of treatment response and the ability to anticipate potential adverse side effects for an individual patient are thus purported to be possible through CYP450 genotyping (26).

Identifying genetic variants with the greatest empirical support is critical for evaluating and implementing combinatorial pharmacogenetic testing. A useful resource that allows researchers and clinicians to query gene-drug interactions, drill down to the primary pharmacogenetic literature, and prioritize the most clinically relevant pharmacogenetic data is the PharmGKB (www.pharmgkb.org) knowledge base. The PharmGKB level-of-evidence scale for gene-drug interactions ranges from preliminary evidence of

TABLE 1. Antidepressant Drug-by-Gene Associations With Moderate to High Levels of Evidence or Included in One of the Combinatorial Pharmacogenetic Tests Evaluated Here^a

Agent	Pharmacodynamic										Pharmacokinetic				
	ADRA2A	BDNF	COMT	CRHR1	FKBP5	GRIK4	HTR1A	HTR2A	SLC6A2	SLC6A4	ABCB1	CYP1A2	CYP2B6	CYP2C19	CYP2D6
Amitriptyline ^b											3				1A
Bupropion															
Citalopram ^b		3			2B			2B		2A	3		1A		3
Desipramine ^b		3													1A
Doxepin ^b															1A
Duloxetine ^b					3			3		2A		1A			1A
Escitalopram ^b		3		3	2B		3			3	3				3
Fluoxetine ^b		3	3				3	3						1A	3
Fluvoxamine ^b											3				1A
Imipramine ^b														2A	1A
Maprotiline															3
Mirtazapine					2B					3			3		
Nefazodone ^b					3						3				
Nortriptyline ^b		3									3				1A
Paroxetine ^b		3	3		2B		3			3	3	3			1A
Sertraline							3			3	3			1A	
Trimipramine ^b															1A
Venlafaxine ^b			3		2B				3		3				2A
Antidepressants, unspecified		3		3	2B	2B	3	2B			3				1A
SSRIs, unspecified	3		2B		2B		3	2B			3				
Number of variants per gene	1	6	2	2	4	2	3	5	1	3	15	9	5	8	14
Interaction type ^c	E	E,T	E	E	E,T	E	E	E,T	E	E,T	E,T	E,T	E,O	E,M,T	E,D,M,T

^a This is not a comprehensive representation of antidepressant drug-by-gene associations; it is limited to the PharmGKB search terms "depressive disorder, major; depressive disorder; depression; [antidepressant name]"; it excludes drug-gene interactions related to "bipolar disorder; anxiety disorder"; it excludes anti-psychotic and some antidepressant drugs; and it excludes many drug-gene associations for which low/preliminary (level 3/4) evidence exists, as defined by PharmGKB. The PharmGKB knowledge base, which was used to generate this table, is not the sole source of relevant pharmacogenetic information. BDNF=brain-derived neurotrophic factor; COMT=catechol O-methyltransferase; SSRI=selective serotonin reuptake inhibitor.

^b These agents have U.S. Food and Drug Administration labeling with CYP450 pharmacogenetic information.

^c Pharmacogenetic information relevant to drug efficacy (E), dosage (D), metabolism/pharmacokinetics (M), toxicity/adverse drug reactions (T), and other (O). Values correspond to a high (1A, 1B), moderate (2A, 2B), or low (3) level of evidence according to the PharmGKB rating scale.

association (level 4) to significant associations with strong effect sizes that have been replicated in multiple cohorts (level 1A). Typically, there are several genetic variants for a single gene with some level of evidence supporting a drug interaction. Therefore, care must be taken when evaluating combinatorial pharmacogenetic tests to ensure that the specific variants with the highest level of evidence are assayed for each gene of interest. As commercial combinatorial pharmacogenetic testing products proliferate and become increasingly more complex, oversight entities such as the U.S. Centers for Disease Control and Prevention have implemented guidelines to evaluate their analytical validity, clinical validity, clinical usefulness, and ethical, legal, and social implications, known as the ACCE model (27). In addition to relevant reviews on the subject (18–21, 23, 28, 29), the Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic (30) and SSRI (31) antidepressants are noteworthy resources. Although these resources and guidelines could serve to equip clinicians with the information needed to make informed combinatorial pharmacogenetic testing choices, the time required to assimilate emerging findings and keep pace with the rapidly evolving literature is prohibitive. In consideration of the need for practical combinatorial pharmacogenetic

testing to augment the precision of antidepressant prescribing, several decision support tools have emerged and are being aggressively marketed to clinicians and, in some cases, directly to patients. Although there are over 30 combinatorial pharmacogenetic testing products on the market throughout the world, only a few provide interpretive reports in a format designed to guide antidepressant prescribing and have been evaluated in a clinical setting (32, 33).

A characteristic feature of combinatorial pharmacogenetic decision support tools is the use of algorithms that aim to identify the gene variants that are most relevant to an individual and match them with the safest, most effective pharmacotherapy. However, in addition to pharmacokinetic-relevant genes, several pharmacodynamic-relevant genes are frequently included in combinatorial pharmacogenetic tests, primarily encoding serotonin and dopamine receptors and transporters. The reports that physicians receive typically stratify genes or drugs into color-coded categories such as "use with caution" (yellow/red) or "use as directed" (green). The level of detail included in the report and the customer support that is offered vary by product. In some cases, consultation with genetic counselors or pharmacists is recommended or provided by the company to help guide the interpretation and implementation of the genetic testing.

TABLE 2. Clinical Trials for Select combinatorial pharmacogenetic Decision Support Tools^a

ClinicalTrials.gov Identifier	Status	Condition	Study Type	Study Design	Comparators	Enrollment	Estimated Completion Date
GeneSight							
NCT02109939 ^b	Recruiting	Treatment-resistant major depression	Interventional	12-week DB RCT, 24-week open-label follow-up	GeneSight versus TAU	1,200 (estimated)	March 2017
NCT02573168	Recruiting	Schizophrenia, schizoaffective disorder	Interventional	8-week 3-arm, parallel group, DB RCT, 12-month follow-up	GeneSight versus enhanced GeneSight versus TAU	531	Dec. 2017
NCT02466477 ^b	Recruiting	Treatment-resistant major depression	Interventional	8-week 3-arm, parallel group, DB RCT, 12-month follow-up	GeneSight versus enhanced GeneSight versus TAU	570 (estimated)	June 2017
NCT02286440	Recruiting	Depression (adolescent)	Interventional	8-week DB RCT, crossover assignment	GeneSight versus TAU	276 (estimated)	Jan. 2018
NCT02189057 ^b	Recruiting	Major depression, bipolar I or II disorder, schizoaffective bipolar disorder	Interventional	8-week DB RCT, crossover assignment	GeneSight versus TAU	276 (estimated)	June 2017
NCT02770339	Recruiting	Pediatric psychiatric crisis	Observational	Prospective	Gene-drug match versus mismatch	TBD	Dec. 2017
NCT01261364	Completed	Major depression, depression NOS	Interventional	8-week DB RCT	GeneSight versus TAU	50	Jan. 2011
NCT01610063	Completed	Major depression, depression NOS	Interventional	8-week randomized open-label pilot	GeneSight versus TAU	227	Nov. 2011
NCT02479464	Completed	Major depression, depression NOS	Interventional	NRC open-label pilot	GeneSight versus TAU	60	Sep. 2010
IDgenetix							
NCT02878928	Completed	Major depression, anxiety	Interventional	12-week prospective multicenter DB RCT	IDgenetix versus TAU	579	Dec. 2016
NCT02411123	Completed	Depression, anxiety	Interventional	4-month prospective randomized clinical study	IDgenetix versus TAU	220	Dec. 2015
NCT02599870	Ongoing	Acute pain surgery	Interventional	Prospective randomized clinical study	IDgenetix versus TAU	56	July 2016
NCT02605343	Completed	Acute pain surgery	Observational	Prospective observational clinical study	IDgenetix versus TAU	110	April 2016
CNSDose							
ACTRN12613001135707	Completed	Major depression	Interventional	12-week prospective DB RCT	CNSDose versus TAU	174	July 2013
GeneCept							
NCT01507155	Completed	Treatment-resistant depression, generalized anxiety disorder	Observational	3-month prospective open-label nonrandomized	Single group assignment	685	May 2014

continued

TABLE 2, continued

ClinicalTrials.gov Identifier	Status	Condition	Study Type	Study Design	Comparators	Enrollment	Estimated Completion Date
GeneCept							
NCT02634177 ^b	Recruiting	Major depression	Interventional	8-week prospective DB RCT	GeneCept versus TAU	335 (estimated)	May 2017
NCT01438242	Withdrawn						
NCT01426516	Terminated						
NCT02883660	Recruiting	Depression adverse effects	Observational	Retrospective case-control study		100	Aug. 2018
NCT01555021	Terminated						
NCT02566057	Recruiting	Psychosis	Interventional	12-month prospective SB RCT	GeneCept versus TAU	100	June 2017

^a DB=double blind; NOS=not otherwise specified; NRC=nonrandomized control; RCT=randomized controlled trial; SB=single blind; TAU=treatment as usual; TBD=to be determined.

^b Active combinatorial pharmacogenetics-guided trials for major depression.

Using the PharmGKB resource, we summarized drug-by-gene interactions with a moderate or high level of evidence in Table 1. Also included in the table are drug-by-gene interactions included in the commercially available combinatorial pharmacogenetic tests that we review in more detail below, even if they are supported by a low level of evidence. It should be noted that Table 1 is not meant to serve as a comprehensive list but as a simple illustration of pharmacogenetic interactions most likely relevant to antidepressant pharmacotherapy and their relative contributions to several decision support tools currently marketed for guidance of major depression treatment.

REVIEW OF COMBINATORIAL PHARMACOGENETIC TESTS: EVIDENCE FOR ENHANCING DEPRESSION TREATMENT OUTCOMES

Several combinatorial pharmacogenetic test products, such as GeneSight, GeneCept, and CNSDose, have undergone clinical trial testing in randomized controlled trials (Table 2), with additional randomized trials under way. Studies evaluating whether these products bring value to the clinical treatment setting could be designed to test several different hypotheses—for example, that their use is associated with significantly greater rates of response and remission with antidepressant pharmacotherapy; significantly better tolerability, resulting in fewer side effects, less nonadherence, or shortened time to achieving target dose; or significantly superior overall cost-effectiveness. Fourteen studies evaluating these products have been published to date, and eight of them evaluated the GeneSight assay (34–49). These investigations used a variety of meta-analytic, prospective, and retrospective designs, with or without blinding of participants or clinicians assessing symptom severity outcomes. All of the prospective clinical trials that were designed to demonstrate that use of the combinatorial pharmacogenetic test produces superior antidepressant outcomes on the basis of change in scores on standardized symptom assessment measures have

notable methodological weaknesses, such as the lack of control groups, lack of blinding, small sample sizes, and potential conflicts of interest among investigators. Because there is controversy as to whether the randomized controlled trial is the proper way to evaluate the merits of combinatorial pharmacogenetics-based decision support tools (22), we included several observational and cost-effectiveness modeling studies in addition to the randomized controlled trials in our review.

GeneSight

In comparison with other algorithm-based combinatorial pharmacogenetic testing products, there is a more substantial evidence base for GeneSight testing, produced by AssureRx Health (a subsidiary of Myriad Genetics, Inc.). Three clinical trials have been completed to assess the clinical practicality and utility of GeneSight testing for treating major depression, resulting in eight publications (34–41). GeneSight uses a drug-gene interpretative report that categorizes drugs into three “bins,” using color-coded descriptors: green, “use as directed”; yellow, “use with caution”; and red, “use with caution and with more frequent monitoring.” The GeneSight test utilizes the Luminex xTAG assay system (Austin, Tex.) to assess polymorphisms among three pharmacokinetic genes (CYP2D6, CYP2C19, and CYP1A2), whereas variation in pharmacodynamic genes, SLC6A and HTR2A, are assessed by polymerase chain reaction (Table 3). The GeneSight test is purported to have a 2-day turnaround time as a result of the multiplex assay method, which in turn might allow physicians to rapidly customize their prescribing strategy on the basis of the patient’s genotype. The clinical utility of the GeneSight interpretative report was assessed using a prospective, nonrandomized, open-label cohort-comparator design (40). After 8 weeks of naturalistic treatment, reduction of depressive symptoms was significantly greater in the GeneSight-guided treatment group than in the treatment-as-usual control group, as determined by the 16-item Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) ($p=0.002$) and the 17-item

TABLE 3. Gene Variants for Selected Combinatorial Pharmacogenetic Guided Decision Support Tools^a

Support Tool and Gene	Variant
GeneSight	
CYP1A2 ^b	-3860 G>A, -2467 T>delT, -739 T>G, -729 C>T, -163 C>A, 2116 G>A, 2499 A>T, 3497 G>A, 3533 G>A, 5090 C>T, 5347 C>T
CYP2B6	*1, *4, *6, *9
CYP2C19 ^b	*1, *2, *3, *4, *5, *6, *7, *8, *17
CYP2C9	*1, *2, *3, *4, *5, *6
CYP2D6 ^b	*1, *2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41, gene duplication
CYP3A4	*1, *13, *15A, *22
SLC6A4 ^b	L, S
HLA-B*1502	Detected/not detected
HTR2A ^b	-1438 G>A
HLA-A*3101	rs1061235 A, T
HLA-A*33	rs1061235 A, T
UGT1A4	*1, *3
UGT2B15	*1, *2
GeneCept	
CYP1A2	*1C, *1D, *1E, *1F, *11
CYP2B6	*5, *6, *7
CYP2C9	*2, *3, *4, *5, *6, *8, *11, *13, *27
CYP2C19 ^b	*2, *3, *4, *5, *6, *7, *8, *9, *10, *17
CYP2D6 ^b	*2, *3, *4, gene deletion (*5), gene duplication, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *29, *41
CYP3A4 ^b	*22
CYP3A5 ^b	*3, *6, *7
SLC6A4 ^b	rs25531, 5-HTTLPR
CACNA1C ^b	Not available
ANKK1 ^b	Not available
5HT2C ^b	Not available
MC4R	Not available
DRD2 ^b	Not available
COMT ^b	Not available
ADRA2A	Not available
MTHFR ^b	C677T, A1286C
BDNF	Not available
OPRM1	Not available
GRIK1	Not available
CNSDose	
CYP1A2	*1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W
CYP2B6	*2, *3, *5, *6, *9, *18, *28
CYP2C19 ^b	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17
CYP2C9	*2, *3, *5, *6, *8, *11, *27
CYP2D6 ^b	*2, *3, *4, *4M, gene deletion (*5), gene duplication (XN), *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *17, *29, *35, *41
CYP3A4	*2, *3, *12, *17, *22
CYP3A5	*1D, *2, *3, *3C, *6, *7, *8, *9
ABCB1 ^b	3435 C>T, 2677 G>A, 2677 G>T
ADRA2A	C-1291G
ANKK1/DRD2	DRD2:Taq1
Apolipoprotein E	ε2, ε4
COMT	Val158Met, c.1-98 A>G
DRD2	-241 A>G, rs2283265, 957 C>T, 939 T>C

continued

TABLE 3, continued

Support Tool and Gene	Variant
CNSDose	
Factor II	20210 G>A
Factor V Leiden	1691 G>A
MTHFR	1298 A>C, 677 C>T
OPRK1	36 G>T, rs6989250, A118G
SLC6A4	La, S, Lg
SULT4A1	rs138097, rs138060
SLCO1B1	521 T>C, 388 A>G
UGT2B15	*2
VKORC1	-1639 G>A, 1173 C>T
ABCC1 ^b	rs212090
UGT1A1 ^b	rs8175347
IDgenetix (NEURO)	
CYP1A2 ^b	Not available
CYP2C9 ^b	Not available
CYP2C19 ^b	Not available
CYP2D6 ^b	Not available
CYP3A4 ^b	Not available
CYP3A5 ^b	Not available
HTR2A ^b	NM_000621.4: c.-998, c.614-2211
HTR2C ^b	NM_000868.2: c.-697, c.-759, c.68
SLC6A4 ^b	NM_001045.4: c.-1760
SLC6A2 ^b	NM_001043.3: c.1287
COMT ^b	NM_000754.3: c.472
OPRM1 ^b	NM_000914.3: c.118
SLCO1B1 ^b	c.521
VKORC1 ^b	c.-1639
MTHFR ^b	c.677, A1298C
ABCB1	NM_000927.4: c.3435
ADRA2A	NM_000681.3: c.-1252, c.*216

^a BDNF=brain-derived neurotrophic factor; COMT=catechol O-methyltransferase; HLA=human leukocyte antigen.

^b Candidate genes that were included in the corresponding combinatorial pharmacogenetic tool at the time of clinical evaluation.

Hamilton Depression Rating Scale (HAM-D) (p=0.04). However, the short duration of the study, the lack of blinding to mitigate placebo effects, and the modest size of the cohort (N=51) are important limitations. Conventional standards of randomization were not used, because sequential enrollment of two discrete patient cohorts defined the two treatment groups.

A larger replication study (N=165) used an identical design but was performed in a different clinic with a different patient cohort (41). Depression was assessed using multiple scoring techniques. Repeated-measures analysis of change in clinical scores over time revealed a significantly greater reduction of symptoms in the GeneSight-guided treatment group than in the treatment-as-usual group after 8 weeks (on the QIDS-C, p<0.001; on the HAM-D, p<0.001; on the Patient Health Questionnaire, p<0.002). Furthermore, there were significant group differences in the proportion of participants meeting criteria for categorical response (44.4% of the GeneSight-guided group, compared with 23.7% the treatment-as-usual group; response was defined as a reduction ≥50% in QIDS-C score from baseline to endpoint) and remission (26.4% of the

guided group, compared with 12.9% of the treatment-as-usual group) at 8 weeks ($p=0.03$). Notably, both the response and remission rates observed in that study were relatively low in comparison with those typically reported for unblinded antidepressant trials. Participants with GeneSight-guided care who were treated with “red-bin” medications had significantly greater symptom improvement than did red-bin participants in the treatment-as-usual group (on the HAM-D, $p=0.01$; on the QIDS-C, $p<0.001$). The authors concluded that precision was improved because medication or dosage was altered from baseline more often in the guided group than it was in the treatment-as-usual group (93.8% compared with 55.6% of cases), resulting in more patients receiving prescriptions for a genotype-concordant (green bin) medication (40% compared with 27.6%) in the guided group after 8 weeks.

Although the results of this larger replication study appear to support the utility of the GeneSight-guided treatment regimen, design weaknesses compromise the validity of the findings. Although the sample size was larger than the previous study ($N=165$ versus $N=51$), the lack of blinding represents a critical flaw; response to placebo or sham interventions in controlled trials of antidepressant interventions, and the patients’ and prescribers’ knowledge that their treatment approach was informed by novel genetic testing, introduces significant potential for positively biasing treatment outcomes (50–52). Other potential confounders include statistically significant differences between treatment groups in their baseline levels of symptom severity, treatment resistance, and CYP2D6 metabolic phenotype distributions, with more “extensive” and “poor” metabolizers in the treatment-as-usual group. One implicit goal of the study was to assess the clinical utility of multi-gene testing as opposed to single-gene testing in which assay results are provided only for the CYP2D6 gene. Single-gene CYP2D6 testing is considered an appropriate comparator for combinatorial pharmacogenetic investigations because it has a central role in the pharmacodynamics of many antidepressants and because CYP2D6 is the most often cited dosing consideration for newer antidepressants whose FDA labels include pharmacogenetic testing recommendations. The fact that experimental groups in the GeneSight study were not matched for CYP2D6 metabolic capacity is therefore a significant design weakness that limits interpretability of the results. Future studies should ensure that experimental groups are matched for CYP2D6 metabolic capacity, and arguably CYP2C19 as well.

Although the initial studies aimed to assess the practicality of implementing the GeneSight interpretative report in a clinical setting, one double-blind randomized controlled trial was explicitly intended to assess its ability to guide treatment with superior depressive symptom reduction (39). In a study of 51 subjects, there was no significant differential reduction of depression symptoms from baseline after 10 weeks of treatment in outcomes assessed by multiple measures (a 30.8% reduction in HAM-D score in the guided treatment group, compared with 20.7% in the treatment-as-usual group;

$p=0.28$). Patients in the guided treatment group had numerically higher remission and response rates, but the differences did not reach statistical significance. Furthermore, there was no statistical difference between treatment groups with respect to total number of medication or dosage changes or number of mental health visits. However, 100% of study subjects who were initially treated with genotype-discordant medications at baseline were switched to concordant medications after 10 weeks in the GeneSight-guided treatment group, as compared with just 50% of the treatment-as-usual group. When percentage improvement in HAM-D score was compared across treatment groups (GeneSight versus treatment as usual) within each advisory category (green, yellow, or red bin), the most pronounced improvement in symptoms was observed among a subset of subjects initially treated with genotype-discordant (red-bin) medications (33.1% in the guided treatment group [$N=7$] compared with 0.8% in the treatment-as-usual group [$N=6$]; $p=0.06$). Although the results are encouraging, the small number of subjects included in the study, especially when stratified by bin status, precludes a reliable interpretation of the clinical impact of the GeneSight assay.

In an effort to increase statistical power, a meta-analysis of the two open-label and one randomized trial was conducted (37). Cumulatively, GeneSight testing was associated with a significant increase in the odds of achieving a categorical response (odds ratio=2.26, $p=0.004$) and remission (odds ratio=1.8, $p=0.07$) and a significantly greater baseline-to-endpoint percentage change in HAM-D depression scores (a 40.5% improvement in the guided group compared with 26.5% in the treatment-as-usual group; $p<0.001$). GeneSight-guided treatment was most beneficial in patients receiving genotype-discordant (red-bin) medications at baseline, as might be expected. The lack of blinding in two of the three studies also limits the validity of the meta-analysis.

The cost-effectiveness and cost savings associated with use of the GeneSight combinatorial pharmacogenetic test have also been evaluated (34–36). In a 1-year, blinded, retrospective study, the number of outpatient health care visits, number of medical absence days, and number of disability claims were found to be significantly greater ($p=0.015$, $p=0.04$, and $p=0.003$, respectively) among patients treated with genotype-discordant medications ($N=9$; red bin) as compared with patients treated with genotype-concordant medications ($N=39$; green bin), equating to a total yearly savings of \$5,174 (34). Of the eight health care utilization measures assessed, several did not attain statistical significance, including inpatient visits. Inclusion of patients with anxiety disorders and lack of a treatment-as-usual group were notable limitations. A cost-effectiveness meta-analysis of the three GeneSight trials that had treatment-as-usual comparator groups found that use of the test significantly increased quality-adjusted life-years. The model predicted a net savings of \$3,764 and estimated an increase of 0.3 quality-adjusted life-years per patient, although no p value for significance was provided (36).

To determine whether composite multi-gene testing is more predictive of treatment response or health care utilization than each gene in the test alone, a meta-analysis was carried out comparing single-gene to multi-gene testing (38). Patients were assigned to green, yellow, or red advisory groups using GeneSight testing or stratification based on single genes. For example, a patient treated with a medication known to be a substrate for CYP2D6 would be assigned to the highest (red) advisory group if he or she were determined to be a poor CYP2D6 metabolizer. In contrast to single-gene testing, the composite GeneSight assessment predicted superior clinical outcomes (percentage improvement from baseline on the HAM-D) for patients in the red advisory group who were treated with medications known to be substrates of CYP2D6 or CYP2C19 ($p=0.002$ and $p=0.004$, respectively). The GeneSight test was not, however, able to predict differences in treatment outcome for patients treated with medications known to interact with other genes in the combinatorial pharmacogenetic panel (CYPIA2, SL6A4, and HTR2A). GeneSight testing was found to be a significant predictor of health care utilization by patients treated with CYP2D6, CYP2C19, and CYPIA2 substrates for which they were genotype discordant ($p=0.04$, $p=0.04$, and $p=0.01$, respectively). Limitations included the small number of study subjects, particularly for single-gene stratification comparisons, and the inclusion of patients who met diagnostic criteria for either major depression or an anxiety disorder while excluding patients with treatment-resistant depression in some cohorts.

According to a recent press release (53), the results of a large ($N=1,200$) clinical trial to evaluate the impact of GeneSight testing will be presented at the APA annual meeting in May 2018. Although “positive results” were announced, it appears that the primary outcome measure, a statistically significant reduction in HAM-D score from baseline to week 8 among subjects receiving GeneSight testing in comparison with treatment as usual, was not achieved.

GeneCept

The GeneCept assay (marketed by Genomind, King of Prussia, Pa.) is similar to the GeneSight assay and includes both pharmacokinetic and pharmacodynamic gene variants (Table 3). The effectiveness of the assay for symptom reduction was assessed in a single prospective unblinded study (45). Genetic testing was elective, and both clinicians and patients completed online surveys to assess symptom severity, history, and experience with medication at baseline and at 1 and 3 months. The study was not specific to patients with a primary diagnosis of major depressive disorder, who represented 42.6% of subjects; primary diagnoses of bipolar disorder and anxiety disorder represented 17.2% and 28.9% of subjects, respectively. Subjects were not excluded on the basis of previous pharmacotherapy trials; 14.9% had no previous trials, and 29% had more than five. Data from clinician surveys for 625 patients were obtained. The surveys indicated that clinicians were influenced by the

combinatorial pharmacogenetic results, leading to increased confidence in selecting medications. Although 94% of patients were reported to have received prescriptions for genotype-concordant medications at 3 months, the proportion of patients receiving concordant and discordant medications at baseline was not reported. Using the Clinical Global Impressions improvement scale, clinicians reported that 63% of patients who were symptomatic at baseline were “much improved” or “very much” improved at the 3-month survey. Self-report surveys for all three time points were received from 197 patients. On the self-rated QIDS, there was a significant mean decrease from 11.9 at baseline to 7.9 at 3 months ($p<0.001$) for patients with a primary diagnosis of major depressive disorder. Compared with patients with other primary diagnoses, patients with major depression reported the highest side effect burden at baseline on the Udvalg for Kliniske Undersøgelser (UKU) scale. The mean UKU side effect burden score was significantly decreased, from 26.4 to 19.2 ($p<0.001$) during the 3-month period for all patients. In the absence of randomization, blinding, and a control group, the study does not provide a rigorous assessment of the GeneCept assay’s ability to improve symptom outcomes.

A second study assessed the influence of GeneCept testing on medication adherence and health care costs but did not evaluate the efficacy of pharmacotherapy (46). This retrospective, unblinded, 4-month observational study included 111 patients who received GeneCept testing and 222 matched patient controls who did not; 37 and 60 patients had primary diagnoses of depression, respectively. The sample included patients with other psychiatric diagnoses, including anxiety disorders, schizophrenia, and dementia. The study found a significant improvement from baseline in medication adherence ($p<0.001$) for patients whose physician had ordered GeneCept testing but not for the control group ($p=0.57$). A higher rate of prescription refills and fewer outpatient visits were observed in the GeneCept-guided treatment group than in the control group, leading to an estimated net savings of \$562 per patient over the 4-month observation window.

IDgenetix

The IDgenetix combinatorial pharmacogenetic test is marketed as a supplement to traditional prescribing resources, such as drug-drug interaction identification tools, and is thought to have particular utility for guiding the treatment of individuals with comorbid psychiatric diagnoses who require treatment regimens with multiple medications. To reduce the potential for adverse drug events, a clinical pharmacist undertakes a medication management review of the IDgenetix combinatorial pharmacogenetic data. Three IDgenetix products are custom tailored for different indications –the Cardio, Neuro, and Thrombophilia gene panels. In a study of 112 long-term-care residents with an average age of 74.2 years taking an average of 19 pharmacologically active compounds, IDgenetix testing was used in conjunction with drug-drug prediction tools to assess the risk of adverse drug events (49). Medications were then categorized into one of two

color-coded advisory groups: green, “use as directed,” and orange, “use with caution.” Prescribing changes were recommended for 54 (48%) patients after the IDgenetix-informed medication management review. CYP450-drug interactions were identified for 43 of these 54 patients, and other gene variants (COMT, OPRM1, SLCO1B1, VKORC1, and MTHFR) were deemed actionable for 33. In total, IDgenetix-guided medication reviews identified the need for changes in medication regimen for 38% more patients than did standard methods. The reduction of psychotropic medications associated with IDgenetix-guided treatment contributed to a cost savings of \$1,300 annually per patient, which exceeded the price of genomic testing within 1 year. The IDgenetix neuropsychiatric test panel was also evaluated in a prospective naturalistic study of 237 subjects with diagnoses including “depression, anxiety, ADHD, and psychosis.” Subjects were randomly assigned to combinatorial pharmacogenetics-guided care (N=178) or standard care (N=59) to evaluate the effect of combinatorial pharmacogenetics-guided treatment on outcomes (47). The majority of subjects had a primary diagnosis of depression (N=97 in the guided care group, N=38 in the standard care group). Subjects were blind to their study group, and clinicians received training on how to interpret the IDgenetix test report. Only 159 subjects completed a computerized neurocognitive test battery at both baseline and 3-month follow-up that included a neuropsychiatric questionnaire and the symbol digit coding test; no significant differences between treatment groups for primary outcomes were observed. Tolerability may have been improved by IDgenetix testing, because significantly fewer subjects in the guided-treatment group reported adverse drug events (28% compared with 53%; $p=0.001$). Additional data from well-controlled randomized controlled trials are needed to understand the clinical utility of the IDgenetix neuropsychiatric test panel.

CNSDose

To date, only one combinatorial pharmacogenetics-guided treatment strategy has been found to significantly improve remission rates among patients with major depression in a double-blind randomized controlled trial (48). The CNSDose test (marketed in the United States by Alpha Genomix Laboratories, Lawrenceville, Ga.) is a pharmacokinetic-focused assay (Table 3). Similar to the GeneSight assay, the CNSDose report categorizes medications into three color-coded advisory groups according to the patient’s genotype. Additional information for each potential gene-drug interaction is provided with an evidence level indicated as “informative” or “actionable,” the latter graphically represented with a red flag. The clinical utility of the CNSDose interpretative report was assessed in a cohort of 148 patients with major depression with moderate to severe symptoms (HAM-D scores ≥ 18 at baseline). No significant differences in the average duration of major depression or number of episodes between patients assigned to the guided treatment and treatment-as-usual comparator arms were found, although past treatment history was not reported. Over the 12-week

study, patients in the guided-treatment arm were 2.52 times more likely to remit (defined as a HAM-D score ≤ 7) than were patients in the treatment-as-usual arm ($p<0.001$). Patients in the treatment-as-usual group were 13% more likely to experience adverse side effects requiring dosage reduction or discontinuation of pharmacotherapy ($p=0.027$). Furthermore, those in the treatment-as-usual group were more likely to take sick leave (4% in the guided treatment group compared with 15% in the treatment-as-usual group; $p=0.027$), whereas the duration of sick leave was longer (7.7 days compared with 4.3 days; $p=0.014$) for the treatment-as-usual group. Among 14 medications, sertraline was the most commonly prescribed antidepressant for both treatment groups (18.9% in the guided treatment group and 16.2% in the treatment-as-usual group), and no significant differences were observed between groups in medication choice. Remission rates were used to assess outcome; response rates were not reported.

A second study evaluated the validity of the CNSDose assay for desvenlafaxine dosing (42). Unlike many antidepressants, desvenlafaxine is metabolized by UGT1A1 rather than by CYP450 enzymes. The study is therefore somewhat limited in scope, but it was designed to investigate the performance of the CNSDose assay independent of CYP450 gene-by-drug interactions. Exclusion of patients who had previously been treated with antidepressants, as well as those with a history of childhood trauma or other psychiatric comorbidities, further limits the scope of the study. Nevertheless, in a 10-week open-label trial in 119 patients with major depression, the desvenlafaxine dosage needed to achieve remission was compared with the dosage predicted by the CNSDose assay. Because combinatorial pharmacogenetic testing was conducted on completion of the study, both the physician and the symptom rater were blind to testing results. Symptom severity was assessed biweekly using the HAM-D, with remission defined as a score ≤ 7 at study end. Concordance between the actual and the CNSDose-predicted desvenlafaxine dosage needed to achieve remission was computed using nonparametric Kendall’s (tau b) and Cohen’s (kappa) correlation coefficients. The results of both statistical tests showed high concordance (tau=0.84, $p=0.001$; kappa=0.82, $p=0.001$) between actual and predicted dosages among remitters, who represented 79.8% of the sample. Although the findings of these studies provide preliminary support of the clinical utility of the CNSDose interpretative report for antidepressant prescribing, replication studies are needed. Notably, the CNSDose assay is somewhat unique in that it includes variants of the multidrug resistance blood-brain-barrier transporters ABCB1 and ABCG1, which have been investigated independently in clinical trials (reviewed in detail below).

ABCB1-GUIDED ANTIDEPRESSANT TREATMENT STRATEGY

Centrally acting drugs, such as antidepressant medications, must accumulate in the brain to exert their therapeutic

effects. A superfamily of ATP-binding cassette (ABC) transporters are transmembrane proteins that serve as CNS efflux pumps for several antidepressants, thereby modulating their pharmacokinetic profile (54). Two ABC genes, ABCB1 and ABCC1, have been investigated in the context of antidepressant response and, in some cases, incorporated into combinatorial pharmacogenetic tests. Although there is little supportive evidence for the role of ABCC1 variants in the response to antidepressants (55), ABCB1 variants have been more widely implicated (56). Studies have shown that expression of ABCB1 differentially affects the brain concentration of antidepressants, which is hypothesized to increase clinical efficacy, thereby establishing some rationale for implementing ABCB1 genotyping (57). Six ABCB1 variants have emerged as the most well studied and empirically supported (56, 58). Some occur frequently (rs1128503, rs2032582, rs1045642, and rs9282564) and affect CNS exposure to some antidepressants (59, 60). The most commonly reported ABCB1 variant, rs1045642, has been implicated in the response to antidepressant treatment (61–64).

At present, the ABCB1 genotype is not included in FDA labeling, and no guidelines for ABCB1 genotyping have been released from the Clinical Pharmacogenetics Implementation Consortium (65, 66). The overall supportive evidence for ABCB1-guided antidepressant treatment strategy is modest, and there are substantial conflicting data (54, 58, 67). For example, there are inconsistencies in the literature regarding the direction of effect for rs1045642, the gene variant included in CNSDose test panel. In studies not specifically involving the CNSDose product, Jeleń et al. (67) reported a better response to antidepressants among patients with the CC genotype as opposed to the CT or TT genotype, whereas others reported the inverse association with treatment response (62, 64). The rs1045642 minor/major allele frequency differs by ethnicity (68), introducing potential confounders in studies lacking equivalent distributions across treatment groups. A recent comprehensive review of ABCB1-guided antidepressant treatments identified a number of limitations and discrepancies among ABCB1 genotyping studies (56). Although promising findings have emerged that may eventually translate to clinical utility, there is significant heterogeneity in the existing clinical trial evidence base with respect to statistical power, outcome measures, population size, and patient composition. Other limitations include the incomplete elucidation of each antidepressant's affinity for ABCB1 and whether the substrate status alone is predictive of treatment outcome. There is little consensus on which polymorphism (or polymorphisms) is most predictive of treatment outcomes and whether ABCB1 genotyping must be used in conjunction with other genotyping for genes that affect the drug's pharmacokinetic properties. Further obscuring the evaluation of this approach is the finding that some antidepressants modulate the activity of ABCB1 itself (59).

Only one study has investigated the clinical application of ABCB1-guided treatment for depression. A pilot study in

58 inpatients participating in the MARS project found that subjects whose ABCB1 genotyping information was used in clinical decision making had greater HAM-D response rates ($t=2.091$, $df=111$, $p=0.020$, one-sided) and greater remission rates ($\chi^2=6.596$, $df=1$, $p=0.005$, one sided) (44). Despite a substantial body of literature evidencing ABCB1 variation in the susceptibility to depression, depression symptomology, response to antidepressant pharmacotherapy, or drug intolerance, there is currently only a low level of support (evidence level 3, PharmGKB) for its implementation in combinatorial pharmacogenetics-guided treatment for major depression. Inclusion of ABCB1 here is not based on the level of evidence supporting its association with the treatment of major depression but rather because the study described above that investigated the clinical utility of ABCB1-guided treatment falls within the purview of this review.

CONCLUSIONS

Genetic variation of the hepatic CYP450 gene family confers differential metabolic capacity among individuals, which can dramatically affect the pharmacokinetic profile of common concurrently administered psychoactive medications and affect individual patient response to some antidepressants. Indeed, incorporation of pharmacogenetic information into clinical practice has already begun in the form of FDA labeling associated with several newer antidepressants. Although pharmacogenetic information in drug labeling has the potential for improving safety, tolerability, and perhaps symptom reduction, whether genotyping at the outset of treatment leads to outcomes superior to those achieved with standard titration schedules and close monitoring remains a critical question. FDA recommendations for adjusting dosage on the basis of genotype do not necessarily translate to coverage for the tests by commercial or federal insurance plans. Allocation of available health care resources for any new diagnostic test or treatment product requires insurance policy makers to review the relevant body of scientific data and find it compelling, with a favorable cost-benefit ratio. Therefore, it is essential that clinical studies investigating the merits of these tools be critically evaluated with regard to the rigor and validity of the conclusions. Although a number of different outcomes, such as improved tolerability, greater symptom reduction, and cost savings, may reflect potential benefits of using combinatorial pharmacogenetic decision support tools, positioning their use as best standard of care for antidepressant pharmacotherapy requires several types of evidence, including outcomes statistically superior to treatment as usual without genetic testing and outcomes superior to results achieved with simple CYP450 pharmacogenetic genotyping. Effect sizes characterizing the magnitude of difference between comparison groups or conditions and cost-effectiveness data are also needed to determine whether and where combinatorial pharmacogenetics belongs in a standard treatment algorithm for major depression. Ultimately, adequately powered randomized controlled trials are

needed, with randomized subject allocation, double blind-ing, and group equivalence on key baseline variables, such as CYP450 metabolic capacity and treatment resistance, to assess whether the product improves treatment outcomes beyond standard care, beyond CYP450 testing alone, or both. An ideal “placebo” condition for a double-blind randomized controlled trial might involve providing a decision tool readout with recommendations based on a false genotype for one group of patients. It is important to note that, as summarized in Table 1, a high level of evidence has been achieved only for the cytochrome P450 genotype data, and none of the pharmacodynamic genotype predictors of treatment response are rated similarly.

The ideal combinatorial pharmacogenetics tool would include all variants for which there is a moderate to high level of evidence supporting an interaction with antidepressant medications while excluding spurious variants that are irrelevant to the treatment of major depression or that have little empirical support. Unfortunately, it is difficult to ascertain how well the available tests conform to this ideal, because some combinatorial pharmacogenetic products do not report the specific gene variants that are interrogated. Furthermore, evaluating the level of evidence for each variant is a painstaking process, even with access to resources such as the PharmGKB knowledge base. With over 30 combinatorial pharmacogenetic tools on the market, evaluating the relative clinical value of each variant independently is not practical, and such an approach does not test the proprietary algorithm-based phenotyping that is unique to each combinatorial pharmacogenetic product. The manner by which combinatorial pharmacogenetic algorithms integrate and weigh the most important genetic variants is not reported by the companies that market them, and the application of information in the combinatorial pharmacogenetic guidance for a given patient may vary significantly from one clinician to the next. Both of these factors reduce the interpretability of results from observational studies, which comprise the majority of combinatorial pharmacogenetic studies sponsored by the companies that sell them.

In this review, we focused on commercial combinatorial pharmacogenetic decision support tools that are purported to improve antidepressant treatment response or side effect burden that have been evaluated in a clinical setting. A number of other candidate genes and gene variants (not yet included in most commercial combinatorial pharmacogenetic tests) have been associated with prediction of response to one or another antidepressant in published reports over the past decade. Examples include the norepinephrine transporter gene (SL6A2) (69, 70); the corticotropin-releasing hormone-binding protein (CRHBP) (71); the FKBP5 gene, which codes for a glucocorticoid receptor cochaperone protein (72, 73); the brain-derived neurotrophic factor (BDNF) gene (74); and the gene for G-protein beta-3 (GNB3) (75). Although substantial ambiguity remains as to which are the most relevant candidates for further development (18, 23, 29, 76, 77), we can envision a day when even more comprehensive

combinatorial pharmacogenetic tests and more elaborate algorithms are available to predict antidepressant efficacy and tolerability for any patient. Assuming that the most clinically relevant genotyping is eventually fully identified, a next generation of investigation will be needed to determine whether the available decision support tools effectively convey actionable information in a manner that improves the treatment of major depression by altering drug prescribing. Clinicians will undoubtedly embrace decision support tools that provide easily consumable pharmacogenetic information, but only if they can be certain that the information is valid and improves the efficacy, tolerability, or affordability of specific pharmacotherapies and that the tool works well in real-life practice, in which patients often have multiple comorbidities and resistance to first-line agents.

Until then, clinicians must evaluate each commercially available combinatorial pharmacogenetic tool according to the results of a few clinical trials in which they were tested and from post hoc retrospective analysis of data from a few flawed trials. The available literature on combinatorial pharmacogenetic products suffers from publication bias, because some products garner more investment than do others, and questions about scientific integrity are inherent in studies conducted by or reports authored by personnel with significant financial interests in the outcome. Although some of the preliminary published data sound promising, particularly with regard to the CYP450 gene variants and side effect burden, we conclude that there is insufficient evidence to support widespread use of combinatorial pharmacogenetic decision support tools at this point in time.

AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry and Behavioral Sciences and the Center for Therapeutic Innovation, University of Miami Miller School of Medicine, Miami; Butler Hospital and the Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence, R.I.; the Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison; the Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, Calif.; Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif.; the Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta; the Department of Psychiatry, Massachusetts General Hospital, Charlestown; and the Center on Aging, University of Miami Leonard M. Miller School of Medicine, Miami.

Address correspondence to Dr. Nemeroff (cnemeroff@med.miami.edu).

Dr. Carpenter has served as a consultant for Magstim, and she has received research grants and equipment for clinical trials (through a contract with Butler Hospital) from Cervel, Janssen, Neosync, and Neuronetics. Dr. Kalin has received research support from NIMH (grants R01 MH046729, P50MH100031, R01 MH081884, R01MH107563); he has served as a consultant for Actify Neurotherapies, CME Outfitters, the Pritzker Neuropsychiatric Disorders Research Consortium, and the Skyland Trail Advisory Board; and he serves as coeditor of *Psychoneuroendocrinology* (Elsevier). Dr. Rodriguez has received research support from NIMH (grant R01MH105461), the Brain and Behavior Research Foundation, and the Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Program, and she has served as a consultant for Allergan, BlackThorn Therapeutics, and Rugen Therapeutics. Dr. McDonald has received research support from Cervel Neurotherapeutics, the National Institute of Neurological Disease and Stroke (NINDS), NeoSync,

Neuronetics, NIMH, the Patient-Centered Outcomes Research Institute, Soterix, and the Stanley Foundation; he has served as a consultant on the Neurological Devices Panel of the Medical Devices Advisory Committee, Center for Devices and Radiological Health, U.S. Food and Drug Administration, and he is an ad hoc member of several NIMH and NINDS study sections; he has served as a speaker for the Telecare Corporation; he receives royalties from Oxford University Press and is a section editor for *Current Psychiatry Reports*; he receives stipends as the Director of Review Course for the American Association of Geriatric Psychiatry and as section editor for *Current Psychiatry Reports*; he is also on the editorial boards of the *American Journal of Geriatric Psychiatry* and the *Journal of ECT*. Dr. Widge has received research support from the Brain and Behavior Research Foundation, Harvard University, NIH, and the U.S. Department of Defense; he has received device donations from Medtronic; he has served as a consultant for Medtronic; and he has multiple patent applications pending in psychiatric diagnostics and novel brain stimulation methods. Dr. Nemeroff has received research support from NIH and the Stanley Medical Research Institute; he has served as a consultant for Bracket (Clintara), Fortress Biotech, Intra-Cellular Therapies, Janssen Research and Development, Magstim, Navitor Pharmaceuticals, Prismic Pharmaceuticals, Sumitomo Dainippon Pharma, Sunovion Pharmaceuticals, TC MSO, Taisho Pharmaceutical, Takeda, and Xhale; he is a stockholder in AbbVie, Antares, BioGen Holdings, Celgene, Corcept Therapeutics Pharmaceuticals, OPKO Health, Seattle Genetics, and Xhale; he has served on scientific advisory boards for the American Foundation for Suicide Prevention, the Anxiety Disorders Association of America, Bracket (Clintara), the Brain and Behavior Research Foundation, the Laureate Institute for Brain Research, Skyland Trail, and Xhale; he has served on boards of directors for the American Foundation for Suicide Prevention, the Anxiety Disorders Association of America, and Gratitude America; income sources or equity of \$10,000 or more include American Psychiatric Publishing, Bracket (Clintara), CME Outfitters, Takeda, and Xhale; and he holds patents on a method and devices for transdermal delivery of lithium (US 6,375,990B1) and a method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2). Dr. Zeier reports no financial relationships with commercial interests.

Received Nov. 27, 2017; revision received March 2, 2018; accepted March 5, 2018; published online Apr. 25, 2018.

REFERENCES

- Kessler RC, Bromet EJ: The epidemiology of depression across cultures. *Annu Rev Public Health* 2013; 34:119–138
- Lopez AD, Murray CCJL: The global burden of disease, 1990–2020. *Nat Med* 1998; 4:1241–1243
- Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; 3:e442
- Reddy MS: Depression: the disorder and the burden. *Indian J Psychol Med* 2010; 32:1–2
- Ustün TB, Ayuso-Mateos JL, Chatterji S, et al: Global burden of depressive disorders in the year 2000. *Br J Psychiatry* 2004; 184: 386–392
- Zhong W, Maradit-Kremers H, St Sauver JL, et al: Age and sex patterns of drug prescribing in a defined American population. *Mayo Clin Proc* 2013; 88:697–707
- Bale TL, Epperson CN: Sex as a biological variable: who, what, when, why, and how. *Neuropsychopharmacology* 2017; 42:386–396
- Reimers A: Hormone replacement therapy with estrogens may reduce lamotrigine serum concentrations: a matched case-control study. *Epilepsia* 2017; 58:e6–e9
- US Food and Drug Administration: Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs; notice. *Fed Regist* 1993; 58:39406–39416
- Cipriani A, Furukawa TA, Salanti G, et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* (Epub ahead of print, Feb 20, 2018)
- Lam RW: Onset, time course, and trajectories of improvement with antidepressants. *Eur Neuropsychopharmacol* 2012; 22(Suppl 3): S492–S498
- Williams LM, Rush AJ, Koslow SH, et al: International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol. *Trials* 2011; 12:4
- Trivedi MH, McGrath PJ, Fava M, et al: Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): rationale and design. *J Psychiatr Res* 2016; 78:11–23
- Widge AS, Ellard KK, Paulk AC, et al: Treating refractory mental illness with closed-loop brain stimulation: progress towards a patient-specific transdiagnostic approach. *Exp Neurol* 2017; 287: 461–472
- Kessler RC, McGonagle KA, Zhao S, et al: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; 51:8–19
- Tansey KE, Guipponi M, Hu X, et al: Contribution of common genetic variants to antidepressant response. *Biol Psychiatry* 2013; 73: 679–682
- GENDEP Investigators; MARS Investigators; STAR*D Investigators: Common genetic variation and antidepressant efficacy in major depressive disorder: a meta-analysis of three genome-wide pharmacogenetic studies. *Am J Psychiatry* 2013; 170:207–217
- Fabbri C, Serretti A: Pharmacogenetics of major depressive disorder: top genes and pathways toward clinical applications. *Curr Psychiatry Rep* 2015; 17:50
- McMahon FJ: Clinically useful genetic markers of antidepressant response: how do we get there from here? *Am J Psychiatry* 2015; 172:697–699
- Nassan M, Nicholson WT, Elliott MA, et al: Pharmacokinetic pharmacogenetic prescribing guidelines for antidepressants: a template for psychiatric precision medicine. *Mayo Clin Proc* 2016; 91:897–907
- Ozomaro U, Wahlestedt C, Nemeroff CB: Personalized medicine in psychiatry: problems and promises. *BMC Med* 2013; 11:132
- Perlis RH: Abandoning personalization to get to precision in the pharmacotherapy of depression. *World Psychiatry* 2016; 15:228–235
- Singh AB, Bousman CA, Ng C, et al: Antidepressant pharmacogenetics. *Curr Opin Psychiatry* 2014; 27:43–51
- Chung WH, Hung SI, Hong HS, et al: Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004; 428:486
- Table of Pharmacogenomic Biomarkers in Drug Labeling. Silver Spring, Md, US Department of Health and Human Services, US Food and Drug Administration, 2018. <https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>.
- Sim SC, Ingelman-Sundberg M: Update on allele nomenclature for human cytochromes P450 and the Human Cytochrome P450 Allele (CYP-allele) Nomenclature Database. *Methods Mol Biol* 2013; 987: 251–259
- Gudgeon JM, McClain MR, Palomaki GE, et al: Rapid ACCE: experience with a rapid and structured approach for evaluating gene-based testing. *Genet Med* 2007; 9:473–478
- Bielinski SJ, Olson JE, Pathak J, et al: Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time: using genomic data to individualize treatment protocol. *Mayo Clin Proc* 2014; 89:25–33
- Porcelli S, Drago A, Fabbri C, et al: Pharmacogenetics of antidepressant response. *J Psychiatry Neurosci* 2011; 36:87–113
- Hicks JK, Sangkuhl K, Swen JJ, et al: Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther* (Epub ahead of print, Dec 20, 2016)
- Hicks JK, Bishop JR, Sangkuhl K, et al: Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and

- CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther* 2015; 98:127–134
32. Bousman CA, Hopwood M: Commercial pharmacogenetic-based decision-support tools in psychiatry. *Lancet Psychiatry* 2016; 3: 585–590
 33. Peterson K, Dieperink E, Ferguson L, et al: Evidence brief: the comparative effectiveness harms, and cost-effectiveness of pharmacogenomics-guided antidepressant treatment versus usual care for major depressive disorder. Washington, DC, US Department of Veterans Affairs, 2011. <https://www.ncbi.nlm.nih.gov/books/NBK384610/>
 34. Winner J, Allen JD, Altar CA, et al: Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. *Transl Psychiatry* 2013; 3:e242
 35. Winner JG, Carhart JM, Altar CA, et al: Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. *Curr Med Res Opin* 2015; 31:1633–1643
 36. Hornberger J, Li Q, Quinn B: Cost-effectiveness of combinatorial pharmacogenomic testing for treatment-resistant major depressive disorder patients. *Am J Manag Care* 2015; 21:e357–e365
 37. Altar CA, Carhart J, Allen JD, et al: Clinical utility of combinatorial pharmacogenomics-guided antidepressant therapy: evidence from three clinical studies. *Mol Neuropsychiatry* 2015; 1: 145–155
 38. Altar CA, Carhart JM, Allen JD, et al: Clinical validity: combinatorial pharmacogenomics predicts antidepressant responses and health-care utilizations better than single gene phenotypes. *Pharmacogenomics J* 2015; 15:443–451
 39. Winner JG, Carhart JM, Altar CA, et al: A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discov Med* 2013; 16:219–227
 40. Hall-Flavin DK, Winner JG, Allen JD, et al: Using a pharmacogenomic algorithm to guide the treatment of depression. *Transl Psychiatry* 2012; 2:e172
 41. Hall-Flavin DK, Winner JG, Allen JD, et al: Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. *Pharmacogenet Genomics* 2013; 23:535–548
 42. Bousman CA, Müller DJ, Ng CH, et al: Concordance between actual and pharmacogenetic predicted desvenlafaxine dose needed to achieve remission in major depressive disorder: a 10-week open-label study. *Pharmacogenet Genomics* 2017; 27:1–6
 43. Breitenstein B, Scheuer S, Brückl TM, et al: Association of ABCB1 gene variants, plasma antidepressant concentration, and treatment response: results from a randomized clinical study. *J Psychiatr Res* 2016; 73:86–95
 44. Breitenstein B, Scheuer S, Pfister H, et al: The clinical application of ABCB1 genotyping in antidepressant treatment: a pilot study. *CNS Spectr* 2014; 19:165–175
 45. Brennan FX, Gardner KR, Lombard J, et al: A naturalistic study of the effectiveness of pharmacogenetic testing to guide treatment in psychiatric patients with mood and anxiety disorders. *Prim Care Companion CNS Disord* 2015; 17 (doi: 10.4088/PCC.14m01717)
 46. Fagerness J, Fonseca E, Hess GP, et al: Pharmacogenetic-guided psychiatric intervention associated with increased adherence and cost savings. *Am J Manag Care* 2014; 20:e146–e156
 47. Olson MC, Maciel A, Garipey JF, et al: Clinical impact of pharmacogenetic-guided treatment for patients exhibiting neuropsychiatric disorders: a randomized controlled trial. *Prim Care Companion CNS Disord* 2017; 19 (doi: 10.4088/PCC.16m02036)
 48. Singh AB: Improved antidepressant remission in major depression via a pharmacokinetic pathway polygene pharmacogenetic report. *Clin Psychopharmacol Neurosci* 2015; 13:150–156
 49. Sugarman EA, Cullors A, Centeno J, et al: Contribution of pharmacogenetic testing to modeled medication change recommendations in a long-term care population with polypharmacy. *Drugs Aging* 2016; 33:929–936
 50. Perahia DG, Wang F, Mallinckrodt CH, et al: Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Psychiatry* 2006; 21:367–378
 51. Rossi A, Barraco A, Donda P: Fluoxetine: a review on evidence based medicine. *Ann Gen Hosp Psychiatry* 2004; 3:2
 52. Apler A: Citalopram for major depressive disorder in adults: a systematic review and meta-analysis of published placebo-controlled trials. *BMJ Open* 2011; 1:e000106
 53. Myriad announces GeneSight psychotropic results from a large prospective trial in patients with major depressive disorder. Mason, Ohio: Assurex Health. Nov 2, 2017. <https://genesight.com/myriad-announces-genesight-psychotropic-results-from-a-large-prospective-trial-in-patients-with-major-depressive-disorder/>
 54. Uhr M, Tontsch A, Namendorf C, et al: Polymorphisms in the drug transporter gene ABCB1 predict antidepressant treatment response in depression. *Neuron* 2008; 57:203–209
 55. Lee SH, Lee MS, Lee JH, et al: MRP1 polymorphisms associated with citalopram response in patients with major depression. *J Clin Psychopharmacol* 2010; 30:116–125
 56. Brückl TM, Uhr M: ABCB1 genotyping in the treatment of depression. *Pharmacogenomics* 2016; 17:2039–2069
 57. Linnet K, Ejsing TB: A review on the impact of P-glycoprotein on the penetration of drugs into the brain: focus on psychotropic drugs. *Eur Neuropsychopharmacol* 2008; 18:157–169
 58. Ray A, Tennakoon L, Keller J, et al: ABCB1 (MDR1) predicts remission on P-gp substrates in chronic depression. *Pharmacogenomics J* 2015; 15:332–339
 59. O'Brien FE, Dinan TG, Griffin BT, et al: Interactions between antidepressants and P-glycoprotein at the blood-brain barrier: clinical significance of in vitro and in vivo findings. *Br J Pharmacol* 2012; 165:289–312
 60. Wolking S, Schaeffeler E, Lerche H, et al: Impact of genetic polymorphisms of ABCB1 (MDR1, P-glycoprotein) on drug disposition and potential clinical implications: update of the literature. *Clin Pharmacokinet* 2015; 54:709–735
 61. Roberts RL, Joyce PR, Mulder RT, et al: A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. *Pharmacogenomics J* 2002; 2:191–196
 62. Singh AB, Bousman CA, Ng CH, et al: ABCB1 polymorphism predicts escitalopram dose needed for remission in major depression. *Transl Psychiatry* 2012; 2:e198
 63. Noordam R, Aarts N, Hofman A, et al: Association between genetic variation in the ABCB1 gene and switching, discontinuation, and dosage of antidepressant therapy: results from the Rotterdam Study. *J Clin Psychopharmacol* 2013; 33:546–550
 64. Lin KM, Chiu YF, Tsai IJ, et al: ABCB1 gene polymorphisms are associated with the severity of major depressive disorder and its response to escitalopram treatment. *Pharmacogenet Genomics* 2011; 21:163–170
 65. Hiemke C, Baumann P, Bergemann N, et al: AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry* 2011; 44:195–235
 66. Xie WW, Zhang L, Wu RR, et al: Case-control association study of ABCB1 gene and major depressive disorder in a local Chinese Han population. *Neuropsychiatr Dis Treat* 2015; 11:1967–1971
 67. Jeleń AM, Sałagacka A, Żebrowska MK, et al: The influence of C3435T polymorphism of the ABCB1 gene on genetic susceptibility to depression and treatment response in Polish population: preliminary report. *Int J Med Sci* 2015; 12:974–979
 68. Peters EJ, Slager SL, Kraft JB, et al: Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. *PLoS One* 2008; 3:e1872
 69. Marshe VS, Maciukiewicz M, Rej S, et al: Norepinephrine transporter gene variants and remission from depression with venlafaxine treatment in older adults. *Am J Psychiatry* 2017; 174:468–475

70. Yoshida K, Takahashi H, Higuchi H, et al: Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. *Am J Psychiatry* 2004; 161:1575–1580
71. O'Connell CP, Goldstein-Piekarski AN, Nemeroff CB, et al: Antidepressant outcomes predicted by genetic variation in corticotropin-releasing hormone binding protein. *Am J Psychiatry* 2018; 175:251–261
72. Binder EB, Salyakina D, Lichtner P, et al: Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet* 2004; 36: 1319–1325
73. Horstmann S, Lucae S, Menke A, et al: Polymorphisms in GRIK4, HTR2A, and FKBP5 show interactive effects in predicting remission to antidepressant treatment. *Neuropsychopharmacology* 2010; 35:727–740
74. Niitsu T, Fabbri C, Bentini F, et al: Pharmacogenetics in major depression: a comprehensive meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; 45:183–194
75. Hu Q, Zhang SY, Liu F, et al: Influence of GNB3 C825T polymorphism on the efficacy of antidepressants in the treatment of major depressive disorder: a meta-analysis. *J Affect Disord* 2015; 172: 103–109
76. Horstmann S, Binder EB: Pharmacogenomics of antidepressant drugs. *Pharmacol Ther* 2009; 124:57–73
77. Biernacka JM, Sangkuhl K, Jenkins G, et al: The International SSRI Pharmacogenomics Consortium (ISPC): a genome-wide association study of antidepressant treatment response. *Transl Psychiatry* 2016; 6:e937