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Personalized assessment and treatment of depression

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The drive to personalize the delivery of psychosocial and pharmacologic treatments is embodied in Gordon Paul's (1967) famous question, '*What* treatment, by *whom*, is most effective for *this* individual with *that* specific problem, and under *which* set of circumstances?' Traditionally, researchers have examined 'what works for whom' via post hoc moderator analyses. However, these efforts have been largely unsuccessful, suffering from poor replication and statistical bias due a lack of random assignment. Recent advances in genetic and biological technologies and statistical methods have facilitated an explosion of research on the personalization of treatment for psychological disorders. The present review examines recent developments in the personalization of depression treatment.

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Research has consistently shown that treatments for depression are effective, with one meta-analysis demonstrating an average response rate of 54% across empirically supported treatments such as cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT) and pharmacotherapy [1]. In the United States, depression has a lifetime prevalence rate of 13% [2], with approximately 15% of depressed individuals suffering from unremitting or recurrent depression — even after multiple treatment approaches [3]. Thus, although treatments for depression are generally effective, there is ample room to improve both the initial efficacy and long-term maintenance of treatment gains. The personalization of treatment design and implementation represents an exciting and burgeoning area for improving outcomes in depression.

Currently, 'Strategy 3.2′ of the National Institute of Mental Health's (NIMH) Strategic Plan [4], calls for mental health researchers to 'expand and deepen the focus to personalize intervention research.' As well, investigators have called for an increased emphasis on idiographic research [5,6] and the director of NIMH has called for research that can 'transform diagnostics and therapeutics' [7]. In medicine, the tailoring of interventions to individual needs is referred to as 'personalized medicine' and it has received a great deal of recent attention from the National Institutes of Health and the Food and Drug Administration [8]. Personalized medicine assumes that variability in treatment outcomes results from idiosyncratic initial conditions (e.g. genetic profiles) among individual patients [8]. The expectation is that identifying patterns of variation at the individual level will yield actionable, prescriptive information about which interventions are best-suited to which patients. Nevertheless, much work remains to be done. A recent systematic review and meta-analysis of clinical trials concluded that the present literature is insufficient to draw meaningful conclusions about personalized treatment for depression [9].

The present review addresses the current (and recently expanding) literature on personalized assessment and treatment of depression, with the ultimate goal of encouraging further research in this domain.

Biological factors: genetics, biomarkers, and medications

Personalized medicine — the use of molecular genetic analysis for selecting and implementing targeted treatments — is a fast-growing area of research for optimizing depression treatment. A burgeoning body of recent literature has explored the role of genetics in the symptom trajectories and treatment outcomes of major depressive disorder (MDD). With recent advances in technology that enhance accessibility to genetic sequencing and analysis, studies have taken off in multiple directions to investigate implications of genetics and other biomarkers in relation to personalized assessment and treatment of depression. Although a recent genome-wide association (GWA) study of 2431 MDD patients and 3673 controls failed to identify a single genetic mechanism or pattern that predicts MDD diagnosis [10], research has begun to examine the relationships between genes and treatment efficacy, indicating possibilities for personalized care. Table 1 provides a summary of recently identified candidate genes and their proposed functional roles.

Pharmacogenetics

The targeted employment of pharmacologic interventions for individuals with specific genetic profiles has been a major point of focus. Mitjans *et al.* [11] demonstrated that

Table 1

Candidate genes and proposed functional roles.

Paper(s)	Gene	Chromosomal locus	SNP	Function of gene	Relationship between gene and depression
Adkins *et al*. (2012), Domschke *et al*. (2013)	DRD4	11p15.5	*na*	Dopamine receptor	Although data are equivocal, there may be an association between the DRD4 gene and unipolar depression. Also, potential risk for psychotic symptoms
Adkins *et al*. (2012), Domschke *et al*. (2013)	DRD2	11q	rs1800497	Dopaminergic function, related to D2 receptor density	Certain alleles of this SNP are possible risk factors for affective disorders and increased risk of psychotic symptoms in depression
Domschke *et al*. (2013)	Unclear	1q42, 22q11, 19p13	*na*	(Multiple genes)	Potential risk loci of schizoaffective disorder
Domschke, *et al*. (2013)	Unclear	6p, 8p22, 10p13-12, 10p14, 13q13-14, 13q32, 18p, 22q11-13	*na*	(Multiple genes)	Potential risk loci of depression, bipolar disorder, and schizophrenia
Domschke *et al*. (2013), O'Leary *et al*. (2013)	DBH	9q34	*na*	Dopamine beta-hydroxylase: converts dopamine to norepinephrine	Increased risk of psychotic symptoms in depression
Domschke *et al*. (2013)	DTNBP1	6p22.3	*na*	Protein-encoding gene necessary for the production of lysosomal organelles	Increased risk of psychotic symptoms in depression; may mediate antidepressant treatment response in psychotic depression
Domschke *et al*. (2013)	GSK-3 beta	3q13.3	*na*	Encodes for a protein called serine–theonine kinase involved in neuronal cell development and energy metabolism	Increased risk of psychotic depression
O'Leary *et al*. (2013)	CYP2D6, CYP2C19	22q13.1, 10q24	*na*	Pharmacokinetic genes related to how antidepressant drugs are metabolized by the liver (specifically, proteins from cytochrome P450 family)	Variants of this gene, resulting in ultra-rapid metabolism of antidepressants, could lead to reduced efficacy of these drugs
O'Leary *et al*. (2013)	ABCB1	7q21.12	rs2032583 rs2235015	P-glycoprotein is a membrane-bound multidrug resistance protein. Acts as 'gatekeeper' to the brain	Certain variants can reduce the absorption of antidepressant drugs
O'Leary *et al*. (2013), Domschke *et al*. (2013)	TPH1	11p	rs18000532	Tryptophan hydroxylase: rate-limiting enzyme for synthesis of serotonin from tryptophan	Certain alleles associated with decreased response to SSRIs; may mediate antidepressant response
O'Leary *et al*. (2013)	TPH2	12q21.1	rs10897346 rs7305115	Tryptophan hydroxylase: rate-limiting enzyme for synthesis of serotonin from tryptophan	Lacking the C allele of the first SNP results in decreased SSRI response; presence of the G allele of the second SNP improves SSRI response
O'Leary *et al*. (2013), Adkins *et al*. (2012), Domschke, *et al*. (2013), Landro *et al*. (2014)	SLC6A4	17q11.2	rs25531	Serotonin transporter (SERT), removes serotonin from synaptic cleft	Variants of certain polymorphisms of this gene (5-HTTLPR, i.e. serotonin transporter gene linked polymorphic region) result in a 'long' and 'short' allele. Presence of the short allele is a risk factor for MDD. The rs25531 SNP in the promoter region, in certain combinations with the 'L' or 'S' alleles, may affect antidepressant response. May also mediate antidepressant response in psychotic depression

Table 1 (*Continued*)

Paper(s)	Gene	Chromosomal locus	SNP	Function of gene	Relationship between gene and depression
O'Leary *et al*. (2013)	HTR1A	5q	rs6925	Encodes $5HT_{1a}$ receptors throughout the brain and CNS	Polymorphisms in this gene have been shown to increase clinical response to antidepressants
O'Leary *et al*. (2013)	SLC6A2	16q12.2	rs5569 rs36029 rs1532701	Noradrenaline transporter, removes noradrenaline from the synaptic cleft	Various SNPs are associated with response to tricyclic antidepressants, NRIs and milnacipran (but not SSRIs)
O'Leary *et al*. (2013), Adkins *et al*. (2012)	DAT1 (SLC6A3)	5p15.3	*na*	Dopamine transporter, removes dopamine from synaptic cleft–primary target of the antidepressant buproprion	Possible association with antidepressant response, association remains unclear
O'Leary *et al*. (2013)	COMT	22q11.21	rs4680 rs2075507, rs165599 (rs165599–rs165774–rs174696) (rs4633–rs4818–rs4680)	Catechol-O-methyltransferase, an enzyme related to catabolism of noradrenaline and dopamine	Certain polymorphisms and haplotypes are associated with better response to antidepressant drugs
O'Leary *et al*. (2013), Adkins *et al*. (2012), Domschke *et al*. (2013)	MAOA	Xp11.3	rs6326	Monoamine oxidase A is an enzyme that metabolizes serotonin, noradrenaline, and dopamine	'Short' alleles may be related to enhanced antidepressant response. Also, increased risk of psychotic symptoms in depression
O'Leary *et al*. (2013)	SLC18A2	10q25	*na*	Encodes a membrane protein that is important for release of monoamine neurotransmitters from the presynaptic terminal	Possibly implicated in antidepressant response; has yet to be investigated extensively
O'Leary *et al*. (2013), Domschke, *et al*. (2013), Cattaneo *et al*. (2013)	BDNF	11p13	Nucleotide position 196, 'Val66met'	Brain derived neurotrophic factor; supports survival of neurons in the brain, effecting neural plasticity	Certain polymorphisms associated with smaller hippocampal volume, and impairments in hippocampal-driven cognition. 'Met' allele carriers have improved response to certain antidepressants (e.g. escitalopram)
O'Leary *et al*. (2013)	GRIK4	11q	rs1954787	Encodes a protein in the glutamate neurotransmitter family	May have an effect on citalopram treatment
O'Leary *et al*. (2013)	TREK1 (aka KCNK2)	1q41	*na*	Neural potassium channel (inhibited by SSRI's)	Associated with clinical response to antidepressants
Mamdani *et al*. (2014)	SMAD7	18q21.1	*na*	Encodes SMA-related and MAD-related protein	Downregulated in antidepressant nonresponders
Mamdani *et al*. (2014)	SIGLECP3	19q13.3	*na*	Sialic acid-binding immunoglobulin-like lectin, pseudogene 3	Downregulated in antidepressant nonresponders
Zajkowska *et al*. (2014)	CNR1	6q15	rs1049353 rs806371	Encode for proteins that lead to formation of endocannabinoid receptors	Certain variants associated with lower susceptibility to depression. Other polymorphisms of these genes are associated with reduced treatment response
Zajkowska *et al*. (2014)	CNR2	1p	Q63R rs2501431	Encode for proteins that lead to formation of endocannabinoid receptors	Certain variants associated with increased severity of depression after 12 weeks of antidepressant treatment
Zajkowska *et al*. (2014)	IL-1B	2q	rs16944 rs1143627	Encodes a cytokine protein which is essential to the immune system (specifically, inflammatory response)	Certain polymorphisms of rs16944 are associated with delayed onset of depression in geriatric samples, and certain combinations of polymorphisms on both SNPs listed are linked to recurrent MDD
Zajkowska *et al*. (2014)	COX-2	1q	rs4648308	Related to immune system function and metabolism of endocannabinoids	Individuals with a certain allele at this SNP are at increased risk of depression following interferon treatment for Hepatitis C

Table 1 (*Continued*)

Paper(s)	Gene	Chromosomal locus	SNP	Function of gene	Relationship between gene and depression
Zajkowska *et al*. (2014), Cattaneo *et al*. (2013), Klengel *et al*. (2013), O'Leary *et al*. (2013)	FKBP5	6p21.31	*na*	Regulates glucocorticoid receptor sensitivity; also involved in immunoregulation and cellular processes such as protein folding	Increases risk of developing psychiatric disorders (allele-specific, related to childhood trauma) by demethylation of glucocorticoid response elements of this gene
Cattaneo *et al*. (2013)	*MIF*	2q11.23	*na*	Macrophage inhibiting factor	Expression levels of this gene are negatively correlated with antidepressant treatment response (escitalopram and nortriptyline). Nonresponders had 48% higher baseline mRNA levels of MIF
Cattaneo *et al*. (2013)	*IL-6*	7p	*na*	Glucocorticoid receptor function, inflammation/ immune response, neuroplasticity	Positive response to antidepressant treatment was associated with a 9% reduction in levels of IL-6
Cattaneo *et al*. (2013)	TNF-A	6p21.3	*na*	Encodes tumor necrosis factor – alpha, which is important in immune function	Nonresponders to antidepressant treatment had 39% higher levels of TNF-a
Cattaneo *et al*. (2013)	VGF	7q22	*na*	Expressed in neuroendocrine cells – exact function is unknown	Success of antidepressant treatment was associated with a 20% increase in VGF
Zajkowska *et al*. (2014)	FAAH	1p	rs324420	Fatty acid amide hydroxylase, a protein involved in hydrolysis of primary and secondary fatty acid amides (including neuromodulatory compounds)	A variant of this gene is associated with reduction of enzymatic activity in FAAH, resulting in increased anandamide levels (in turn associated with reduced depression)
Wray *et al*. (2012)	*ADCY3*	2p23.3	rs2384061	Encodes adenylate cyclase 3 which catalyses synthesis of cyclic adenosine monophosphate, related to serotonergic signaling	Possible candidate gene for MDD: depressed patients display reduced activity of this gene. Suggestive, but not statistically significant, effects in a genome-wide association study
Wray *et al*. (2012)	GAL	11q13.3	*na*	Encodes the neuropeptide galanin, which inhibits activity of dopaminergic cells (leading to anhedonia and decreased motor activity). Also regulates serotonin	Emerged as the top candidate gene for MDD in a genome-wide association study

the rs806368 polymorphism of the *CNR1* gene predicted citalopram response, with G carrier men exhibiting greater treatment response than TT homozygous men or women. Adkins *et al*. [12] examined five monoamine candidate genes and found that carriers of the dopamine D4 5-repeat allele exhibited increasing depression during the transition to adulthood, whereas male carriers of the *MAOA3.5* repeat allele exhibited a similar rise in late adolescence. In a study of 243 Han Chinese men and women with MDD, Yeh *et al*. [13] found that variations in the norepinephrine transporter gene *SL6A2* were associated with remission of depression after venlafaxine treatment. In a review of pharmacogenetic and molecular genetic studies, Domschke found that the heritability of psychotic depressive phenotypes was 39%, and that psychotic depression shared several potential chromosomal loci with schizophrenia, schizoaffective disorder, and bipolar disorder [14]. In addition, Domschke found that variants of several genes possibly conferred an increased risk for psychotic symptoms, including *BDNF*, *DBH*, *DTNBP1*, *DRD2*, *DRD4*, *GSK-3beta*, and *MAO-A*. Thus, future pharmacogenetic work may facilitate the development of individually tailored treatments for psychotic phenotypes based on individual genotypes.

Mamdani *et al*. [15] examined genetic predictors of citalopram response. They identified *SMAD7* and *SIGLECP3* as two candidate genes. These genes were the most differentially expressed and significantly downregulated in responders to treatment. Menke [16] found that the most promising candidate genes for depression treatment response are those related to the hypothalamic–pituitary–adrenal (HPA) axis, inflammation, and neuroplasticity; however, another study looking to identify single nucleotide polymorphisms (SNPs)

predictive of antidepressant response found that looking at SNPs related to the HPA axis, endocannabinoid, and immune systems together predicted antidepressant response better than looking at these polymorphisms in isolation [17•]. In a GWA study in a sample of over 10,000 individuals, Wray *et al.* [10] failed to detect main effects for any SNP on depression. These authors estimated that samples 1.8–2.4 times greater are required to sufficiently power genetic association studies of MDD. In addition, Preskorn *et al.* [18•] warn that personalized medicine based solely on genetics may be misleading, given differences between 'predictor genes' and 'target genes' for antidepressive medications. That is, the biomolecules affected by pharmacological treatment (thereby improving symptoms) can be unrelated to the genes that predict individual response to treatment [19•].

Therapygenetics

Targeted interventions based on prescriptive genetics are not limited to pharmacotherapy. Researchers have recently begun to uncover genetic profiles that may predict preferential fit with psychosocial interventions. Perhaps the most promising therapygenetic research to date is Eley *et al.*'s [20••] finding that children with a short–short genotype for the *5HTTLPR* serotonin transporter gene were more probably to benefit from CBT. Still, Eley [21••] cautions that although therapygenetics offers an encouraging potential benefit, its utility remains limited due to small effect sizes and a lack of replication. Bockting *et al.* [22•] were unable to replicate the preferential role of *5HTTLPR* in CBT. However, these authors examined the gene by treatment effects on recurrence in remitted adults with depression; future research should examine whether population, diagnosis, or stage of care accounts for the lack of replication. Eley [21••] has proposed a move away from candidate-gene studies to GWA studies to increase power (preferably with large sample sizes), and Lester and Eley [23•] have suggested developing prediction algorithms based on machine learning and the aggregation of multiple genes and polymorphisms.

Finally, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D [24•]) study examined the relationship between ancestral background and outcome after depression treatment in a large cohort of 1892 individuals. Robust correlations between ancestry and both drug efficacy and side effects were observed in 89 different treatment-outcome combinations. These data support the notion that heritable factors (indexed by ancestry) influence side effects as well as outcome of depression treatment.

Other biological approaches

Transcranial magnetic stimulation (TMS), the stimulation of regions of the brain via an electromagnetic coil, is an FDA-approved intervention for MDD. Arns *et al.* were able to reliably identify non-responders to TMS treatment with low false-positive rates [25]. Non-responders tended to exhibit, first, increased fronto-central theta electroencephalography (EEG) power; second, a slower anterior individual alpha peak frequency; third, a larger P300 amplitude; and fourth decreased pre-frontal delta and beta concordance. Fox *et al.* [26•] demonstrated that individual differences in dorsolateral prefrontal cortex connectivity, as revealed through functional magnetic resonance imaging (fMRI), could be used to individually tailor TMS treatment of depression via the personalized targeting of focal TMS. Finally, Takizawa *et al.* [27] found that near-infrared spectroscopy could be used to accurately distinguish individuals with MDD from other patient populations with depressive symptoms and may be an important tool for differential diagnosis and personalized care.

Psychosocial factors and patient characteristics

In addition to promising biological and genetic approaches, researchers have explored patient characteristics and patient-related psychosocial factors that are predictive of treatment outcome. Hill *et al.* [28•] have argued that current statistical measurement of change in psychotherapy is too coarse to detect individual complexity and requires augmentation with qualitative and individualized approaches. To this end, Trujols *et al.* [29•] have proposed the Individual Burden of Illness Index for Depression as a personalized metric for severity and recovery, and Lindhiem *et al.* [30•] have developed the probability of treatment benefit chart, a probabilistic, individualized metric for determining the chances a given treatment will benefit an individual with various baseline characteristics.

Huang *et al.* [31] analyzed the electronic health records of 40,651 patients via Least Absolute Shrinkage and Selection Operator logistic regression models. These authors found that they were able to predict future diagnosis of depression as much as a year in advance, with an area under the receiver operating characteristic curve (AUC) of 0.70–0.80. In addition, they were able to differentiate minimal/mild depression from severe depression with an AUC of 0.72. In turn, baseline depression severity was the strongest predictor of treatment response for both pharmacotherapy and psychotherapy – with higher levels of depression predicting poorer outcome in both cases.

DeRubeis *et al.* [32••] recently introduced the Personalized Advantage Index (PAI) to facilitate optimal selection of treatment plans by five variables (marital status, employment, life events, personality disorder, prior medication trials). Participants were assigned to their 'optimal' or 'non-optimal' treatment based on PAI scores; those assigned to 'optimal' treatment had significantly better treatment outcomes suggesting that this index is useful in guiding treatment selection. Although applied specifically to a pharmacologic versus psychotherapeutic choice,

this method can be applied to any two therapies with existing archival data.

Model-based and statistical methods

Traditionally, researchers have examined 'what works for whom' [33] via moderator analyses. However, these efforts have been largely unsuccessful, suffering from poor replication and statistical bias due a lack of random assignment. Wallace *et al.* [34] recently proposed a novel approach for detecting and interpreting moderator effects via the combination of multiple individual moderators. In a sample of 291 depressed adults, they demonstrated that the combined moderator provided a disordinal (i.e. crossover) effect whereby the preferential benefit of medication was found below the cross point and psychotherapy above the cross point.

Other recent statistical innovations include latent class analysis (LCA) and growth mixture modeling (GMM), which are able to isolate clusters (classes) of responders in psychotherapy outcome data [35–37], with the assumption that understanding the predictors of class membership can generate insight into optimal interventions. In one study, GMM was used to demonstrate that CBT was superior to medication in severely depressed young women at one-year follow-up, with no difference between the interventions at one year in those with moderate depression [38•]. Another study found no relationship between intervention modality and treatment response, but demonstrated that non-responder class membership was predicted by coping strategies, emotional lability, and introversion [39].

Two studies have recently examined the latent class structures of interpersonal profiles in MDD. Grosse Holtforth *et al.* [40] used LCA to examine the distribution of interpersonal circumplex structures in 361 depressed patients and 959 patients with other primary diagnoses. These authors found eight distinct interpersonal classes, with a significantly greater distribution of submissive personality types within the depressed patients. Moreover, class membership was significantly related to baseline severity, with highly introverted individuals exhibiting the most severe depression. Cain *et al.* [41] conducted an LCA of 312 depressed patients and returned six interpersonal classes — extraverted, dominant, arrogant, cold, submissive, and unassuming. Submissive personality predicted greater chronicity and poorer functioning, indicating a possible need for more intensive or specialized care in these individuals.

Patient preference

Perhaps the most obvious and direct way to personalize treatment is to confer directly with depressed individuals in order to tailor interventions to their preferences. Wittink *et al.* [42] recently provided a method for determining 'values markers,' profiles of patient values and perceptions of what needs to change in depression treatment. LCA of these makers yielded three preference profiles: a pro-counseling/anti-medication profile, a medical setting preference with an aversion to powerful medications, and a preference for medication over counseling. Most participants were classified in 'profile 1′ in the context of severe depression, and participants generally preferred mental health treatment settings over primary care or spiritual settings. Gaudiano *et al.* [43] found that men and women may have different beliefs about the cause of their depression, and differing views on the acceptability of treatment regimens. These authors examined the perceived causes of depression and acceptability of medication in 52 psychiatric inpatients and found that women were more likely to make biological causal attributions, and that men who made such attributions were less willing to undergo pharmacologic treatment.

Future directions

Bellon and colleagues have developed the predictD algorithm for determining the presence, level, and risk of onset of MDD for primary care intervention [44•]. These investigators are currently conducting a randomized controlled trial of predictD versus usual care, with preliminary results suggesting that patients are comfortable learning about their personal risk of depression [45]. Saveanu and colleagues recently reported initial outcomes from the International Study to Predict Optimized Treatment in Depression (iSPOT-D), an RCT examining escitalopram, sertraline, and venlafaxine-extended release in 1008 treatment-seeking outpatients [46••]. Having demonstrated equivalent results across the three treatments, these authors intend to identify potential neurobiological and genetic predictors of optimal treatment.

Finally, our group is currently conducting a proof-of-concept trial based on recent work by the first author [47]. Individuals with MDD and/or generalized anxiety disorder complete brief, phone-based surveys related to the clinical criteria for both disorders, four times per day for 30 days. These data are analyzed to distil the core, latent factors for each individual and the dynamic, predictive relationships among symptoms moment-to-moment. The results of these analyses are then used to make prescriptive decisions about the construction and implementation of modular therapies on a person-by-person basis.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Westen D, Morrison K: **A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: an empirical examination of the status of empirically supported therapies**. *J Consult Clin Psychol* 2001, **69**:875-899.

2. Hasin DS, Goodwin RD, Stinson FS, Grant BF: **Epidemiology of major depressive disorder: results from the national**

epidemiologic survey on alcoholism and related conditions. *Arch Gen Psychiatry* 2005, **62**:1097-1106.

3. Berlim MT, Fleck MP, Turecki G: **Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview**. *Ann Med* 2008, **40**:149-159.

4. Insel TR: **Translating scientific opportunity into public health impact: a strategic plan for research on mental illness**. *Arch Gen Psychiatry* 2009, **66**:128-133.

5. Molenaar PCM: **A manifesto on psychology as idiographic science: bringing the person back into scientific psychology, this time forever**. *Measurement* 2004, **2**:201-218.

6. Barlow DH, Nock MK: **Why can't we be more idiographic in our research?** *Perspect Psychol Sci* 2009, **4**:19-21.

7. Insel TR: **From inconvenient truth to urgent opportunity**. *Observer* 2013, **26**.

8. Hamburg MA, Collins FS: **The path to personalized medicine**. *N Engl J Med* 2010, **363**:301-304.

9. Cuijpers P, Reynolds CF, Donker T, Li J, Andersson G, Beekman A: **Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review**. *Depress Anxiety* 2012, **29**:855-864.

10. Wray NR, Pergadia ML, Blackwood DHR, Penninx BWJH, Gordon SD, Nyholt DR, Ripke S, MacIntyre DJ, McGhee KA, Maclean AW *et al.*: **Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned**. *Mol Psychiatry* 2012, **17**:36-48.

11. Mitjans M, Serretti A, Fabbri C, Gastó C, Catalán R, Fañanás L, Arias B: **Screening genetic variability at the CNR1 gene in both major depression etiology and clinical response to citalopram treatment**. *Psychopharmacology* 2013, **227**:509-519.

12. Adkins DE, Daw JK, McClay JL, van den Oord EJCG: **The influence of five monoamine genes on trajectories of depressive symptoms across adolescence and young adulthood**. *Dev Psychopathol* 2012, **24**:267-285.

13. Yeh Y-W, Chen C-J, Jang F-L, Kuo SC, Chen CY, Liang CS, Ho PS, Yen CH, Shyu JF, Wan FJ *et al.*: **SLC6A2 variants may predict remission from major depression after venlafaxine treatment in Han Chinese population**. *J Psychiatric Res* 2015, **61**:33-39.

14. Domschke K: **Clinical and molecular genetics of psychotic depression**. *Schizophr Bull* 2013, **39**:766-775.

15. Mamdani F, Berlim MT, Beaulieu M-M, Turecki G: **Pharmacogenomic predictors of citalopram treatment outcome in major depressive disorder**. *World J Biol Psychiatry* 2013, **15**:135-144.

16. Menke A: **Gene expression: biomarker of antidepressant therapy?** *Int Rev Psychiatry* 2013, **25**:579-591.

17. • Zajkowska ZE, Englund A, Zunszain PA: **Towards a personalized treatment in depression: endocannabinoids, inflammation and stress response**. *Pharmacogenomics* 2014, **15**:687-698.
This study found that examining SNPs related to the HPA axis, endocannabinoid, and immune systems in combination predicted antidepressant response better than looking at these polymorphisms by themselves. This could provide more insight into the types of genes we can use to predict antidepressant response. In addition, depression treatment response may be influenced by multiple genes or systems of genes in concert with one another.

18. • Preskorn SH, Kane CP, Lobello K, Nichols AI, Fayyad R, Buckley G, Focht K, Guico-Pabia CJ: **Cytochrome P450 2D6 phenoconversion is common in patients being treated for depression: implications for personalized medicine**. *J Clin Psychiatry* 2013, **74**:614-621.
Preskorn *et al*. warn that personalized medicine based solely on genetics can be potentially misleading. While the idea that treatment for depression could be assigned solely based on genotype is exciting, it may be important to consider a person's current functioning (i.e. their phenotype). On the basis of one's genotype, it should be possible to detect how drugs would be metabolized by *CYP2D6* isoenzymes. However, certain drugs given for depression can change the phenotype (changing how the drugs are metabolized) without changing the genotype. This highlights the necessity to consider patients' environments in addition to their genetic profile, as sole focus on genotype may cause important predictors of treatment response to be missed.

19. • Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, Craig IW, Anacker C, Zunsztain PA, McGuffin P, Pariante CM: **Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'**. *Neuropsychopharmacology* 2013, **38**:377-385.
This study reports a key difference between 'predictor genes' and 'target genes' of antidepressive medications. Predictor genes and target genes can differ in terms of their influence on treatment outcome: the genes that may be predictive of individual treatment response (when sampled at baseline) may be different from the genes that actually change over the course of antidepressant treatment. This is important to consider when interpreting findings. This finding suggests that depression treatment response is a complex phenomenon that could be difficult to predict by genetic factors alone.

20. •• Eley TC, Hudson JL, Creswell C, Tropeano M, Lester KJ, Cooper P, Farmer A, Lewis CM, Lyneham HJ, Rapee RM *et al.*: **Therapygenetics: the 5HTTLPR and response to psychological therapy**. *Mol Psychiatry* 2012, **17**:236-237.
In a study of 584 Australian children with anxiety disorders, those who had the short form (homozygous S) variant of the *5HTTLPR* (serotonin transporter) gene had 20% better response to manualized CBT relative to those with the heterozygous SL or long-form gene variants. This type of therapygenetics study design could be implemented in adults with depression to gain a better understanding of genetic factors which may underpin adults' response to psychosocial interventions for depression.

21. •• Eley TC: **The future of therapygenetics: where will studies predicting psychological treatment response from genomic markers lead?** *Depress Anxiety* 2014, **31**:617-620.
Eley points out that the utilization of genes to predict psychotherapy response offers a great potential benefit but is also far from presently feasible due to small effect sizes, inconsistency, and a lack of replication of current research in this domain. The article proposes a move away from candidate-gene studies to GWA studies in order to increase statistical power. Additionally Eley asserts that the field of clinical psychology should address fears related to confidentiality and stigma based on an individual's genotype.

22. • Bockting CLH, Mocking RJ, Lok A, Koeter MWJ, Schene AH: **Therapygenetics: the 5HTTLPR as a biomarker for response to psychological therapy[quest]**. *Mol Psychiatry* 2013, **18**:744-745.
In this study, 187 patients with remitted MDD were genotyped. Participants received either usual care, or CBT to prevent recurrence of depressive symptoms. Though the authors hypothesized that presence of the short form variant of the *5HTTLPR* gene would predict recurrence, this was not supported. Although the study had a relatively small sample size, this finding speaks to the lack of replication in candidate-gene therapygenetics studies. While potentially a stumbling block for therapygenetics, much future work remains in order to understand the genetic factors related to psychotherapy response in depressed patients.

23. • Lester KJ, Eley TC: **Therapygenetics: using genetic markers to predict response to psychological treatment for mood and anxiety disorders**. *Biol Mood Anxiety Dis* 2013, **3**:4.
In this article the authors review the extant literature on genetics and treatment outcomes. They note that the effectiveness of psychotherapies (e.g. CBT) for mood and anxiety disorders is highly variable between individuals, and consider the possibility that this reflects differential genetic predispositions toward response or nonresponse from certain interventions. Although therapygenetics is a relatively new field, there have been some candidate genes identified as possibly related to therapy response (e.g. the 5-HTT polymorphic region). The authors underscore the importance of gene × environment interactions, which are probably to exert additional influences on therapy response.

24. • Adkins DE, Souza RP, Åberg K, Clark SL, McClay JL, Sullivan PF, van den Oord EJ: **Genotype-based ancestral background consistently predicts efficacy and side effects across treatments in CATIE and STAR*D**. *PLoS ONE* 2013, **8**:e55239.
The STAR*D study examined the relationship between ancestral background and outcome after depression treatment in a large cohort of 1892 individuals. Robust correlations between ancestry and both drug efficacy and side effects were observed in 89 different treatment-outcome combinations. This provides important evidence in support of the influence of heritability (indexed by ancestry) on treatment outcome and the presentation of side effects.

25. Arns M, Drinkenburg WH, Fitzgerald PB, Kenemans JL: **Neurophysiological predictors of non-response to rTMS in depression**. *Brain Stimul* 2012, **5**:569-576.

26. • Fox MD, Liu H, Pascual-Leone A: **Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity**. *Neuroimage* 2013, **66**:151-160.

This research explored an individualized targeting approach for TMS based on functional connectivity in the brain. Fox *et al*. demonstrated that individual differences in connectivity (specifically to the dorsolateral prefrontal cortex, which is targeted in TMS treatment) are profound, and are reproducible across sessions. They proposed that, in this way, functional connectivity analyses can be used to personalize targeting of DLPFC TMS, and this approach may be more effective than previous targeting methods based on group-averaged connectivity.

27. Takizawa R, Fukuda M, Kawasaki S, Kasai K, Mimura M, Pu S, Noda T, Niwa S, Okazaki Y: **Neuroimaging-aided differential diagnosis of the depressive state**. *Neuroimage* 2014, **85**:498-507.

28. • Hill CE, Chui H, Baumann E: **Revisiting and reenvisioning the outcome problem in psychotherapy: an argument to include individualized and qualitative measurement**. *Psychotherapy* 2013, **50**:68-76.

These authors argue that current statistical measurement does not allow researchers to capture nuanced, idiographic changes throughout the process of therapy. Hill *et al*. recommend that researchers include personalized and qualitative approaches to assess psychotherapy outcome. Individualized studies could include multiple measurements within an individual throughout the course of psychotherapy in order to detect person-specific differences in the trajectory from baseline to post-treatment. This may be a useful tool for distilling what aspects of psychotherapy are effective for different types of participants.

29. • Trujols J, Portella MJ, Pérez V: **Toward a genuinely patient-centered metric of depression recovery: one step further**. *JAMA Psychiatry* 2013, **70**:1375.

This article reports the use of the 'Individual Burden Index for Depression,' which was developed using patient input and self-report, to promote a more accurate metric of recovery compared to solely clinician's observations/report. A patient-centered metric of treatment outcome is useful in assessing patient perceptions of recovery. Clinicians and clients may have differing definitions of progress throughout therapy, so it will probably be helpful to capture more detail about clients' own perception of treatment gains.

30. • Lindhiem O, Kolko DJ, Cheng Y: **Predicting psychotherapy benefit: a probabilistic and individualized approach**. *Behav Therapy* 2012, **43**:381-392.

This study employed an approach based on the probability of treatment benefit in determining what type of intervention would most benefit children and adolescents. On the basis of individual patient characteristics, projections for the likelihoods of improvement from various interventions were generated. These projections were individual-specific and designed to aid caregivers in selecting an intervention. Offering patients an individually tailored map of information provides a way for patients to make more informed, evidence-based decisions. Such an approach may facilitate therapeutic alliance, perceptions of effectiveness, and potentially treatment outcome.

31. Huang SH, LePendu P, Iyer SV, Tai-Seale M, Carrell D, Shah NH: **Toward personalizing treatment for depression: predicting diagnosis and severity**. *J Am Med Inform Assoc* 2014, **21**:1069-1075.

32. •• DeRubeis RJ, Cohen ZD, Forand NR, Fournier JC, Gelfand LA, Lorenzo-Luaces L: **The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration**. *PLoS ONE* 2014, **9**:e83875.

DeRubeis *et al*. introduce the 'PAI' to aid in the selection of individual treatment plans via five variables (marital status, employment, life events, personality disorder, and prior medication trials). To test this, participants were assigned to their 'optimal' or 'non-optimal' treatment based on PAI scores; those assigned to 'optimal' treatment had significantly better treatment outcomes suggesting that this index is useful in guiding treatment selection.

33. Paul GL: **Strategy of outcome research in psychotherapy**. *J Consult Psychology* 1967, **31**:109.

34. Wallace ML, Frank E, Kraemer HC: **A novel approach for developing and interpreting treatment moderator profiles in randomized clinical trials**. *JAMA Psychiatry* 2013, **70**:1241-1247.

35. Lutz W, Stulz N, Kock K: **Patterns of early change and their relationship to outcome and follow-up among patients with major depressive disorders**. *J Affect Dis* 2009, **118**:60-68.

36. Stulz N, Lutz W, Leach C, Lucock M, Barkham M: **Shapes of early change in psychotherapy under routine outpatient conditions**. *J Consult Clin Psychol* 2007, **75**:864-874.

37. Schumm JA, Walter KH, Chard KM: **Latent class differences explain variability in PTSD symptom changes during cognitive processing therapy for veterans**. *Psychol Trauma Theory Res Pract Policy* 2013, **5**:536-544.

38. • Siddique J, Chung JY, Brown CH, Miranda J: **Comparative effectiveness of medication versus cognitive-behavioral therapy in a randomized controlled trial of low-income young minority women with depression**. *J Consult Clin Psychol* 2012, **80**:995-1006.

This study identified latent classes of depression response in low-income minority women. Two latent trajectory classes were returned: first, severe baseline depression and second, moderate baseline depression and anxiety. Women in the first category had exhibited no difference between CBT and medication response at six months but CBT showed superior treatment gains at one year follow-up. For women in the second category, medication was superior at six months, but no differences were observed after one year. This type of approach may be useful for making predictions about who will respond to certain interventions and the trajectory of response during and after treatment. Moreover, this research emphasizes the importance of diversity, which may become increasingly important as the field moves toward personalized treatment approaches. It is possible that we could leverage strategies for tailoring treatment to create more accessible, culturally relevant interventions for underserved populations.

39. Thibodeau MA, Quilty LC, De Fruyt F, De Bolle M, Rouillon F, Bagby RM: **Latent classes of nonresponders, rapid responders, and gradual responders in depressed outpatients receiving antidepressant medication and psychotherapy**. *Depress Anxiety* 2014, **32**:213-220.

40. Grosse Holtforth M, Altenstein D, Krieger T, Flückiger C, Wright AGC, Caspar F: **Interpersonal differentiation within depression diagnosis: relating interpersonal subgroups to symptom load and the quality of the early therapeutic alliance**. *Psychother Res* 2013, **24**:429-441.

41. Cain NM, Ansell EB, Wright AGC, Hopwood CJ, Thomas KM, Pinto A, Markowitz JC, Sanislow CA, Zanarini MC, Shea MT *et al.*: **Interpersonal pathoplasticity in the course of major depression**. *J Consult Clin Psychol* 2012, **80**:78-86.

42. Wittink M, Morales K, Cary M, Gallo J, Bartels S: **Towards personalizing treatment for depression**. *Patient* 2013, **6**:35-43.

43. Gaudiano BA, Nowlan K, Hughes JA, Miller IW: **Gender differences in hospitalised patients' perceived reasons for their depression**. *J Psychiatr Intensive Care* 2014, **10**:23-32.

44. • Bellon J, Conejo-Ceron S, Moreno-Peral P, King M, Nazareth I, Martín-Pérez C, Fernández-Alonso C, Ballesta-Rodríguez MI, Fernández A, Aiarzaguena JM *et al.*: **Preventing the onset of major depression based on the level and profile of risk of primary care attendees: protocol of a cluster randomised trial (the predictD-CCRT study)**. *BMC Psychiatry* 2013, **13**:171.

This article describes an RCT to test the 'predict-D' algorithm. This algorithm incorporates individual demographic information, SF-12 scores, and other known risk factors for depression to quantify an individual's risk of depression. This intervention will be implemented by general-practice physicians to identify and prophylactically treat those at risk of developing a MDD diagnosis. This type of preventive treatment could be especially useful from a public-health perspective, by identifying those at risk in an individual-specific way we can hopefully reduce the burden of depression while also using resources (e.g. clinicians' time) more efficiently.

45. Bellon JA, Moreno-Peral P, Moreno-Kustner B, Motrico E, Aiarzagüena JM, Fernández A, Fernández-Alonso C, Montón-Franco C, Rodríguez-Bayón A, Ballesta-Rodríguez MI *et al.*: **Patients' opinions about knowing their risk for depression and what to do about it. The predictD-qualitative study**. *PLoS ONE* 2014, **9**:e92008.

46. •• Saveanu R, Etkin A, Duchemin A-M, Goldstein-Piekarski A, Gyurak A, Debattista C, Schatzberg AF, Sood S, Day CV, Palmer DM *et al.*: **The International Study to Predict Optimized Treatment in Depression (iSPOT-D): outcomes from the acute phase of antidepressant treatment**. *J Psychiatr Res* 2015, **61**:1-12.

This large international trial investigated individual predictors of response to three common antidepressant medications. Treatment outcome did not differ across the 1008 outpatients with depression who were randomly assigned to one of three antidepressants. Variables such as baseline anxiety severity were predictive of treatment response. Future research from this group will continue to delve into the individual factors associated with non-response.

47. Fisher AJ: **Toward a dynamic model of psychological assessment: implications for personalized care**. *J Consult Clin Psychol* 2015 http://dx.doi.org/10.1037/ccp0000026. May 25, Advance online publication.