

Biomarkers in Psychiatry: Potentials, Pitfalls, and Pragmatics

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ABSTRACT

Advances in fundamental neurobiology, neuroimaging, neurophysiology, behavioral genetics, and other current high-throughput "omics" fields have yielded considerable advances in understanding the machinery of the brain and how it is altered in disorders of the mind. A recurrent theme for several decades of psychiatric research has been an interest in clinical biomarkers, namely, those biologic features that inform diagnosis, prognosis, or response to treatment. Recent research findings have increased the visibility of several promising biomarker approaches; some illustrative examples are drawn from studies of physiologic measures in mood disorders. The potential for biomarkers to advance the care of mental illness is great, but several caveats must be considered in order to avoid pitfalls that prevent adoption by the field. Pragmatic aspects of evaluating biomarker technologies are proposed that may guide useful development and possible adoption of these techniques.

INTRODUCTION

Biomarkers are commonplace in most branches of medicine: specific biologic features of an individual patient provide critical information about that person's diagnosis, prognosis, or predicted response to treatment. Examples include tumor markers in oncology,¹⁻⁴ troponin in cardiology,⁵⁻⁷ α -feto-protein in obstetrics,⁸ and inflammatory markers and specific serum antibody levels in rheumatology.⁹ Additionally, the use of biomarkers may

Needs Assessment: Recent research advances have raised the potential for clinical application of biomarkers in psychiatric care. It is important for clinicians to understand not only the benefits that biomarkers may bring to practice, but also the needed scientific hurdles these advances should clear before they can be embraced by the field.

Learning Objectives:

- Describe what biomarkers may be able to contribute to care for mental illnesses.
- Discuss proposed characteristics of a clinically-appropriate biomarker in psychiatry.
- Evaluate the applicability of potential biomarkers to patient care.

Target Audience: Primary care physicians and psychiatrists.

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be useful in drug discovery and development, by monitoring response to a test exposure of an experimental medication.¹⁰ Nonetheless, in the field of psychiatry, the biologic features of a patient's illness generally continue to be eclipsed by the central role played by clinical signs and symptoms.¹¹

While numerous new research findings suggest that biomarkers may soon be suitable for clinical use in psychiatric disorders, the quest for biomarkers to improve the care of mental illnesses is not new in the 21st century. For several decades, measurements of specific molecules in cerebrospinal fluid (eg, homovanillic acid, 5-hydroxy-indoleacetic acid),¹² metabolites of neurotransmitters in urine (eg, 3-methoxy-4-hydroxyphenylglycol),¹³ and serum markers of neuroendocrine dysregulation (dexamethasone suppression test)^{14,15} have been complemented by studies of sleep architecture,^{16,17} eye movement abnormalities,^{18,19} and electrodermal and other autonomic responses.²⁰ Other recent investigations have used imaging methods to detect the presence and location of abnormal proteins^{21,22} or abnormal organization of white matter tissue,²³ to monitor neurochemistry with spectroscopy,²⁴ or to detect brain metabolic responses to cognitive "stress tests."²⁵ While these approaches greatly expanded knowledge of the neurobiology of psychiatric disorders by serving as research tools, they have unfortunately found limited application in daily clinical practice or in evidence-based practice guidelines.^{11,26} As biologic measures ("biomeasures"²⁶) and new techniques are reported and considered for use as clinically-applicable biomarkers, it is important for clinicians to understand how these may or may not be "ready for prime time."

THE POTENTIAL

Biomarkers have great potential for improving care for psychiatric patients. Three areas in particular can be identified, including enhanced diagnostic accuracy, prognostic information about the natural course of an individual's illness, and prediction of response to treatment.

As noted above, clinical signs and symptoms are the central basis for establishing psychiatric diagnoses.¹¹ Yet, some symptoms may be present in multiple diagnoses; a reduction in sleep can be a diagnostic element of a depressive episode, a manic episode, or generalized anxiety disorder. Biomarkers have promise for enhancing diagnostic accuracy in this arena. Consider, for example, a patient 20 years of age with a 2-month bout of disabling depression. Is this depression a component of unipolar major depressive disorder (MDD) or does the person really suffer from bipolar disorder but has not yet experienced a floridly manic episode? In an older patient with mild but clear cognitive impairments, are these problems orig-

inating from the neurodegenerative changes of Alzheimer's disease, from ischemic damage in vascular dementia, or from MDD (the "pseudo-dementia" of depression)? In a child, are inattention and disruptive behaviors a part of attention-deficit/hyperactivity disorder, the early onset of bipolar disorder, or simply reflective of coping skills that are overwhelmed by stressful circumstances (eg, parental divorce)? For most patients, clinical information is sufficient to converge on the salient psychiatric diagnosis rapidly, but for some, diagnostic ambiguity may challenge even expert clinicians. The use of biologic markers has potential to assist in this important process, but more work is needed before the field will have useful tools for this application.

Prognostic information is another area where biomarkers could offer valuable insights. In oncology, the elevation of a tumor marker may lead to a workup for a recurrence of disease and initiation of treatment, even before clinical manifestations would have prompted a re-evaluation. In psychiatry, in contrast, an impending full relapse of psychosis in schizophrenia is heralded principally by the return of symptoms. In recurrent depressions, the question can be framed by a patient as "when is a bad day just a 'bad day,' and when is it the start of a new episode?" In the care of older adults with depression, some will likely progress from late-life depression to dementia,²⁷ but identification of this subset of patients remains problematic. Lastly, many patients with mood disorders experience recurrent thoughts of death and perceive life as painful and/or meaningless. While this group of patients has an elevated risk for suicidal behaviors, accurately determining which individuals will go on to harm themselves and which will not cannot be forecast reliably on clinical or historical grounds.²⁸ Some preliminary work suggests measures of brain structure and function²⁹ or genotyping^{30,31} may be developed to refine this process. Rather than believing that research will eventually identify the single, measurable factor that leads to a phenomenon as complex as suicide, it may be more reasonable to anticipate that the greatest utility for this prediction may emerge from a model combining genetic and neurobiologic features with current and past clinical features and familial history, though the relative weightings of these factors remains indeterminate at this time.

Prediction of individual treatment response is viewed by some as a critical area for improvement in psychiatry. While treatments are effective for managing psychiatric illnesses in general, no single treatment works for everyone with a given disorder, and selection of the best treatment for each patient remains a challenge. The general standard of care is to embark upon a course of treatment that is likely to be effective for

that disorder, based on evidence from randomized clinical trials and myriad other data (eg, clinical experience, past patient response to treatment); one then monitors for a good outcome and allows for course correction if improvement fails to occur. Both steps fundamentally rely on clinical findings to assess the degree of symptomatic or functional response. Nobel laureate Niels Bohr is often considered to have observed that “prediction is difficult, especially about the future,” and this statement rings true in this aspect of psychiatric care. The failure of depressive symptoms to improve early in treatment is often a harbinger of poor eventual outcome,³² but what is true on a group level does not necessarily provide useful guidance patient by patient, and some patients simply may take longer than others to respond to treatment that will eventually work well for them.³³ Measurement-based care,^{34,35} with its systematic collection of clinical data with rating scales, can improve detection of good or poor response to treatment with greater utility than a clinician’s global impression, but fundamentally these are better observations of what is already occurring, rather than predictions of future outcomes.

Genetic factors have been examined with inconsistent results (eg, as summarized by Rasmussen-Torvik and McAlpine³⁶). In the largest prospective treatment trial dataset examined in MDD, several genes have been linked with response to antidepressants, including serotonin-2A receptor polymorphisms,³⁷ differences in the GRIK4 gene encoding for a glutamate receptor,³⁸ and a chaperone protein that may regulate hypothalamic-pituitary-adrenal axis function (FKBP5 gene).³⁹ While group differences between responders and non-responders can be found, none of these genetic factors have yet shown adequate utility for guiding individual patient treatment decisions. Similarly, the Evaluation of Genomic Applications in Practice and Prevention Working Group was convened by the federal Centers for Disease Control and Prevention to evaluate the evidence for genetic tests and other genomics applications, and their recommendation for depression was that routine genotyping was not yet supported by the evidence.⁴⁰ In the care of schizophrenia, there is promise that polymorphisms in the genes that relate to drug metabolism may help guide medication dosing,⁴¹ but the choice of a specific agent for any given patient cannot yet be guided by biomarkers. In terms of anxiety disorders, it appears that some genes may predispose individuals to develop anxiety disorders under conditions of stress, but predicting individual response to treatment remains elusive.⁴² Indeed, it may be that consideration of gene-environment interactions becomes essential to take full advantage of genetic information in the care of psychiatric patients.⁴³

Three physiologically based biomarker approaches to predicting outcomes have emerged in recent years in the area of

depression with peer-reviewed publication and independent replication of findings, and can serve as useful examples for evaluating a candidate biomarker for clinical use.

The first measure uses changes in resting-state prefrontal brain activity (“quantitative electroencephalography [EEG] cordance”)⁴⁴ over the course of a test exposure to an antidepressant; that early change is predictive of later treatment outcome with that agent for an individual patient’s care, in studies using either serotonin reuptake inhibitors or dual-reuptake inhibitors. (n=7,⁴⁵ n=51,⁴⁶ n=12⁴⁷).⁴⁵⁻⁴⁹ Cordance is a measure which combines features of absolute and relative EEG power. Because cordance is better correlated with regional cerebral blood flow than other EEG measures,⁴⁴ findings with this measure can be interpreted within the same conceptual framework as other functional neuroimaging studies. A multi-site replication and extension project (NCT00375843) has recently closed enrollment (200 subjects), and data analysis is now underway. The relationship between early change in cordance and later clinical outcome was independently replicated in an inpatient sample (n=17).⁵⁰ These findings collectively supported an even larger collaborative, multi-site trial, Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (NCT00289523; n=375), using a related EEG measure (the antidepressant treatment response [ATR] index). The ATR can be computed using a simplified electrode array with five electrodes placed over prefrontal and frontal brain regions, instead of approximately 35–40 electrodes placed over all scalp locations for measuring cordance (“full head montage”); thus, this is a technology well suited for use in outpatient physicians’ offices, avoiding the need to send patients to a dedicated EEG facility. After a 1-week test period of escitalopram, subjects were randomized to receive either continued escitalopram treatment, a switch to bupropion, or a combination of the two medications; EEG data were recorded before and after the 1-week test period. In a real-world sample of outpatients with MDD, individuals who received treatment consistent with their biomarker prediction were significantly more likely to experience response and remission than individuals who were randomized to a treatment not predicted to be useful.⁵¹⁻⁵³ Further development and replication projects are underway and must be completed before this paradigm of early physiologic change can be considered for clinical application.

The second approach utilizes an EEG measure which is proposed to reflect central serotonergic activity, the loudness dependent auditory evoked potential (LDAEP),⁵⁴⁻⁵⁶ though some other reports have suggested that the interpretation may be more complex than just central serotonergic activity.^{57,58} EEG data recorded prior to treatment are interpreted to indi-

cate whether a depressed patient has a low or high level of serotonergic activity, and those with low activity are predicted to have a favorable response to a serotonergic medication (while high activity is linked to better outcomes with a noradrenergic agent). This method has been examined using treatment with serotonergic reuptake inhibitors ($n=29$,⁵⁹ $n=15$,⁶⁰ $n=100$ ⁶¹) or a noradrenergic agent ($n=14$,⁶² $n=20$ ⁶³). The relationship between level of serotonergic activity and predicted treatment response has been observed in all these studies, though data presented in these reports generally does not permit evaluation on an individual case-prediction level. That level of detail in reporting of results would facilitate evaluation of the LDAEP approach for use in guiding clinical decisions. LDAEP values were calculated using dipole source analysis methods and data from full-head EEG electrode arrays.

The third approach links resting-state pretreatment measures of activity in the rostral anterior cingulate cortex (rACC) to outcome with a variety of treatments, including sleep deprivation ($n=15$,⁶⁴ $n=36$ ⁶⁵), numerous different medications ($n=18$ ⁶⁶), nortriptyline ($n=18$ ⁶⁷), and paroxetine ($n=27$ ⁶⁸). Across all these studies, higher rACC activity was significantly associated with good treatment response. All utilized positron emission tomography methods to study regional brain metabolism, except one study⁶⁷ in which an EEG method (low resolution electromagnetic tomography) was used to determine the level of electrical activity at current sources located in the rACC. An inexpensive, non-invasive measure, such as that used by Pizzagalli and colleagues,⁶⁷ presents an intriguing approach, and independent replication with that methodology would be important for evaluating clinical applicability.

SOME PITFALLS

There are numerous pitfalls that prior biomarker work has encountered, and researchers and clinicians should learn from past experiences. Perhaps most worrisome is the problem of premature clinical application, both because of the risk for harm to patients (misdirected in treatment decisions) and for the cynicism about biomarkers in general this engenders; still, the need for useful biomarkers is so great that sometimes enthusiasm and optimism may overtake consideration of results from carefully conducted controlled clinical trials. To paraphrase the film *Jerry Maguire*, “show me the data!” must be the watchword if clinicians are to make prudent choices for their patients. The usual vetting of new biomedical innovations—procedures, techniques, medications, and devices—requires peer review of findings and independent replication.

What applicability is there to a biomarker if it has only been shown to work in a single laboratory and other researchers are unable to validate the results? Furthermore, it must be clearly disclosed what patient group was used to develop the biomarker, as this has great relevance to generalizability. In the universe of all patients with any psychiatric disorder, only a minority will have a syndrome that is refractory to multiple treatments; yet, this is just the sort of patient who may seek out expert care in desperation and consequently be enrolled in a biomarker discovery research program. The generalizability of such a biomarker may be quite limited, and without clear disclosure of these details it is difficult to evaluate the quality of a biomarker.

An additional caveat about biomarkers relates to the heterogeneity within a given clinical diagnosis. With current clinically defined diagnostic categories, there is variety both in the patients who seek care and in the individuals enrolled in research projects. A telling example is shown in Table 1, in which two individuals who both meet the diagnostic criteria for MDD have zero symptoms in common. Thus, development of biomarkers also should disclose the nature of the patient population and consider evaluating whether the accuracy and reliability of the measure are improved or degraded in some sub-populations (eg, psychotic depression, depression in bipolar type I versus bipolar type II patients).

While biomarkers should have a high degree of clinical utility in order to be considered for use, there is also a need for them to be interpretable in the context of the rest of neuroscience. What aspect of a patient’s pathophysiology is being assessed by a test? Is it the form of a reuptake transporter that is associated with greater or lesser efficiency, the level of activity in a particular brain region, or a component of a neuroendocrine feedback loop? Biomarker methods which fail to be comprehensible within or integrated into the extant body of neurobiologic

TABLE 1
HETEROGENEITY WITHIN DIAGNOSES*

<i>Patient A</i>	<i>Patient B</i>
Depressed mood	Anhedonia
Insomnia	Hypersomnia
Weight loss	Weight gain
Agitation	Psychomotor slowing
Reduced concentration	Feelings of worthlessness, guilt
Fatigue	Suicidal ideation

* Two patients both meet criteria for major depressive disorder, yet have no symptoms in common.

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knowledge are unlikely to gain clinical acceptance, even if an empiric trial suggests that they might be useful.

Finally, it is worthwhile to note that statistical significance is not the same thing as clinical significance. Studies may report that a result is significant at the $P < .05$ level, meaning simply that there is less than one chance in 20 that a finding arose by chance alone. Given a large enough sample, even a clinically-irrelevant difference (eg, a very small improvement on a clinical rating scale) might be reported to occur with an impressive P -value. An important measure for evaluating biomarkers includes the number needed to treat,⁶⁹ which assesses the number of patients needed to be treated differently (eg, with biomarker guidance, with a new medication) in order to have one additional patient experience the desired, positive outcome. Predictive biomarkers are also often characterized by a series of metrics which can help evaluate the usefulness of a potential biomarker, ie, receiver operating characteristic (ROC) curves and measures such as sensitivity, specificity, and overall predictive accuracy.⁷⁰⁻⁷² Sensitivity is the ratio of “true positive” tests to the number of individuals with the condition. For an outcome predictor, it would be the number of people in a sample who are predicted to respond to a treatment, divided by the total number of people who actually respond. Specificity is the ratio of “true negative” tests to the number of people who do not have a particular condition. In the outcome predictor context, this would be the number of people predicted not to respond divided by the total number of non-responders. Overall predictive accuracy is the proportion of predictions that are correct. ROC curves plot the trade-offs between sensitivity and specificity as different thresholds (cut-points) are used to differentiate between positive and negative tests (eg, between predicting response and non-response to a treatment).

PRAGMATIC EVALUATION OF BIOMARKERS FOR PSYCHIATRIC MANAGEMENT

Given the potential for improving care and the pitfalls that may await possible biomarkers, how then can one judge a biomarker for use in psychiatric management? Table 2 summarizes some key, desirable characteristics of psychiatric biomarkers. Many of them follow directly from the pitfalls detailed above, but the last three on the list merit special mention.

First, the information provided by the biomarker must be timely, clinically useful, and cost effective. A test that is able to predict 8-week treatment response at week 5 is much less timely than a prediction made at week 1. A biomarker that identifies an individual with a treatment-refractory illness (a

“biomarker of doom”) is less useful than one which points the way to an alternative treatment strategy. It is unlikely that the field would adopt a biomarker which consumes more resources than it saves, either by direct expenses or by wrongly suggesting an alternative treatment.

Second, the technology needed to assess the biomarker must be available and well tolerated by the target patient population. For example, some neuroimaging methods may be well suited to neuroscience research applications, where a small number of subjects can be observed with great detail, but if the scanning technology costs too much to be deployed widely in the community, the method may not come to be translated into practice. Similarly, a procedure that is perceived as painful (eg, lumbar puncture) or challenging (eg, agitated children remaining conscious yet immobile during a scanning procedure) may have low penetration into the clinical arena for reasons of practicality.

Third, methods that can be seamlessly integrated into existing clinical care practice patterns are more likely to be accepted than those that require major shifts in the delivery of care. For example, sending a patient to a different facility for a biomarker procedure and waiting for test results is less desirable than being able to perform a test in one’s office or ward.

CONCLUSION

Biomarkers have great potential for improving the care of patients with psychiatric disorders, much as they have in other medical specialties. Adoption of biomarkers into clinical care, however, requires careful and thorough evaluation, and there is risk to patients if measures are embraced prematurely. A set of proposed criteria can be used in the pragmatic evaluation of candidate biomarkers. **PP**

TABLE 2
DESIRABLE CHARACTERISTICS OF BIOMARKERS IN PSYCHIATRY

- Test reliability, accuracy, and limitations are well characterized
- Biomarker development process is clearly disclosed
- Findings are reproducible with independent replication and peer review
- Interpretative framework for biomarker allows comparison with other neurobiologic observations
- Information provided by the biomarker is timely, clinically useful, and cost effective
- Technology is available and well tolerated by target patient population
- Methodology can be integrated into clinical care practice patterns

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REFERENCES

- Bast RC Jr, Lijja H, Urban N, et al. Translational crossroads for biomarkers. *Clin Cancer Res*. 2005;11(17):6103-6108.
- Cho WC. Contribution of oncoproteomics to cancer biomarker discovery. *Mol Cancer*. 2007;6:25.
- Rhodes DR, Chinnaiyan AM. Bioinformatics strategies for translating genome-wide expression analyses into clinically useful cancer markers. *Ann N Y Acad Sci*. 2004;1020:32-40.
- Goonewardene TI, Hall MR, Rustin GJ. Management of asymptomatic patients on follow-up for ovarian cancer with rising CA-125 concentrations. *Lancet Oncol*. 2007;8(9):813-821.
- Manenti ER, Bodanese LC, Camey SA, Polanczyk CA. Prognostic value of serum biomarkers in association with TIMI risk score for acute coronary syndromes. *Clin Cardiol*. 2006;29(9):405-410.
- Wu AH, Jaffe AS, Apple FS, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: use of cardiac troponin and B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. *Clin Chem*. Oct 22, 2007 [Epub ahead of print].
- de Ferranti SD, Rifai N. C-reactive protein: a nontraditional serum marker of cardiovascular risk. *Cardiovasc Pathol*. 2007;16(1):14-21.
- Reddy UM. Prediction and prevention of recurrent stillbirth. *Obstet Gynecol*. 2007;110(5):1151-1164.
- Landewé R. Predictive markers in rapidly progressing rheumatoid arthritis. *J Rheumatol Suppl*. 2007;80:8-15.
- Ahmed S, Mozley PD, Potter WZ. Biomarkers in psychotropic drug development. *Am J Geriatr Psychiatry*. 2002;10(6):678-686.
- Vergare MJ, Binder RL, Cook IA, et al. *Psychiatric Evaluation of Adults*. 2nd ed. Arlington, VA: American Psychiatric Association; 2006.
- Berger PA, Faulk KF, Kilkowski J, et al. CSF monoamine metabolites in depression and schizophrenia. *Am J Psychiatry*. 1980;137(2):174-180.
- Garvey M, Hollon SD, DeRubeis RJ, Evans MD, Tuason VB. Does 24-h urinary MHPG predict treatment response to antidepressants? I. A review. *J Affect Disord*. 1990;20(3):173-179.
- Carroll BJ, Cassidy F, Naftolowitz D, et al. Pathophysiology of hypercortisolism in depression. *Acta Psychiatr Scand Suppl*. 2007;(433):9-103.
- Carroll BJ. Dexamethasone suppression test: a review of contemporary confusion. *J Clin Psychiatry*. 1985;46(2 Pt 2):13-24.
- Rush AJ, Weissenburger JE. Melancholic symptom features and DSM-IV. *Am J Psychiatry*. 1994;151(4):489-498.
- Howland RH, Thase ME. Biological studies of dysthymia. *Biol Psychiatry*. 1991;30(3):283-304.
- Lee KH, Williams LM. Eye movement dysfunction as a biological marker of risk for schizophrenia. *Aust N Z J Psychiatry*. 2000;34(suppl):S91-S100.
- Copolov D, Crook J. Biological markers and schizophrenia. *Aust N Z J Psychiatry*. 2000;34(suppl):S108-S112.
- Crowell SE, Beauchaine TP, Gatzke-Kopp L, et al. J. Autonomic correlates of attention-deficit/hyperactivity disorder and oppositional defiant disorder in preschool children. *J Abnorm Psychol*. 2006;115(1):174-178.
- Nichols L, Pike VW, Cai L, Innis RB. Imaging and in vivo quantitation of beta-amyloid: an exemplary biomarker for Alzheimer's disease? *Biol Psychiatry*. 2006;59(10):940-947.
- Small GW, Bookheimer SY, Thompson PM, et al. Current and future uses of neuroimaging for cognitively impaired patients. *Lancet Neurol*. 2008;7(2):161-172.
- Kumar A, Ajilore O. Magnetic resonance imaging and late-life depression: potential biomarkers in the era of personalized medicine. *Am J Psychiatry*. 2008;165(2):166-168.
- Olvera RL, Caetano SC, Fonseca M, et al. Low levels of N-acetyl aspartate in the left dorsolateral prefrontal cortex of pediatric bipolar patients. *J Child Adolesc Psychopharmacol*. 2007;17(4):461-473.
- Bookheimer SY, Strojwas MH, Cohen MS, et al. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med*. 2000;343(7):450-456.
- Kraemer HC, Schultz SK, Arndt S. Biomarkers in psychiatry: methodological issues. *Am J Geriatr Psychiatry*. 2002;10(6):653-659.
- Smith GS, Gunning-Dixon FM, Lotrich FE, Taylor WD, Evans JD. Translational research in late-life mood disorders: implications for future intervention and prevention research. *Neuropsychopharmacology*. 2007;32(9):1857-1875.
- Baldessarini RJ, Conwell Y, Fawcett JA, et al. *Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors*. Arlington, VA: American Psychiatric Association; 2003.
- Pompili M, Ehrlich S, De Pisa E, et al. White matter hyperintensities and their associations with suicidality in patients with major affective disorders. *Eur Arch Psychiatry Clin Neurosci*. 2007;257(8):494-499.
- Laje G, Paddock S, Manji H, et al. Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. *Am J Psychiatry*. 2007;164(10):1530-1538.
- Perlis RH, Purcell S, Fava M, et al. Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. *Arch Gen Psychiatry*. 2007;64(6):689-697.
- Nierenberg AA, McLean NE, Alpert JE, Worthington JJ, Rosenbaum JF, Fava M. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. *Am J Psychiatry*. 1995;152(10):1500-1503.
- Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28-40.
- Trivedi MH, Rush AJ, Gaynes BN, et al. Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR*D measurement-based care. *Neuropsychopharmacology*. 2007;32(12):2479-2489.
- Sussman N. Translating science into service: lessons learned from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. *Prim Care Companion J Clin Psychiatry*. 2007;9(5):331-337.
- Rasmussen-Torvik LJ, McAlpine DD. Genetic screening for SSRI drug response among those with major depression: great promise and unseen perils. *Depress Anxiety*. 2007;24(5):350-357.
- McMahon FJ, Buervenich S, Charney D, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet*. 2006;78(5):804-814.
- Paddock S, Laje G, Charney D, et al. Association of GRIK4 with outcome of antidepressant treatment in the STAR*D cohort. *Am J Psychiatry*. 2007;164(8):1181-1188.
- Lekman M, Laje G, Charney D, et al. The FKBP5-gene in depression and treatment response-an Association Study in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) cohort. *Biol Psychiatry*. Jan 10, 2008 [Epub ahead of print].
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. *Genet Med*. 2007;9(12):819-825.
- Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry*. 2007;12(8):707-747.
- Xu K, Ernst M, Goldman D. Imaging genomics applied to anxiety, stress response, and resiliency. *Neuroinformatics*. 2006;4(1):51-64.
- Caspi A, Moffitt TE. Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nat Rev Neurosci*. 2006;7(7):583-590.
- Leuchter AF, Uijtdehaage SH, Cook IA, O'Hara R, Mandelkern M. Relationship between brain electrical activity and cortical perfusion in normal subjects. *Psychiatr Res*. 1999;90(2):125-140.
- Cook IA, Leuchter AF. Prefrontal changes and treatment response prediction in depression. *Semin Clin Neuropsychiatry*. 2001;6(2):113-120.
- Cook IA, Leuchter AF, Morgan M, et al. Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacology*. 2002;27(1):120-131.
- Cook IA, Leuchter AF, Morgan ML, Stubbeman V, Siegan B, Abrams M. Changes in prefrontal activity characterize clinical response in SSRI nonresponders: a pilot study. *J Psychiatr Res*. 2005;39(5):461-466.
- Leuchter AF, Cook IA, Uijtdehaage SH, et al. Brain structure and function and the outcomes of treatment for depression. *J Clin Psychiatry*. 1997;58(suppl 16):22-31.
- Hunter AM, Cook IA, Leuchter AF. The promise of the quantitative electroencephalogram as a predictor of antidepressant treatment outcomes in major depressive disorder. *Psychiatr Clin North Am*. 2007;30(1):105-124.
- Bareš M, Brunovsky M, Kopeček M, et al. Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: a pilot study. *J Psychiatr Res*. 2007;41(3-4):319-325.
- Leuchter AF, Cook IA, Marangell LB, et al. Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD): Predictors of Clinical Treatment Response. Poster presented at: the Annual Meeting of the Society of Biological Psychiatry, San Diego, CA; May 17, 2007.
- Leuchter AF, Cook IA, Gilmer W, et al. EEG-guided Antidepressant Selection May Improve Response Rates: Insights from the BRITE-MD Trial. Poster presented: the 47th Annual Meeting of the New Clinical Drug Evaluation Unit, Boca Raton, FL; June 11-14, 2007.
- Leuchter AF, Cook IA, Marangell LB, et al. Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD): Predictors of clinical response and remission to escitalopram. Poster presented at: the Annual Meeting of the American College of Neuropsychopharmacology; Boca Raton, FL; December 8-12, 2007.
- Hegerl U, Juckel G. Identifying psychiatric patients with serotonergic dysfunctions by event-related potentials. *World J Biol Psychiatry*. 2000;1(2):112-118.
- Nathan PJ, Segrave R, Phan KL, O'Neill B, Croft RJ. Direct evidence that acutely enhancing serotonin with the selective serotonin reuptake inhibitor citalopram modulates the loudness dependence of the auditory evoked potential (LDAEP) marker of central serotonin function. *Hum Psychopharmacol*. 2006;21(1):47-52.
- Pogarell O, Juckel G, Norra C, et al. Prediction of clinical response to antidepressants in patients with depression: neurophysiology in clinical practice. *Clin EEG Neurosci*. 2007;38(2):74-77.
- Norra C, Becker S, Bröcheler A, Kawohl W, Kunert HJ, Buchner H. Loudness dependence of evoked dipole source activity during acute serotonin challenge in females. *Hum Psychopharmacol*. 2008;23(1):31-42.
- Guille V, Croft RJ, O'Neill BV, Illic S, Phan KL, Nathan PJ. An examination of acute changes in serotonergic neurotransmission using the loudness dependence measure of auditory cortex evoked activity: effects of citalopram, escitalopram and sertraline. *Hum Psychopharmacol*. Jan 15, 2008; [Epub ahead of print].
- Gallinat J, Botflender R, Juckel G, et al. The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. *Psychopharmacology (Berl)*. 2000;148(4):404-411.
- Mulert C, Juckel G, Augustin H, Hegerl U. Comparison between the analysis of the loudness dependency of the auditory N1/P2 component with LORETA and dipole source analysis in the prediction of treatment response to the selective serotonin reuptake inhibitor citalopram in major depression. *Clin Neurophysiol*. 2002;113(10):1566-1572.
- Lee TW, Yu YW, Chen TJ, et al. Loudness dependence of the auditory evoked potential and response to antidepressants in Chinese patients with major depression. *J Psychiatry Neurosci*. 2005;30(3):202-205.
- Linka T, Müller BW, Bender S, Sartory G, Gastpar M. The intensity dependence of auditory evoked ERP components predicts responsiveness to reboxetine treatment in major depression. *Pharmacopsychiatry*. 2005;38(3):139-143.
- Mulert C, Juckel G, Brunmeier M, et al. Prediction of treatment response in major depression: integration of concepts. *J Affect Disord*. 2007;98(3):215-225.
- Wu JC, Gillin JC, Buchsbaum MS, Hershey T, Johnson JC, Bunney WE Jr. Effect of sleep deprivation on brain metabolism of depressed patients. *Am J Psychiatry*. 1992;149(4):538-543.
- Wu J, Buchsbaum MS, Gillin JC, et al. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am J Psychiatry*. 1999;156(8):1149-1158. Erratum in: *Am J Psychiatry*. 1999;156(10):1666.
- Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport*. 1997;8(4):1057-1061.
- Pizzagalli D, Pascual-Marqui RD, Nitschke JB, et al. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *Am J Psychiatry*. 2001;158(3):405-415.
- Saxena S, Brody AL, Ho ML, et al. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *Am J Psychiatry*. 2003;160(3):522-532.
- Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med*. 1988;318(26):1728-1733.
- Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chemistry*. 1993;39(8):561-577.
- Altman DG, Bland JM. Diagnostic tests 1: sensitivity and specificity. *BMJ*. 1994;308(6943):1552.
- Altman DG, Bland JM. Diagnostic tests 2: predictive values. *BMJ*. 1994;309(6947):102.