

A Blood Test for Depression?

Anthony J. Rothschild, MD

In the early 1980s after publication of Dr Bernard Carroll's seminal paper standardizing the dexamethasone suppression test (DST) for melancholia (endogenous depression),¹ the popular media ran headlines proclaiming that a blood test had been discovered for depression. Approximately 6 years later, the clinical utility of the DST in everyday practice was determined to be limited.² The excitement over a simple blood test to diagnose depression launched the research careers of many young psychiatrists, including this author. In this issue of the *Journal*, Bilello and colleagues³ report on a panel consisting of 9 biomarkers associated with the neurotrophic, metabolic, inflammatory, and hypothalamic-pituitary-adrenal axis pathways that, along with gender and body mass index (BMI) data, was able to identify people with major depressive disorder (MDD) with an accuracy of over 90%. The theoretical basis for this commercial test is that the 9 biomarkers in the panel are associated with alterations in key pathways associated with unipolar depression.⁴⁻¹⁰

Having been down this path before, as a clinician and researcher, I would urge caution about embracing the utility of a blood test for depression for several reasons.

Bilello and colleagues³ report excellent sensitivity and specificity of their test for MDD and have replicated a previous study⁴ that used the same panel without including gender and BMI as variables. In the earlier study, the panel and associated algorithm produced good clinical sensitivity and specificity (92% and 81%, respectively) in differentiating MDD patients from normal healthy individuals. However, a notable limitation in both studies is that the sample size is not large. As a means of comparison, the 2013 study by Papakostas et al⁴ had a sample size of 36 MDD patients and 43 nondepressed controls, and the Bilello et al study³ had 68 MDD patients and 86 nondepressed controls, while the 1981 Carroll et al study² had 215 patients with a diagnosis of melancholia, 100 patients with nonendogenous depression, and 70 nondepressed controls.

Apart from the methodological questions, it is important that the clinical application be thoughtfully weighed by both practitioners and researchers. What does this blood test for MDD add to the diagnosis and treatment of patients? In the study, the patients already met criteria for MDD, so what does the test add? The authors state that it is not a screening test, so what is it? Is the test better than the diagnostic

acumen of a board-certified psychiatrist or other mental health professional using well-studied *DSM-5*¹¹ criteria for MDD? According to the website of Ridge Diagnostics, Inc, which provides the test, the test costs \$800.¹² Is this cost-effective? What information, if any, does this \$800 add that has not been already obtained from the trained mental health professional?

A testimonial on the company website¹³ from a psychiatrist states that the test might be used by family practice physicians who are not as well-trained as psychiatrists to diagnose MDD. While the basis for this statement is not clear (family practice residencies do include training in diagnosing MDD), there are better, less costly models for diagnosing MDD in the general practice setting, such as integrated collaborative care.¹³

Back in the 1980s, the argument was made by Carroll and others that MDD was too heterogeneous a category to be useful for the study of biomarkers.¹⁴ Having a biomarker for MDD is like having a biomarker for all cancers, regardless of tissue source. Carroll originally focused on the use of the DST in the more narrow subtype of melancholia (endogenous depression), while others focused on other narrow subtypes of depression, such as psychotic depression.¹⁵ Given the broad nature of MDD, which most likely includes patients with many diverse etiologies, it would be of interest to apply this biomarker panel to more narrow subtypes such as melancholia or psychotic depression, or even other criteria such as the Research Domain Criteria,¹⁶ with a focus on constructs under the "negative valence systems" domain (acute threat, potential threat, sustained threat, loss, and frustrative nonreward).¹⁷

What would be helpful for clinicians is a biomarker test with results that would convert to those seen in a normal control as the patient improves or, even better, convert *before* the changes are clinically noticeable in the depressed patient, as had been reported with the DST.¹⁸ Could this test measure the risk for developing MDD in never-depressed individuals or in the family members of people who have suffered from MDD? Could the test differentiate patients with MDD from patients in the depressed phase of bipolar disorder? Could the test point toward the use of particular somatic treatments, as has been reported with inflammatory biomarkers¹⁹ or pharmacogenomics?²⁰

In summary, the study by Bilello and colleagues³ presents a potential serum-based biologic diagnostic test for MDD. What remains unclear is whether the test provides added value for the diagnosis of MDD above and beyond what a trained clinician can do without the test. If the test could provide answers to questions about the patient *that are not already known* by the trained clinician (eg, predict whether the patient is responding to the treatment before it is clinically noticeable or predict risk in nondepressed patients), then

Submitted: September 15, 2014; accepted September 15, 2014.

Corresponding author: Anthony J. Rothschild, MD, Department of Psychiatry, University of Massachusetts Medical School and UMass Memorial Health Care, 55 Lake Ave N, Worcester, MA 01655 (anthony.rothschild@umassmemorial.org).

J Clin Psychiatry 2015;76(2):e218-e219 (doi:10.4088/JCP.14com09515).
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there would be added value for the care and treatment of MDD. Although we are not there yet, hopefully that day is coming soon.

Author affiliations: University of Massachusetts Medical School and UMass Memorial Health Care, Worcester.

Potential conflicts of interest: Dr Rothschild has been a consultant for Allergan, Eli Lilly, GlaxoSmithKline, Noven, Omnicare, and Pfizer; has received grant/research support from Alkermes, AssureRx, Cyberonics, National Institute of Mental Health, and St Jude Medical; and has received royalties for the Rothschild Scale for Antidepressant Tachyphylaxis (RSAT)[™] and from American Psychiatric Press.

Funding/support: None reported.

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