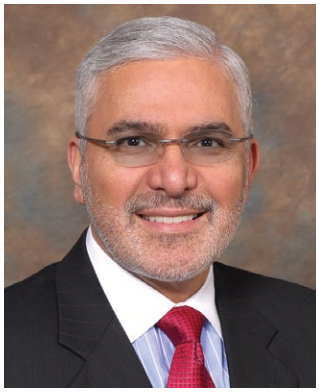

Henry A. Nasrallah, MD
Editor-in-Chief

Lab tests for psychiatric disorders: Few clinicians are aware of them

The lack of laboratory tests to validate the clinical diagnosis of schizophrenia is widely accepted and lamented by psychiatric practitioners. In a recent survey I conducted on CurrentPsychiatry.com, most respondents guessed there are 3 known biomarkers for schizophrenia and 4 for major depression.

There are 273 biomarkers for schizophrenia, but none are included in DSM-5

The media's view tends to be harsh, exploiting the ostensible absence of diagnostic biomarkers in psychiatry to cast unfair aspersions on the scientific validity of DSM-5 and its diagnostic guidelines.[1] They seem to believe that lab tests for mental illness will never be feasible. Clearly, they have not done their homework.

Consider schizophrenia. It would come as a surprise to most people inside or outside the psychiatric community that 365 biomarkers for schizophrenia have been discovered, 273 of which are identifiable in plasma.[2] Of these, 81 are diagnostic, 77 are markers of drug response, and 115 are for both. Some of these tests have been replicated at least 5 times (brain-derived neurotrophic factor, S100B, prolactin, interleukin (IL) 6, IL2, IN5, leptin, IL 1 receptor antagonist, IL8, and IL2 receptor α). The biologic functions of these 273 biomarkers include inflammatory disease or response, respiratory disease, cellular movement, lipid metabolism, molecular transport, immunologic disease, hematologic disease, renal and urologic disease, cell-to-cell signaling, cellular growth and proliferation, cardiovascular disease, genetic disorders, psychological disorders, metabolic disease, small molecule biochemistry, molecular transport, nutritional disease, endocrine system disorders, cell death, tissue morphology, organismal survival, lymphoid tissue structure and development, antigen presentation, tissue development, carbohydrate metabolism, organ morphology, embryonic development, behavior, and digestive system development and functions.[2] Obviously, schizophrenia biomarkers overlap with multiple tissues and key biochemical and cellular processes in brain and body.

So why do none of these 273 blood tests appear in DSM-5, which had aspired to include objective methods in psychiatric diagnosis? The answer: heterogeneity. Schizophrenia and other major psychiatric illnesses are not 1 disorder but syndromes comprised of numerous clinically similar but biologically different disorders. There is extensive variability among the "schizophrenias" in genetic and nongenetic etiological factors and significant heterogeneity in neurobiology, treatment response, and clinical and functional outcomes. None of the individual 273 biomarkers alone can serve as a diagnostic tool for the schizophrenias because there will be high rates of false positives and false negatives. A lab test for a *syndrome* is impossible!

continued

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From the Editor

One company recently attempted to develop a blood test for schizophrenia.[3] It used 51 biomarkers to comprise that test because none of them alone is a viable test[3] (see this article at CurrentPsychiatry.com for a list of these 51 biomarkers). The totality of the 51 biomarkers significantly increases the likelihood of diagnostic utility but still will be short of 100% specificity.

What is the point of identifying 273 blood tests if they have not been used to diagnose a heterogeneous syndrome? I believe there are many potentially useful applications for these biomarkers:

- To identify biologic subtypes of schizophrenia
- To shed light on the multiple pathophysiologies of schizophrenia, which may provide valuable clues for new treatments
- To help identify and characterize stages of schizophrenia. Some biomarkers have been found in the early stages, while others appear only in the chronic stages
- To help predict biologic predisposition to 1 of the schizophrenias. It is possible that the various susceptibility genes that have been identified in schizophrenia may be associated with certain biomarkers during fetal neurodevelopment, childhood, or the prodrome stage
- To explore the overlapping biologic features of psychotic disorders. For example, 21 biomarkers have been found to differentiate schizophrenia or bipolar disorder from healthy controls. Some biomarkers may point to the likelihood of psychiatric comorbidities such as depression or obsessive-compulsive disorder or medical comorbidities such as cardiovascular, immunologic, or gastrointestinal diseases
- Some biomarkers may identify *state* (ie, the psychotic phase only) vs *trait* (throughout life). Other biomarkers may be associated with the presence of a specific type of hallucination (auditory, visual, olfactory, or gustatory), delusion (bizarre vs simple), negative symptom (flat affect vs apathy vs avolition) or cognitive deficit (verbal memory vs learning deficit vs executive dysfunction)
- Biomarkers may assist in developing personalized medicine and designing customized evaluations and treatments for patients suffering from 1 of the many schizophrenias.

Lab tests for psychiatric disorders are indeed available but their use will not mirror traditional physical exam tests. The complex heterogeneity of most psychiatric syndromes means that biomarkers will help unravel the rich neurobiology of those disorders and help elucidate the multiple neurobiologic underpinnings of these syndromes. Psychiatrists should look forward with great optimism to a bright future for psychiatric diagnosis, combining a set of clinical signs and symptoms with a confirmatory cluster of lab tests. It may take time, but psychiatric clinicians will be using biomarkers in the future and the media and the public finally will perceive psychiatry as a "mature" medical discipline.

In the survey I mentioned at the beginning of this editorial, 60.5% of responders predicted that the DSM-6 (approximately a decade from now) will contain laboratory tests for psychiatric diagnosis. They may very well be right!

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Editor-In-Chief

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Table

Biomarkers for schizophrenia

α-1 antitrypsin	IL-7
Apolipoprotein A1	IL-10
Apolipoprotein A2	IL-11
Apolipoprotein B	IL-17
Apolipoprotein CI	KIM-1
Apolipoprotein H	LH
β-2 microglobulin	MCP-2
Betacellulin	MDC
BDNF	MIF
CA	MIP-1 α
Calbindin	MMP-2
Cancer antigen 125	Prolactin
CD5L	Prostatic acid phosphatase
Complement 3	PYY
Cortisol	Serum amyloid P
CTGF	Sortilin
EGFR	Testosterone
Endothelin 1	Thrombopoietin
Ferritin	TIMP 1
Fetuin A	TNF R 2
FSH	Trail R3
Haptoglobin	Transferrin
ICAM1	TSH
IgA	VEGF
IgM	Vitronectin
IL-6 receptor	

BDNF: brain-derived neurotrophic factor; CD5L: CD5 molecule-like; CTGF: connective tissue growth factor; EGFR: epidermal growth factor receptor; FSH: follicle-stimulating hormone; ICAM1: intercellular adhesion molecule 1; IgA: immunoglobulin A; IgM: immunoglobulin M; IL-6 receptor: interleukin 6 receptor; IL-7: interleukin 7; IL-10: interleukin 10; IL-11: interleukin 11; IL-17: interleukin 17; KIM-1: kidney injury molecule-1; LH: luteinizing hormone; MCP-2: monocyte chemotactic protein 2; MDC: mature dendritic cell; MIF: macrophage migration inhibitory factor; MIP-1 α: macrophage inflammatory protein 1 α; MMP-2: matrix metalloproteinase 2; PYY: peptide YY; TIMP 1: TIMP metallopeptidase inhibitor 1; TNF R 2: tumor necrosis factor receptor 2; TSH: thyroid-stimulating hormone; VEGF: vascular endothelial growth factor

Source: Schwarz E, Izmailov R, Spain M, et al. Validation of a blood-based laboratory test to aid in the confirmation of a diagnosis of schizophrenia. Biomark Insights. 2010;5:39-47