

The dawn of precision psychiatry

Imagine being able to precisely select the medication with the optimal efficacy, safety, and tolerability at the outset of treatment for every psychiatric patient who needs pharmacotherapy. Imagine how much the patient would appreciate not receiving a series of drugs and suffering multiple adverse effects and unremitting symptoms until the “right medication” is identified. Imagine how gratifying it would be for you as a psychiatrist to watch every one of your patients improve rapidly with minimal complaints or adverse effects.

Precision psychiatry is the indispensable vehicle to achieve personalized medicine for psychiatric patients. Precision psychiatry is a cherished goal, but it remains an aspirational objective. Other medical specialties, especially oncology and cardiology, have made remarkable strides in precision medicine, but the journey to precision psychiatry is still in its early stages. Yet there is every reason to believe that we are making progress toward that cherished goal.

To implement precision psychiatry, we must be able to identify the biosignature of each patient's psychiatric brain disorder. But there is a for-

midable challenge to overcome: the complex, extensive heterogeneity of psychiatric disorders, which requires intense and inspired neurobiology research. So, while clinicians go on with the mundane trial-and-error approach of contemporary psychopharmacology, psychiatric neuroscientists are diligently deconstructing major psychiatric disorders into specific biotypes with unique biosignatures that will one day guide accurate and prompt clinical management.

Psychiatric practitioners may be too busy to keep tabs on the progress being made in identifying various biomarkers that are the key ingredients to decoding the biosignature of each psychiatric patient. Take schizophrenia, for example. There are myriad clinical variations that comprise this heterogeneous brain syndrome, including level of premorbid functioning; acute vs gradual onset of psychosis; the type and severity of hallucinations or delusions; the dimensional spectrum of negative symptoms and cognitive impairments; the presence and intensity of suicidal or homicidal urges; and the type of medical and psychiatric comorbidities. No wonder every patient is a unique and fascinating clinical puzzle, and yet, patients with schizophrenia are still being homogenized under a single DSM diagnostic category.

In the meantime, psychiatric investigators are stratifying schizophrenia



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Table

Schizophrenia biomarkers

Genetic
Neuroimaging—structural
Neuroimaging—functional
Neuroimaging—spectroscopic
Neuroimaging—tractographic
Neuroinflammation
Oxidative and nitrosative stress
Neuroplasticity
Apoptosis
Neurochemistry
Neurophysiology
Neurocognition
Auto-antibodies
Connectomics
Neuroendocrine
Neuromotor
Sensory integration
Language and speech pathologies
Microbiome
Neurologic soft signs
Minor physical anomalies
Neuropharmacologic
Neuronal integrity
Microglia, astroglia, and oligodendroglia
Laterality shift
Acoustic
Visual and retinal pathologies
Sexual functions
Mortality
Postmortem histopathology
Metabolomics
Suicide predictors
Homicide predictors
Aggressive behavior
Addictions
Comorbid physical illness
Comorbid psychiatric illness

into its many endophenotypes, and linking hundreds of schizophrenia biotypes to an array of biomarkers (*Table*) that can be diagnostic, predictive, prognostic, or useful in monitoring efficacy or safety.

There are hundreds of biomarkers in schizophrenia,¹ but none can be used clinically until the biosignatures of the many diseases within the schizophrenia syndrome are identified. That grueling research quest will take time, given that so far >340 risk genes for schizophrenia have been discovered, along with countless copy number variants representing gene deletions or duplications, plus dozens of de novo mutations that preclude coding for any protein. Add to these the numerous prenatal pregnancy adverse events, delivery complications, and early childhood abuse—all of which are associated with neurodevelopmental disruptions that set up the brain for schizophrenia spectrum disorders in adulthood—and we have a perplexing conundrum to tackle.

Precision psychiatry will ultimately enable practitioners to recognize various psychotic diseases that are more specific than the current DSM psychosis categories. Further, precision psychiatry will provide guidance as to which member within a class of so-called “me-too” drugs is the optimal match for each patient. This will stand in stark contrast to the chaotic hit-or-miss approach.

Precision psychiatry also will reveal the absurdity of current FDA clinical trials design for drug development. How can a molecule with a putative mechanism of action relevant to a specific biotype be administered to a hodgepodge of heterogeneous biotypes that have been lumped in 1 clinical category, and yet be expected to exert efficacy in most biotypes? It is a small miracle that some new drugs beat placebo despite the extensive variability in both placebo responses and drug responses. But it is well known that in all FDA placebo-controlled trials, the therapeutic response across the patient population varies from extremely high to extremely low, and worsening may even occur in a

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subset of patients receiving either the active drug or placebo. Perhaps drug response should be used as 1 methodology to classify biotypes of patients encompassed within a heterogeneous syndrome such as schizophrenia.

Precision psychiatry will represent a huge paradigm shift in the science and practice of our specialty. In his landmark book, Thomas Kuhn defined a paradigm as “an entire worldview in which a theory exists and all the implications that come from that view.”² Precision psychiatry will completely disrupt the current antiquated clinical paradigm, transforming psychiatry into the clinical neuroscience it is. Many “omics,” such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, and metagenomics, will inevitably find their way into the jargon of psychiatrists.³

A marriage of science and technology is essential for the emergence of precision psychiatry. To achieve this transformative amalgamation, we need to reconfigure our concepts, reengineer our methods, reinvent our models, and redesign our approaches to patient care.

As Peter Drucker said, “The best way to predict the future is to create it.”⁴ Precision psychiatry is our future. Let’s create it!



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