In a study published in *Nature* in February 2017, investigators from the Infant Brain Imaging Study (IBIS) described promising findings in screening children for autism spectrum disorders (ASDs). Using brain magnetic resonance imaging (MRI) to assess cortical development and brain volume, investigators were able to predict in infants as young as 6–12 months of age at risk for ASD—that is, with an ASD-affected sibling—which children would develop ASD by 24 months of age. While this study requires further validation in a larger cohort—15 of 106 high-risk subjects ultimately developed ASD—it speaks to the vast unmet medical need of biomarkers for neurodevelopmental and psychiatric disorders. This need is especially striking given evidence that early intervention may be critical for correcting an array of mental illnesses. For instance, with particular regard to ASDs, a long-term follow-up of the parent-mediated social communication therapy for young children with autism (PACT) controlled trial, published in *The Lancet* in November 2016 showed that autistic children receiving therapy between 2–4 years of age showed clinical improvement up to six years after the therapy had ended.

The global burden of mental illness is staggering, with recent data published in *The Lancet* in February 2016 suggesting that psychiatric disorders are the leading cause of years lost to disability. These data are simply estimates, though, largely confounded by how mental illnesses are classified and diagnosed. At present, the approved diagnoses of all psychiatric disorders—from schizophrenia and major depressive disorder (MDD) to obsessive-compulsive disorder and ASDs—are arrived at through reporting of mental and behavioral symptoms by patients or caregivers to mental health professionals. Many disorders catalogued in the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases describe a spectrum of symptoms. For example, for a diagnosis of MDD, a patient must display at least five of nine symptoms in the DSM. It is therefore feasible that two patients, both with MDD, share only one common symptom. Cultural and social norms and stigmas can further complicate patient and caregiver reporting of symptoms or how these symptoms are interpreted by mental health professionals. Co-morbidities with other psychiatric disorders are also not uncommon and contribute to a dizzying heterogeneity in possible diagnoses. Clinical biomarkers could help transcend these limitations.

Unlike many other diseases, there are no approved clinical tests for psychiatric disorders beyond mental and behavioral evaluation. There are no presymptomatic risk prediction tests, like the PLAC test to measure lipoprotein phospholipase A2 for risk of cardiovascular events. There are no diagnostic or monitoring tests, like blood hemoglobin A1c for diabetes management. There are no prognostic tests, like the gene array MammaPrint in breast cancer for risk of tumor recurrence. Despite considerable maturation of fundamental neuroscience in the last decades, owing largely to technological advances allowing sophisticated interrogation of the brains of model organisms and humans, our understanding of the biological underpinnings of psychiatric disease is still in its infancy.

There is considerable optimism, though, that we are nearing a turning point in psychiatric disease research, which could pave the way not only for much-needed new therapies, but also for the critical risk assessment, diagnostic, and prognostic clinical tests required to identify and monitor disease. Initially proposed in 2008, the National Institutes of Mental Health at the US NIH proposed a new way of categorizing mental illness—bridging genetics, neuroscience (looking at molecules, cells, neural circuits, and physiology of the brain), and behavioral science. These Research Domain Criteria (RDoC) aspire to classify illness based on observable behavioral and neurobiological measures.

In keeping with the RDoC ethos, a number of independent researchers and large consortia aim to address mental disorders from a quantifiable biological perspective. Among many others, several consortia include: the Psychiatric Genomics Consortium (PGC), looking for genetic relationships to disease; brain banking repositories from the Stanley Medical Research Institute and Pritzker Neuropsychiatric Disorders Research Consortium, looking for molecular, cellular, and anatomical markers of illness; repositories of resting state and functional MRI or positron emission tomography (PET) imaging data, including the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) group, Functional Imaging Biomedical Research Network, and the Autism Brain Imaging Data Exchange. Further strategies include looking for blood-based biomarkers of disease using proteomics and metabolomics, along with profiling the gut microbiota of patients, as the latter has recently been associated with various mental disorders. Along with approved diagnostic criteria, many clinical trials are now investigating some or all of genetic, imaging, electrophysiological, and blood-based profiling as secondary readouts of therapeutic interventions. Perhaps the largest problem in translating ever-expanding datasets into clinically-relevant outputs will be in integrating the gathered information. However, consortia such as PGC and ENIGMA also aim to bring together data scientists to share algorithms for mining data and turning it into a framework for so-called computational psychiatry.

Recent genomics and transcriptomics studies have already begun to bear fruit, discovering genetic loci and transcriptional profiles associated with increased risk for schizophrenia, ASDs, MDD, and other mental illnesses. A number of these findings suggest many psychiatric disorders are genetically complex, without a single causative variation. Defining polygenic signatures of disease remains an obstacle to overcome. Another obstacle regards brain imaging data. Because of the infrastructure required to perform these studies, they are often too underpowered to confidently assign hallmarks of disease. It is hoped that a multi-center consortium approach will allow researchers not only to image the healthy brain to arrive at a “gold standard”—another factor sorely lacking when compared to, say, a normal range of hemoglobin A1c levels in...
healthy and diabetic patients—but will also identify clinically-relevant image-based biomarkers for psychiatric illness. Perhaps the closest to clinical utility for psychiatric biomarkers will be in patient stratification and pharmacogenomics-based drug responses. For instance, recent studies have identified biomarkers for prediction of treatment response to antipsychotics in schizophrenia or to lithium in bipolar disorder. Identifying the most efficacious treatment regimen as early as possible could have longstanding benefits for patients, as exemplified by the PACT trial.

In the current issue of EBioMedicine, Chattopadhyay et al. highlight the above themes of early intervention and biomarker discovery in psychiatric disorders. Imaging adolescents with MDD, the authors found high resting state connectivity in brain regions involved in emotional processing, unlike adult MDD patients. Importantly, this connectivity dysfunction could be normalized when subjects were assigned to a cognitive behavioral therapy intervention. Indeed, finding reliable biological signatures of mental illness can not only inform diagnosis of patients, but also allow physicians to monitor patient responses to therapies, critical issues in psychiatric disorders where subjects may—thus far, unpredictably—experience waxing and waning bouts of illness and remission. With the emergent technologies in the neuroscience toolkit to probe the brain, broad multi-center collaboration to allow sufficiently-powered experiments, large data-mining efforts, and increasing social acceptance of psychiatric disorders to encourage participation of subjects in research studies, we look forward to what we believe is a new dawn for biologically-inspired classification of mental disorders.