# The NIMH Research Domain Criteria (RDoC) Project: Precision Medicine for Psychiatry

"*How small, of all that human hearts endure, That part which laws or kings can cause or cure.*"—Samuel Johnson

Johnson's pessimism notwithstanding, over the past five decades biomedical scientists have made extraordinary progress, discovering causes and finding cures for both infectious and noninfectious diseases. One aspect of this progress that may be underappreciated is how the path to better therapeutics has often required better diagnostics. The National Research Council's report on precision medicine (1) captured the critical need for deconstructing current diagnostic groups with biomarkers to predict and improve response to treatment. As one example, a new drug for cystic fibrosis is highly effective, but for only 4% of patients, those with just one of the more than 1,500 mutations in the CFTR gene that can produce this disease (2).

What would precision medicine look like for psychiatry? Could our approach to diagnosis be more precise as a guide to disease mechanisms or a predictor of treatment response? The current diagnostic systems, ICD and DSM, were developed to provide a common language based on observable signs and symptoms, explicitly agnostic about pathophysiology or treatment response. While we can improve psychiatric diagnostics by more precise clustering of symptoms, diagnosis based only on symptoms may never yield the kind of specificity that we have begun to expect in the rest of medicine. Behavioral symptoms are multidetermined, so diagnoses based only on presenting complaints are unavoidably heterogeneous in terms of pathophysiology. The symptom of anxiety, for instance, can represent an endocrine disorder, a psychotic process, a drug response, or one of the currently recognized anxiety disorders. Beyond heterogeneity, when diagnosis is limited to symptoms, treatments may be limited to symptom relief, precluding cures or preventive interventions.

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Why don't we use biomarkers to improve the precision of psychiatric diagnosis? So far, we don't have rigorously tested, reproducible, clinically actionable biomarkers for any psychiatric disorder. Genetic findings are statistical associations of risk, not diagnostic of disease; neuroimaging findings report mean group changes, not individual differences; and metabolic findings are not specific. We can improve the resolution with each of these modalities, but we may never have a biomarker for any symptom-based diagnosis because these diagnostic categories were never designed for biological validity (3).

The National Institute of Mental Health (NIMH) launched the Research Domain Criteria project (RDoC; www.nimh.nih.gov/research-priorities/rdoc/index.shtml) to address the need for a new approach to classifying mental disorders, an approach that would begin with, but not be limited to, symptoms. The project was

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described in the *Journal* in 2010 (4), but there is continuing confusion about its intent. RDoC's ultimate goal is precision medicine for psychiatry—a diagnostic system based on a deeper understanding of the biological and psychosocial basis of a group of disorders that is unambiguously among the most disabling disorders in medicine (5).

At this point, however, RDoC is not a diagnostic system, it's merely a framework for organizing research. It begins with the humble realization that we do not know enough to develop a precision medicine approach to mental disorders. We need a decade of intense scientific work—from molecular factors to social determinants—to understand normal and abnormal behavior, based on a deep understanding of mechanisms. Although this work cannot be limited by the current symptom-based diagnostic classifications, current diagnoses will be an important starting point. That is, studies might deconstruct any of the current categories or might identify core features (e.g., a deficit in working memory or anhedonia) that cross several of the current categories. Most important, this framework needs to integrate many different levels of data to develop a new approach to classification based on pathophysiology and linked more precisely to interventions for a given individual.

How will RDoC develop this framework? NIMH has started with five general cognitive and motivational domains to organize the effort. We are already funding a diverse range of scientists, from genetics, imaging, and cognitive science, to begin to populate a matrix that describes these domains across many levels of analysis. These domains and levels of analysis are not the entire universe of psychopathology—they are a starting point. They do not yet incorporate the critical role of development, environmental exposures, or the evolution of psychopathology over time. The domains and the levels of analysis will evolve as tools improve and the clinical database expands.

But RDoC is already freeing investigators from the rigid boundaries of symptom-based categories. For instance, the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) studies patients across several different DSM-IV-defined psychotic disorders. An integration of cognitive, imaging, and physiological abnormalities demonstrates dimensions that are not correlated with symptoms but might be better predictors of pathophysiology or prognosis (6).

Recent studies of people with a range of anxiety disorders demonstrate that those with a diagnosis of posttraumatic stress disorder may be at opposite extremes for startle reactivity, suggesting two biologically different disorders sharing the same diagnosis (7). Imaging findings may be useful for predicting response to antidepressants (8), and genomics is beginning to untangle the complex heterogeneity of autism spectrum disorder (9).

How will RDoC integrate vast amounts of diverse data and translate this into knowledge? As suggested in the precision medicine report (1), NIMH will host an information commons, inviting global input to integrate and share data from a broad range of scientists. The National Database for Autism Research (NDAR; ndar.nih.gov) is a good example of what this could look like for all mental disorders. NDAR already hosts genomic, physiologic, imaging, and clinical data (including treatment response) on nearly 70,000 individuals meeting criteria for autism, a syndrome that may represent a score of different disorders. Data mining can now begin to identify the links across levels, including the factors that will yield categories predicting prognosis or treatment response for individual patients. The information commons requires standardization, integration, and sharing of data by the scientific community. In other areas of medicine, the commons has not been

limited to scientists—increasingly, providers, patients, and families have begun to share data to accelerate progress in biomedical research (10).

Four decades ago, Robins and Guze (11) suggested five criteria for validating diagnosis (clinical description, laboratory tests, delimitation, follow-up studies, and family data), where the goal was specifying prognosis. These five criteria did not converge, but the Research Diagnostic Criteria (RDC) that ensued (12) were immensely helpful for developing DSM-III, which revolutionized psychiatry in the 1980s. Today, the "-omics" are transforming diagnosis across medicine, leading to breakthroughs in therapeutics (as in cystic fibrosis). The question is simply whether psychiatry is ready to embrace contemporary biology, cognitive science, and social science to augment the reliable assessment of signs and symptoms.

RDoC might be considered a 21st-century version of RDC, building on clinical description and subjective experience to create a matrix of information for individual patients, leading ultimately to precision medicine for psychiatry. This is not a short-term project. The problems are complex; our tools are still primitive. We recognize that no framework will yield a "cause or cure" for "all that human hearts endure," but we must not accept the current state of the art. Patients and their families are understandably demanding better outcomes. It is precisely because of this urgent unmet medical need that we must embark on a new approach to diagnosis. RDoC is a first step toward that approach, inviting a diverse research community to bring precision medicine to psychiatry.

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