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Advancing pediatric psychiatry research: linking neurobiological processes to novel treatment and diagnosis through Research Domain Criteria (RDoC)

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More than half of adult mental illness begins by the age of fourteen, and over two-thirds by age eighteen.¹ Suicide rates across the life course remain static. Rates of most psychiatric conditions are either stable or increasing and while successful treatment of mental illness is commonly discussed, this seems to be in lieu of being able to cure or prevent psychopathology. The significance of these findings increases when one considers the economic challenges facing all fields of medicine. In the United Kingdom in 2014, one-third of the disease burden was associated with mental illness, while only 13% of medical care funding was appropriated for its treatment. Less than 6% of funding allocated to mental health was for child mental health. In the United States, only two cents per health care dollar are spent on children's services. In 2014, seven states reduced mental health budgets and Alaska, Louisiana, Nebraska, North Carolina and Wyoming cut funding in both 2013 and 2014. This occurred while estimates from 2007- 2010 indicated that child mental health services rose 24% over those four years and psychopharmacological treatment of children increased 10%.² These numbers illuminate both a lack of attunement to the developmental origins of psychopathology, and a lack confidence in foreseeable significant, meaningful advances in child mental health treatment.

Mental illness is intricately entwined with physical illnesses. The majority of negative health outcomes, both mental and physical, including cardiovascular disease, diabetes, obesity, hypertension, and cancer, as well as depression, schizophrenia, and bipolar disorder, appear to originate early in the life course, and the link between mental and physical illness is seen in the bidirectional effects on disease burden.³ Psychopathology in adults is associated with higher rates of negative physical health outcomes.⁴ Similarly for common physical illnesses such as cardiovascular disease or diabetes, comorbid psychiatric disease frequently confounds treatment effectiveness.⁵ Early adversity increases the risk and impacts of both negative physical and mental health outcomes,⁶ and the prevailing hypothesis is that the biological embedding of early adversity occurs through altered neurobiological, socioemotional and cognitive pathways.^{7,8} While these findings suggest that the clinical separation of mental and physical illnesses is largely artificial, the diagnosis and treatment

of mental illness remain distinct from the rest of medicine. The limited evidence of concrete biological markers of illness and inadequate diagnostic specificity reveal the largest gap. Outside of psychiatry, biomarker development and enhanced diagnostic specificity through biologic and molecular phenotyping has resulted in dramatic improvements in disease cure rates and positive treatment outcomes. Modeling the successes in other areas of medicine, the NIMH Research Domain Criteria (RDoC) project proposes to do this for mental health.

Molecular genetics has proven invaluable across health conditions, in which increased diagnostic capability from a greater understanding of differential disease progression and pathophysiology has led to marked advancements in treatment response and novel insights into drug design. Although on the surface the recent advances in cystic fibrosis (CF) may seem far afield from mental illness, we propose that these advances, because of molecular studies, enhanced precision in defining individual pathophysiologic consequences, and disease subtyping, represent an alternative model with direct implications for the clinical application of RDoC to mental illness. CF is the most common life-threatening monogenetic disorder in Caucasians. The gene responsible for CF, *CFTR* (Cystic Fibrosis Transmembrane conductance Regulator), was cloned and sequenced in 1989 by a scientific group that included Francis Collins, the current director of the NIH.⁹ Similar to the enthusiasm that followed Caspi's seminal study of the interaction between adverse life events and the *5httlpr* polymorphism in the *5HTT* gene predicting depression,¹⁰ the aspiration was that once the gene was characterized, individuals with CF could be more easily identified and cured. However, CF, even though monogenetic in etiology, proved far more complex -- similar to the complexity found in mental illness. First, not all individuals with CF have the same phenotype. Similar to most psychiatric diagnoses, the "typical" symptoms differ between individuals, and these differences are often related to underlying differences in the specific molecular defect in *CFTR*. Second, early life experiences (later age at diagnosis, more frequent illness exacerbations, elevated stress exposure and poorer nutrition) influence disease course and prognosis, an all too common complication of psychiatric conditions. Third, even though CF is monogenetic in etiology, not all individuals carry the same mutation, and more importantly, at the molecular level these mutations function differently. For example, the most common mutation Δ 508 results in loss of the receptor translocation to the cell membrane; however, another mutation, G551D, influences receptor function rather than localization. Genetic subtyping of individuals with CF resulted not only in enhanced precision in relation to disease progression, but also identified profound differences in treatment response to pharmacologic agents.¹¹ Had genetic research not examined individual differences in disease pathophysiology at the genetic level, in combination with individual differences in clinical presentation and symptoms, the powerful effectiveness of some agents for a subset of individuals would have been missed.¹² Similarly, genetic phenotyping in pediatric leukemia has resulted in not only treatments that have markedly increased survival rates, but also decreased medication side effects.^{13,14} Success stories like these provided the impetus for the development of the RDoC project.

Research in mental illness is currently stymied, as were the initial efforts to treat cystic fibrosis. As a field, psychiatry was ahead of other areas of medicine in recognizing psychosocial support, family history, and early experience as critical covariates in disease

onset and progression. However, psychiatry lags behind in the understanding of the underlying neurobiological mechanisms. The gold standard for diagnosis of mental illness, the Diagnostic and Statistical Manual of Mental Disorders, provides a much needed grounding and characterization of the current best evidence for classifying mental disorders, yet the substantial co-morbidity across disorders and the developmental and familial heterotypic continuity suggests that greater precision is needed. Unfortunately, the current characterization of individual differences in pathophysiology is superficial at best, limited mostly to self-reported symptom descriptions. Even within the DSM there is little reference to biological or familial contributions as potential factors influencing prognosis or diagnostic specificity. While the DSM serves a critical role within the clinical realm it has yet to provide the precise research scaffolding required to enhance understanding of the mechanisms underlying the efficacy of both psychotherapeutic treatments and pharmacologic agents. Most importantly, the effectiveness of even the best evidenced-based treatments remains low and, for the most part, there are currently no accepted “cures.”

Although the precedent has been set by other areas of medicine, the application of a new paradigm for the diagnosis and treatment of mental illness is complex. Many of the current constructs found within the RDoC matrix are admittedly based on insufficient evidence, particularly in youth. Accordingly, strategies to appropriately measure these constructs across development represent a prominent challenge that only researchers familiar with child psychiatry/psychology are prepared to investigate and address. Balanced against this underdeveloped aspect of the RDoC initiative is its clear potential to identify better targets for treatment and personalized medicine. An additional benefit of RDoC is that an enhanced functional, neurobiological and molecular definition of mental illness may clarify very real scientific underpinnings of illness, further decreasing mental illness stigma. Most importantly, more precise matching of neurobiological mechanisms to clinical presentation may both improve and expedite effective treatment.

The opportunities to test novel mechanisms in child psychiatry are myriad. For example, a treatment study could enroll children based on their exposure to a particular adversity and then divide treatment planning based on a neurobiological marker. One example would be to recruit children exposed to a particular traumatic experience, for example documented physical abuse or documented exposure to a natural disaster. While exposure would be the central criteria for enrollment, psychiatric symptoms and impairment from these symptoms would be part of defining the study population, with children requiring a minimum number of symptoms, but no specific diagnosis. Children would then be assigned to treatment modalities based on attentional biases, a well-defined neurobiological process implicated in a number of psychiatric diagnoses and having direct relevance to potential mechanisms of treatment efficacy. Children lacking attentional bias could receive standard cognitive behavioral therapy or monotherapy with a pharmacologic agent, while those with attentional biases would be assigned to attentional training. Evidence of genetic phenotyping contributing to enhanced treatment specificity has already been demonstrated for both pharmacologic treatment and psychotherapy.^{15,16} A child with the *s* allele of the *5HTTLPR* appears to respond better to cognitive behavioral therapy (CBT), while individuals with the *met* allele of the gene encoding Brain Derived Neurotrophic Factor (*BDNF*) appear to

differentially respond to SSRI's.¹⁷ Data from completed studies can be re-examined, as was done in CF trials, to determine if there were neurobiological or genetic predictors or moderators of treatment response. While sample size would likely limit genome wide approaches, targeted genetic studies leveraging known functional variants and defined neurobiological hypotheses are likely to be adequately powered. Greater precision in clinical decision-making may occur when integrated with biological phenotyping, yet neither is likely to ever be replaced.

Advancing the care of children with mental illness through this paradigm requires more effective collaborations among researchers, pharmaceutical companies, biotechnology companies, clinicians, families, community stakeholders, and advocacy groups. This information must be transmitted bi-directionally- from scientist to subject, and subject to scientist, as well as from clinician to the community, and from the community to the clinician. Research that occurs in clinical isolation, or is not translated effectively back to practitioners and families, even if compelling, is less likely to be transformative. Strengthening the bi-directional nature of these partnerships will best position child psychiatry to make meaningful scientific advances that improve clinical practice and achieve the long-term goal of lowering the morbidity and mortality of mental illness. These advances will require all those invested in child mental health to embrace RDoC, not as a replacement for decades of established clinical knowledge and the theories captured in the DSM-5, but instead as an invitation. RDoC's focus on cross domain analyses, inclusion of environmental and developmental factors, and specific directive for researchers to challenge existing paradigms and expand innovation, is an unprecedented opportunity for clinicians, researchers, pharmaceutical companies, families and other stakeholders to jointly think both inside and outside the black box that currently plagues advances in mental health. Change may be difficult, slow, and the advances, at times, uncertain. Yet, when the goal is to improve the health of children and reduce both the immediate and long-term impacts of mental illness, these changes appear worth the risks.

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