DOCUMENT SUMMARY

This document is a perspective article by Kapur, Phillips, and Insel (2012) that critically examines why biological psychiatry has failed to produce clinically useful diagnostic tests for mental disorders. The authors argue that this failure stems from systemic issues: the lack of a biological "**gold standard**" for **DSM**-defined illnesses, a proliferation of underpowered studies with small effect sizes, "**approximate replications**" that fail to confirm or refute findings, and a focus on clinically irrelevant comparisons between prototypical patients and healthy controls. As a solution, they propose a shift away from diagnosing **DSM** categories and toward "**stratified psychiatry**"—using biomarkers to identify biologically homogenous subtypes that cut across traditional diagnoses to better predict outcomes and guide treatment.

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- **Related Docs**: This paper provides a high-level critique of the diagnostic systems and research challenges that are relevant to the real-world consequences detailed in "The Price of Knowing" and the clinical complexities in "Rumball_2020_research_article_trauma_ptsd_autism."

FORMATTED CONTENT

Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

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PERSPECTIVE

Patients with mental disorders show many biological abnormalities which distinguish them from normal volunteers; however, few of these have led to tests with clinical utility. Several reasons contribute to this delay: lack of a biological '**gold standard**' definition of psychiatric illnesses; a profusion of statistically significant, but minimally differentiating, biological findings; '**approximate replications**' of these findings in a way that neither confirms nor refutes them; and a focus on comparing prototypical patients to healthy controls which generates differentiations with limited clinical applicability.

> Overcoming these hurdles will require a new approach. Rather than seek biomedical tests that can 'diagnose' **DSM**-defined disorders, the field should

> focus on identifying biologically homogenous subtypes that cut across phenotypic diagnosis—thereby sidestepping the issue of a gold standard.

To ensure clinical relevance and applicability, the field needs to focus on clinically meaningful differences between relevant clinical populations, rather than hypothesis-rejection versus normal controls. Validating these new biomarker-defined subtypes will require longitudinal studies with standardized measures which can be shared and compared across studies—thereby overcoming the problem of significance chasing and approximate replications. Such biological tests, and the subtypes they define, will provide a natural basis for a '**stratified psychiatry**' that will improve clinical outcomes across conventional diagnostic boundaries.

INTRODUCTION

Biological psychiatry aims to understand mental disorders in terms of the biological function of the nervous system. By several measures it has been a tremendous success... Despite these successes, it has not led to **clinical tests** that can be routinely used in the diagnosis and treatment of mental disorders. In the early 2000s, a series of white papers expressed hope that the advances in genetics, imaging and new technologies might lead to a biologically supported psychiatric classification and diagnostic system. But a decade later, as we stand at the threshold of a new version of the **DSM**, there are few biological **clinical tests** central to diagnosing psychiatric illnesses (other than those used to exclude physical illnesses). This article explores why this journey has been difficult for psychiatry and what can be done about it.

THE MISSING GOLD STANDARD

To create a biological test to assist in the diagnosis of an illness one needs a stable and biologically valid concept of the illness. As the standardised classification systems have been constantly revised (from ICD-6 to ICD-10 and from DSM-I to DSM-IV), they have remained a descriptive taxonomy based on expressed feelings and observed behaviour. On the one hand, these successive editions of **DSM** and **ICD** lead to increasing psychometric precision. On the other hand, the ever increasing fractionation of mental distress into smaller and more numerous categories, without a priori biological validity, makes it harder to find specific biomedical tests that diagnose or predict the disorders.

> Thus, psychiatry seems to be in a Catch-22: the current diagnostic system was not designed to facilitate biological differentiation and it does not. The biological studies to date have not been able to propose a clinically viable alternative system.

This lack of a **gold standard**, and the consequent circularity, is not unique to psychiatry. A number of disorders in physical medicine defy simple biological definitions. Breast lumps were categorised based on different symptoms and clinical courses, until histopathological differentiation and molecular markers turned them into distinct illnesses.

SIGNIFICANCE CHASING WITH UNDERPOWERED STUDIES

The vast majority of biological findings in psychiatry are of a small or moderate effect size—even though many of them survive the 'P<0.05' test of statistical significance. Although these risks are not unique to biological psychiatry, it is particularly vulnerable to '**significance chasing**' because the studies in this field generally tend to be underpowered, have small sample sizes, measure multiple dimensions and use subjective outcomes. Chasing small effects with underpowered studies has meant that even though the field has led to a large output of publications, there are few findings with effect-sizes large enough that could be converted into **clinical tests**.

APPROXIMATE REPLICATIONS

One might expect that failure to replicate the findings would induce scientists to lose interest... Unfortunately, an initial underpowered study is often followed by another study of similar size but with a few additional measures and variables to give it some novelty and distinction. These subsequent studies usually have only modest statistical power to decisively confirm or refute the original finding, but do have sufficient multiplicity of new measures to generate some significant finding—even though not precisely the one observed in the first study—thus providing an '**approximate replication**'. As a result, the 'literature' in the field grows without decisively replicating/rejecting the precise original finding, but instead creates a penumbra of "P<0.05" findings around the first.

EXTREME COMPARISONS

Nonetheless, some biological findings have stood the test of time and replication, and have reasonably large effect sizes... However, these large differences have been noted mostly in studies comparing prototypical patients versus picture-perfect healthy controls. Clinically, one is rarely taxed with distinguishing a textbook patient from a perfectly healthy individual. The real challenge is in distinguishing those who demonstrate the superficially similar symptoms that may merit rather different treatments and outcomes. Experience in the rest of medicine shows that the predictive value of a biological differentiator decreases as we move from extreme contrasts to more clinically relevant ones.

FROM SUBTYPES TO 'STRATIFIED MEDICINE'—THE PLAUSIBLE GOAL FOR PSYCHIATRY

A more feasible opportunity for psychiatry, as for the rest of medicine, is '**stratified medicine**': the identification of **biomarkers** or cognitive tests that stratify a broad-illness phenotype into a finite number of treatment-relevant subgroups.

Progress in oncology illustrates this approach well: overexpression of human epidermal growth factor subtype 2 (**HER2**) in breast cancer tissue was first identified as a subtype with a poor prognosis. As the differential biology of this subtype was better understood, it led to the development of monoclonal antibody therapies (trastuzumab or Herceptin) which increased long-term survival for this particular subtype of breast cancer.

This approach to '**stratified medicine**' has several important lessons for psychiatry: First, it bypasses the nosological debates about the precise diagnostic boundaries and does not need an external '**gold standard**', as the approach justifies itself by its utility. Second, stratification does not require a complete understanding of aetiology. Third, one does not have to wait for new treatments to arrive. Finally, these tests become useful in clinical medicine across diagnoses without requiring wholesale diagnostic reclassification.

> Thus, in a '**stratified psychiatry**', these tests could coexist alongside the conventional diagnostic systems (such as DSM5 or ICD11). The patients could be first diagnosed along conventional grounds, but then stratified by markers that predict prognosis or suggest differential treatments.

STRATIFIED PSYCHIATRY—IMPLICATIONS FOR HOW DATA ARE COLLECTED AND SHARED

For the last three decades, the majority of the grants and papers in biological psychiatry had three characteristics: strict allegiance to a **DSM** or **ICD** diagnoses; focus on differentiation of patients with the diagnoses from normal controls; and usually a short-term cross-sectional evaluation. **Stratified psychiatry** will require a change in this mind-set.

> The field will have to collect data across the current diagnostic categories, focus on comparing across disorders as much as comparing versus normal controls and will need to collect and curate data, so that it can be widely shared and collated.

The National Institutes of Mental Health... has already initiated such an approach... The **Research Domain Criteria (RDoC)** is an approach that attempts to link behavior and cognitive symptoms to the underlying neurobiological systems and genetic predispositions in a way that cuts across the categories within the current diagnostic systems.

CONCLUSION

Biological psychiatry and the related neurosciences have changed mankind's view of itself and of mental illness, but have yet to provide biomedical tests for routine clinical practice. The delay is understandable... On the other hand, the opportunity afforded by the progress in genomics and imaging combined with the computational abilities is unprecedented and could deliver useful **clinical tests**. These tests will identify homogenous populations for whom one could develop targeted new therapeutics thus realising a vision of a new **stratified psychiatry** that cuts across the traditional diagnostic boundaries while simultaneously transforming them.