Q&A: How to jump-start new psychiatric and neurological drug development

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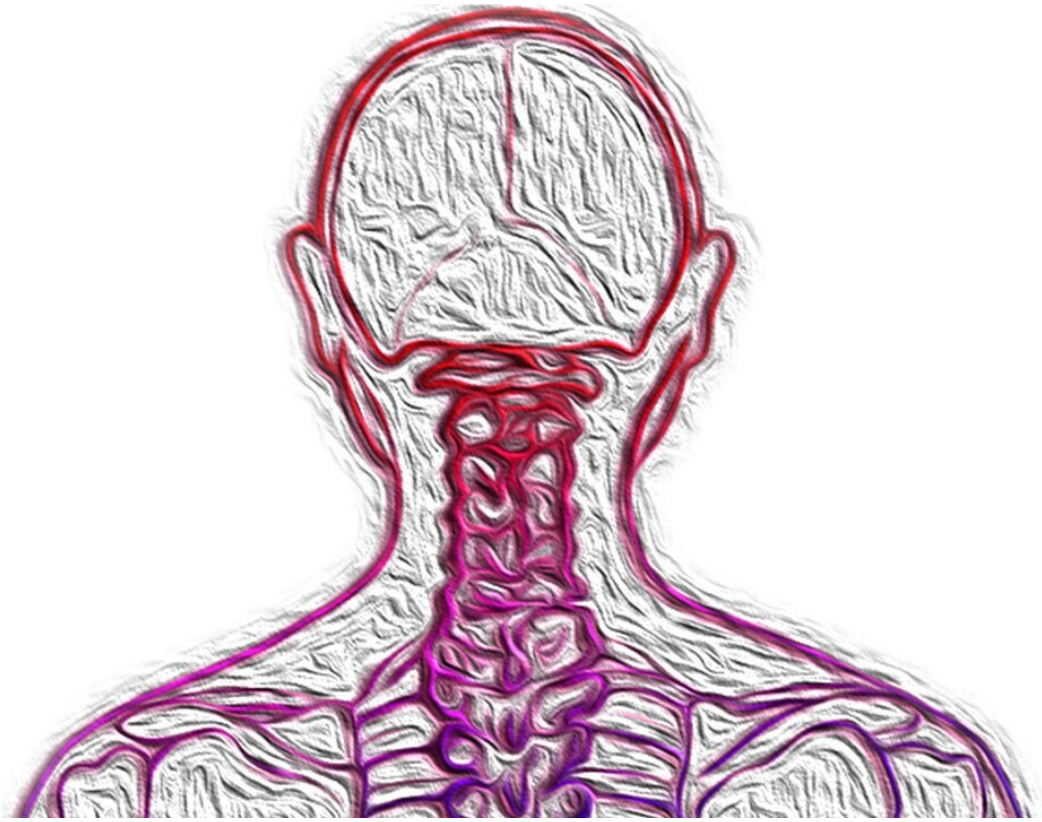

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Psychiatric and neurological disorders are widespread, yet the pace of drug development for these conditions lags far behind that of heart disease, cancer, and other conditions. Brain disorders are difficult to

study and many drug candidates have failed in clinical trials, causing pharmaceutical companies to reduce their investments or even exit the field entirely.

But a new path for bringing treatments to patients is starting to emerge. In a review in *Science Translational Medicine*, Steven Hyman, director of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, and colleagues in the National Academies of Science, Engineering, and Medicine (NASEM) Forum on Neuroscience and Nervous System Disorders—which includes industry—sketched out a six-point framework for re-invigorating psychiatric and neurological drug development that addresses many of the unique challenges this field faces.

They wrote that a deeper understanding of the molecular mechanisms driving these disorders will improve diagnosis, enhance patient stratification in clinical trials, and lead to better therapeutics.

To achieve this, the authors called for more genetics and longitudinal data types from patients of diverse ancestries, more data- and tool-sharing across sectors, the development of quantitative biomarkers for measuring disease mechanisms, and more.

We asked Hyman, who is also a core institute member at Broad, to talk about the new framework and what he thinks are the biggest opportunities.

Why did you and your colleagues with the NASEM Forum decide to write this report?

One of our long abiding concerns has been the pharmaceutical industry's progressive exit from R&D on treatments for central nervous system

disorders apart from Alzheimer's and for large companies a nearly complete exit from new research in psychiatry.

We all recognize the vast, unmet medical need. We have no treatments for the disabling cognitive and deficit symptoms of schizophrenia, and no pharmacologic treatments for the core communication difficulties of autism. We do very poorly at treating the depressed phase of bipolar disorder. And we have no pharmacologic treatments for anorexia nervosa, which at approximately 20% has the highest long-term mortality rate in psychiatry.

So the need and the markets are there. The question becomes, under what circumstances would industry rebuild the infrastructure they need to re-engage in neuroscience and psychiatric development?

What do you think it will take for industry to re-engage in this space?

The single biggest problem for psychiatric disorders is that we lack the ability to look underneath the surface phenomena such as symptoms and disease course to group or stratify patients according to disease mechanisms.

To use the example of depression, there have been many large, costly clinical trials in which drugs fail to separate convincingly from placebo but ultimately prove effective for a subset of patients. The key problem is that there appear to be many different underlying mechanisms that lead to depression. The genetic risk factors are highly complex, and they intersect with environmental risk factors ranging from infections to stress that are also diverse in their nature and effects (and which deserve intensive study).

Without robust biomarkers, we cannot account for this mechanistic diversity and appropriately match patients with candidate treatments in clinical trials. Lumping everyone under this umbrella diagnosis of depression ignores the heterogeneous nature of this disorder, dilutes any signal that we might see in a clinical trial, and prevents us from learning from failures.

Biomarkers could take many forms. Based on recent success in Alzheimer's disease and amyotrophic lateral sclerosis, companies are very interested in quantifiable fluid biomarkers, which for neuroscience has meant markers that can be measured initially in CSF (cerebrospinal fluid).

Studies of Alzheimer's disease are teaching us that it's possible to measure some clinically important CSF biomarkers in blood. Some may even be measurable using positron emission tomography, which has the added benefit of providing information about where in the brain a biomarker is present.

For some neurologic and psychiatric disorders, perhaps including depression and obsessive-compulsive symptoms, system-level biomarkers—ones that provide functional information about whole circuits instead of individual cells or molecules—appear promising. Thus magnetic resonance imaging or EEG studies may supplement molecular studies in ways that could prove to be highly useful in, for example, stratifying individuals with schizophrenia. At the Stanley Center, we are already gaining powerful evidence for this using EEG.

Your review article discussed the need to study genetically diverse patient samples. Can you expand on that?

Without a strong commitment to broadening the populations and societal contexts included in research, the promise of precision medicine rings rather hollow. It is becoming quite clear that even when disease mechanisms are alike across populations, polygenic scores and other genetic tools for risk prediction and stratification perform poorly across ancestries. The same may prove true for particular biomarkers.

We cannot know—and cannot claim to be making equitable contributions to global public health—without significantly expanding the diversity of the populations we study. The Stanley Center has made it a central goal to increase population diversity in neuropsychiatric genetics l while increasing our sample sizes overall.

There is both scientific benefit and a health equity imperative in looking across all of humanity. I see this as a moral necessity.

How important will new animal models be?

Industry is quite skeptical, and based on long experience rightly so, when it comes to the use of model systems for studying human psychiatric disorders. However, if we are to gain the most benefit from studies of genetics and neurobiology, diverse model systems—including animal models—are critical for investigating candidate disease mechanisms.

Human stem cell-derived models and human brain organoids can help address questions arising from human genetics, especially ones related to human polygenic backgrounds. However, organoids are not brains. Animal models, carefully interpreted, are absolutely critical if we are to investigate relevant neurobiology and candidate disease mechanisms in living brains

Where do industry and research institutes like the

Stanley Center fit into your framework?

Our foremost goal at the Stanley Center is to work both "bottom-up" from genetics up and "top down" from phenotypes and systems-level neuroscience to understand disease mechanisms. It's from an understanding of mechanisms that you have the best chance of identifying meaningful biomarkers and therapeutic targets.

Academic centers, and certainly the Stanley Center, ultimately want to share the biomarkers that we discover with industry to ensure that these tools are robust and reliable enough for use in clinical trials. And of course industry has a huge role in optimizing compounds and, above all, in designing and running clinical trials that exceed the financial capacities and core capabilities of academic organizations.

Do you think the roadmap you've laid out is something the players in the field will find realistic?

There's a long way to travel, but it's not a Pollyanna-ish report. Following this path and breathing new life into treatment development is going to be a multi-sector effort. To meet the vast unmet needs of people with brain disorders, we must commit ourselves to moving forward.

Thanks to the amazing discoveries that have come out of genetics over the last decade or so, basic research on psychiatric disorders has finally gained its first durable insights into disease mechanisms. There are now important translational opportunities, beginning with biomarkers. Let's pursue these opportunities effectively and energetically.

More information: Dimitri Krainc et al, Shifting the trajectory of therapeutic development for neurological and psychiatric disorders, *Science Translational Medicine* (2023). DOI:

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