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What lies beneath

A focus on specific biological targets rather than constellations of symptoms heralds a more scientific approach to the treatment of neuropsychiatric disorders.

It is difficult to decide which is the more dispiriting statement: that one person in four suffers from a mental-health problem at some point in their lives, or that the sorry state of care for the millions of people affected is often discussed only in the immediate aftermath of the actions of a single mentally ill individual. One can quibble about statistics and diagnostic standards, but the bottom line is that neuropsychiatric disorders account for one of the greatest burdens of disease in the developed world, yet patients are not receiving the help they need.

Part of the problem is that, for many people, the available therapies simply do not work, and that situation is unlikely to improve any time soon. By the early 1990s, the pharmaceutical industry had discovered — mostly through luck — a handful of drug classes that today account for most mental-health prescriptions. Then the pipeline ran dry. On close inspection, it was far from clear how the available drugs worked. Our understanding of mental-health disorders, the firms realized, is insufficient to inform drug development.

With industry pulling out, the burden of developing therapies for mental disorders is increasingly falling on academic researchers. And with its strapped budget, it comes as no surprise that the US National Institute of Mental Health (NIMH) in Bethesda, Maryland, wants to make quick and decisive changes to the way its money is spent.

For several years, the NIMH has been trying to forge a different approach, and late last month institute director Thomas Insel announced that the agency will no longer fund clinical trials that do not attempt to determine a drug or psychotherapy's mechanism of action (see page 288). Without understanding how the brain works, he has long maintained, we cannot hope to know how a therapy works.

According to the NIMH's new grant framework, clinical trials must be designed to yield scientific knowledge as well as to determine whether a therapy works. This will allow researchers to decide quickly whether to proceed with a trial, modify it or end it before too much money is spent on recruiting and testing patients. To receive funding, scientists will have to show how they intend to test whether a therapy targets a particular brain circuit, for instance, or what mechanism a therapy uses to alter a person's behaviour.

The move will certainly ruffle feathers. Insel notes that more than half of the trials that the NIMH currently supports would not receive funding under the new requirements, at least not without modifications. For example, a trial that focuses on changes in attention span as a means of testing a behavioural-intervention therapy in children with a broadly defined disorder such as attention-deficit hyperactivity disorder would not be funded unless researchers could present a controlled way to study how the therapy takes effect. The NIMH would rather see trials that aim to recruit people with a common trait — say, hallucinations — regardless of their specific psychiatric diagnosis, treat them with a drug that acts on a specific brain receptor, and measure changes in brain activity.

The change applies to trials of drugs and behavioural therapies alike: the key is that they are set up in such a way that a single variable can be changed and a single effect seen. An example would be deep brain stimulation (DBS), which has proved an effective treatment for disorders ranging from Parkinson's disease to depression, but whose underlying mechanism is largely unknown. When a major trial of DBS for depression failed last year, scientists were left not knowing whether they had sited the devices wrongly or recruited the wrong group of patients. It is becoming increasingly apparent that the optimal placement of and frequency used by such devices to stimulate neurons may differ from person to person (see page 290).

"Our understanding of mental-health disorders in insufficient to inform drug development."

Critics will argue that the NIMH has exchanged a difficult problem — treating mental illness — for an even more challenging one, understanding the brain. But the institute's new direction on trials may also aid an effort to free research on mental-health disorders from the limits of existing diagnostic categories — an approach for which *Nature* has previously expressed support (see *Nature* **496,** 397–398; 2013).

A project called the Research Domain Criteria, which the NIMH is developing, places patients on a matrix on the basis of both their symptoms and biomarkers such as brain activity. According to the NIMH, more and more grant applicants are using these criteria, although no trials have yet been completed. If this work throws up new targets for possible intervention, industry may once again see psychiatric drugs as a market worth investing in. It is a gamble — and a variety of approaches are still needed — but the potential pay-off is worth it. ■

How to get ahead

The success of the $1,000 genome programme offers lessons for fostering innovation.

Genome technologists are on the verge of fulfilling a goal that was once considered so far off as to be almost fictional: the sequencing of human genomes for US$1,000 apiece. Eleven years ago, when genome sequencing cost tens of millions of dollars, scientists from the US National Human Genome Research Institute (NHGRI) in Bethesda, Maryland, said that, should it be met, the $1,000 goal "would revolutionize biomedical research and clinical practice".

The price of sequencing has indeed dropped — and this development is changing science and beginning to change medicine. In retrospect, it may seem that it was inevitable that the cost would come down from what it was at the close of the Human Genome Project