Conference Report: Psychiatric Genomics Consortium Meeting: Pathways to Drugs, London, March 2017

To the Editor:

The Psychiatric Genomics Consortium (PGC) (www.med.unc.edu/pgc) is delivering an increasing flow of discoveries about the fundamental basis of psychiatric disorders. Moving from the discovery of genome-wide association study (GWAS) loci toward delivering new therapeutic approaches is a challenge that requires a new wave of multidisciplinary work and close liaison between academia and industry. The PGC has recently initiated a new research program to deliver "actionable" findings that 1) reveal the fundamental biology of psychiatric disorders, 2) inform clinical practice, and 3) deliver new therapeutic targets. Working with industry will be essential, but there is a lack of a forum to exchange ideas with academia. With the aim of filling this gap, the first PGC Pathways to Drugs industry–academia workshop was held at the Institute of Psychiatry, Psychology and Neuroscience, King's College London on March 2 and 3, 2017. We review the main advances in the field (1).

The PGC works on schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder, eating disorders, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, Alzheimer's disease, obsessive-compulsive disorder, Tourette syndrome, and substance use disorders. The PGC has identified more than 300 genetic associations in seven disorders and the aim of the next 5 years is to increase sample sizes to more than 100,000 cases for each psychiatric disorder and find new treatments (1). There is considerable potential for the knowledge derived from GWASs to revitalize industry drug discovery efforts (2). In addition, the complex nature of psychiatric disorders means that the study of biological pathways is also of paramount importance (3).

Strong examples of translation are emerging, exemplified by the new anorexia GWAS results, which are inspiring a reconceptualization of anorexia nervosa as both a metabolic and psychiatric disorder (4). Major contributions to the PGC from the Lundbeck Foundation Initiative for Integrative Psychiatric Research and others are advancing the genetics of attention-deficit/hyperactivity disorder and autism spectrum disorder (1). Likewise, the UK Biobank (5) (www.ukbiobank.ac.uk) is an extensive resource of approximately 500,000 genotyped individuals. UK Biobank mental health phenotyping on 157,000 patients is available and will reach more than 300,000 individuals, meaning that the UK Biobank will become the largest cohort with mental health questionnaire data worldwide (1). Multiple psychiatric disorders are achieving successful GWASs, leading to the hope that new therapeutic leads can be identified. Finally, the PGC is developing a pipeline for the identification of drug candidates using GWAS results (6). However, these hypotheses are only a first step in the drug discovery process and need to be followed up by functional and pharmacological studies, in collaboration with industry, and validated by clinical trials.

Determining mechanistic hypotheses arising from a GWAS association is a general problem across medicine. Some regions occasionally implicate a single gene with clarity; e.g., genetic evidence for major depressive disorder has highlighted *LRFN5*, *TCF4*, *PTPN1*, and *NEGR1*. Other loci are intergenic and far from any known genes; still other loci can contain many genes or lie within regulatory regions. Connecting GWAS findings to salient genes and mapping regulatory regions is crucial to identifying targets.

Discussions at the conference focused on the integration of three sets of methods. First, statistical methods to evaluate gene sets, which have been used to demonstrate the salience of major depressive disorder and schizophrenia GWAS findings to the targets of antidepressant and antipsychotic medications (6,7). Second, bioinformatics approaches to leverage functional genomic data [gene expression (2), DNA–DNA looping (8), and epigenomics (9)]. Data from the National Institute of Mental Health PsychENCODE Consortium on brain samples from people with severe psychiatric disorders will further enable this intent (9). Finally, large-scale genetic editing may be needed (10). Together, the above steps can be used to generate hypotheses, narrow an interval to include regulatory regions, or identify key elements.

After identifying potentially relevant genes, a key challenge is to determine which of the corresponding proteins are "druggable" to find drugs that could bind to these proteins, regulate their production, prevent protein–protein interactions, or in any way have an influence on their biological mechanism(s). These steps are enabled by chemoinformatics and bioinformatics approaches encompassing machine learning, molecular modelling, and data mining. There is an increasing quality of data available in databases collecting drug/target affinities (3) (ChEMBL, PHAROS, K_i DB, etc.). Open Targets (www.targetvalidation.org) is a relatively new free platform that collects target/phenotype associations from various sources (including UniProt, GWAS Catalog, European Variation Archive, and Gene2Phenotype). These public databases, many partly funded by industry, are complemented by new open-source drug laboratory resources that can be used to allow screening of the entire druggable G protein–coupled receptor receptorome (1).

Polygenic risk scores (PRSs) summarize an individual's genetic loading for a disorder in a single measure. Their power is increasing, and it is now possible to calculate PRSs for common side effect profiles, such as hypertension and type 2 diabetes. In designing clinical trials, the use of PRSs could allow the recruitment of individuals at high genetic risk, or for stratifying response. Post hoc analysis of PRSs in completed clinical trials may improve the understanding of drug response profiles and encourage the pharmaceutical industry to move genetics earlier within the trial pipeline, to ultimately develop companion diagnostics with PRSs. Using the power of clinical trial samples will require interaction between the research

community and industry to test the utility of PRSs for improved prescribing and clinical trials.

In conclusion, our discussions pointed out the need to integrate multiple data sources to discover new treatments for psychiatric disorders: gene expression in different tissues, drug/target affinities, GWAS results, bioinformatics, chemoinformatics, and pharmacogenomics. New drug development could be further aided by the adoption of precision medicine for psychiatric clinical trials, as exemplified by PRSs and "precision psychiatry." Ultimately, however, new drug discovery in psychiatry will be best enabled if academia and industry join forces and if open data- and sample-sharing initiatives are encouraged. Joint industry–academia conferences will be essential to achieve these goals, identify main research objectives, and find a shorter route for drug discovery pipelines.

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