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## **"Large-scale genomics: a paradigm shift in psychiatry?"**

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It was the best of times, it was the worst of times..." Charles Dickens, A Tale of Two Cities.

The past decade has been one of unprecedented discovery in psychiatry. Large-scale genomic studies have identified hundreds of molecular risk factors, and illuminated the genetic architectures of major psychiatric conditions. And yet, with this knowledge has come a realisation that these disorders are highly polygenic, and that there is widespread pleiotropy of the risk alleles involved. These findings confirm long-held suspicions that our diagnostic categories do not describe biologically distinct conditions, and pose fundamental challenges for the approaches to disease modelling that have helped understand simpler Mendelian disorders. So, while progress has been immense, when and how will the promised impacts on clinical care be delivered?

A major justification for the pursuit of psychiatric genomics is that it offers a potentially unbiased route into understanding pathogenesis, and, as a consequence, the promise of new, rationally designed treatments. The challenges presented by polygenicity and pleiotropy are formidable, requiring us to relate myriad complex patterns of genomic variation in individuals, to complex patterns of clinical variation, and to interpret them in terms of altered function of the most complex organ in the body. Overcoming these challenges will require new analytic and experimental approaches, many examples of which are described eloquently in this issue. Notwithstanding the difficulties, our view is that, given significant heritabilities together with the complexity and inaccessibility of the brain, such studies offer the surest foundations on which to build mechanistic research. However, we need to be clear that it will require a coordinated and well-funded effort that will play out over the next decade or more and that therapeutic advances may take even longer.

A second major justification of genomics is its potential to provide diagnostic tests or biomarkers for use in research into aetiology and mechanism, and also in clinical settings as we move towards precision psychiatry. How will emerging genomic discoveries impact here? Genomic discoveries are already being applied in psychiatry, albeit more so by medical geneticists than psychiatrists. Identification of CNVs through Chromosomal Microarrays

(CMA) is increasingly becoming part of routine clinical testing for childhood neurodevelopmental disorders (1), and it seems likely sequencing to detect rare coding variants (RCVs) will become part of the clinical tool-kit. There have also been calls for extending CMA testing to schizophrenia (2). These developments will require suitably trained psychiatrists working with genetic counselors and medical geneticists. The results of such tests may offer patients and families a degree of diagnostic explanation, point to the need for genetic counseling, and indicate increased risk for associated physical co-morbidities. However, they do not currently offer much in the way of predictive information about specific psychiatric or behavioral outcomes, which can be highly variable between carriers of the same risk allele, or information of direct therapeutic relevance. Given the rarity of the pathogenic mutations, informative research will require coordinated data sharing across many centers perhaps along lines developed for rare genetic disorders (3).

Another area where genomics may be poised to impact on clinical practice is in risk prediction. Various methods have been developed to quantify risk from common alleles (4). In the case of psychiatric disorders, these are underpowered for general population screening, but power is increasing as data from larger GWAS become available (4). The predictive power of polygenic testing has more immediate potential in groups already at increased risk, but the value of prediction depends not only on accuracy, but also on the availability of effective interventions that can be targeted to the high-risk groups to either prevent or mitigate the emergence of disorder. Further research is now needed to evaluate both power and utility in different groups and clinical settings and to evaluate decision aids based on combining polygenic scores with other risk variables. Areas showing some promise include first-episode psychosis (5) and clinical high-risk syndrome (6).

The long-term aim of medical genomics is to pave the way for precision medicine in which healthcare, including prevention, treatment and care pathways, can be tailored more effectively to the needs of individuals or groups. Recent advances in genomics are grounds for considerable optimism, but, if genomics is to play its anticipated role, there are three important limitations of current knowledge that will need to be overcome. The first is the lack of ancestral diversity in GWAS studies, the vast majority of which have been carried out in European ancestry samples. Significantly less heritable variation in liability is explained when risk profiles derived from equivalent powered GWAS are applied trans-ethnically, and therefore well-powered GWAS studies are required in diverse populations, as are methods to deal with mixed ancestry, if we are to avoid further exacerbation of current global health disparities (4).

The second limitation is that polygenic risk scores (PRS) and similar metrics are dirty signals in the epidemiological sense. GWAS have usually been based on prevalent samples from clinical populations, while control populations are often unrepresentatively healthy, and otherwise enriched for traits and behaviors that are associated with inclusion in research. Thus, the current PRS may be biomarkers not just for liability but also for chronicity (including non-response to, or non-compliance with, treatment), progression, factors influencing illness-behavior, and confounders such as educational attainment and socio-economic status that influence access to care. Genomic research using a range of different ascertainment approaches will be required to understand these issues, but the payoff might be great; whereas variants associated with disease occurrence may be useful in informing prevention, those involved in disease progression may be more suitable for the development of new treatments (7).

The third limitation of current findings is that most of the samples used for psychiatric GWAS have not been clinically phenotyped even to a depth normally considered appropriate in psychiatric research and, when they have, inconsistent methods have been employed across sites. Moreover, the majority of samples have been assessed at a single time-point, yet there is huge variability in disease course and outcome within our current diagnoses. It is unclear to what extent this reflects diagnostic

heterogeneity, pharmacogenetic factors, environmental exposures, or a host of other variables influencing individual differences impacting behavior but there is a need to establish this. This will require a major effort to collate and collect suitably powered, well-phenotyped samples, to coordinate phenotyping across sites and make the data available to other researchers. Current and emerging population studies and cohorts can play a role here but typically mental health data are scanty in such samples, and there is a substantial ascertainment bias against people with severe psychiatric disorders such as schizophrenia and childhood neurodevelopmental disorders. It is hard to see how the required datasets can be achieved economically without access to routinely collected clinical data, ideally at a population level. In this endeavor, advances in 'Big Data' approaches including access to electronic health records and digital phenotyping offer great potential.

Pharmacogenomics in relation to treatment response or adverse effects is another area ripe for development in psychiatry. To date, most interest has been focused upon studies of candidate genes encoding known drug metabolizing enzymes and the HLA system in determining risk to adverse effects (8). Genomics offers the prospect of undertaking wider, unbiased, searches, but again the key issue will be access to sufficiently powered samples containing reliable and valid phenotype data. There are however promising signs of progress from genomics. For example, common genetic variants have large effects on the metabolism of clozapine and its metabolites, opening the way for clinical studies assessing the use of pharmacogenomics in the clinical management of patients with treatment-resistant schizophrenia (9). Moreover, a recent study (10) has demonstrated that the high rates of neutropenia seen in African ancestry individuals taking clozapine are due to the high frequency of Benign Ethnic Neutropenia (BEN), and that this can be diagnosed with a simple SNP test. Acceptability and cost efficiency studies are still lacking, but in principle, such a test would allow a much higher proportion of individuals of African ancestry to access clozapine treatment, individuals who are currently denied such access due to undiagnosed BEN.

In conclusion, genomics has made impressive progress in identifying genetic risk factors and in beginning to clarify genetic architectures of a range of psychiatric conditions. Work is also underway to relate the complex genetic signals to specific biological processes. These advances are being driven by the application of increasingly sophisticated genomic, functional genomic and epidemiological methods. However, it is our view that, if these are to yield mechanistic and clinical insights that will benefit patients and lead to a paradigm shift in psychiatric practice, they must be coupled with more sophisticated approaches to defining and measuring phenotypes. It is time to put more psychiatry into psychiatric genomics if we want to put genomics into psychiatric practice.

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