

## Question

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# How can genetic factors be best leveraged to explain individual differences in risk to onset, course of illness and response to treatment in depression and other mood disorders?

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## Context

The clinical field of depression and other mood disorders is characterised by the vast heterogeneity between those who present for care, and the highly variable degree of response to the range of psychological, pharmacological and physical treatments currently provided. These individual differences likely have a genetic component, and leveraging genetic risk is appealing because genetic risk factors point to causality. The possibility that individual genotyping at entry to health care may be a key way forward is worthy of discussion (Torkamani et al., 2018).

To date, the use of pharmacogenetic variants has received most discussion, and this year, the Clinical Pharmacogenetics Implementation Consortium has published specific guidelines about genetic variants in three genes associated with drug metabolism that may help to inform prescribing of antidepressant medications (Bousman et al., 2023).

The last ten years have seen a massive shift in the ability to identify genetic risk variants for depression across the genome, only made possible through worldwide collaborative efforts. Polygenic risk scores derived from these studies have been shown to predict depression risk in independent samples (Wray et al., 2021). However, in-clinic evaluation of the utility of results from genome-wide association studies in risk prediction is still in its infancy, and genetic risk factors will most likely need to be combined with other phenotypic or contextual factors to achieve clinical utility (Murray et al., 2021). While the use of genetic factors to predict course of illness and response to treatment is appealing, currently, there is a dearth of informative data sets. Additionally, the role genetics may play in particular sub-populations such as pregnant women prior to birth, those exposed to earlier risks including perinatal or childhood infection or immune exposures, those exposed to specific traumatic experiences, those exposed to COVID-19 infection or those with specific phenotypic features such as psychotic or circadian syndromes, has not been extensively explored.

## Questions

Major research questions remain as to what the foci of international research efforts should be. What data sets should be generated to use latest omics technologies to penetrate clinical heterogeneity? How ready are new findings for transfer to clinical practice? Which commercial offerings have a significant evidence base to back their claims? How should research studies now be designed to best answer some of the most immediate challenges in the field?

## How to contribute to this Question

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**Competing interests.** IBH is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney, Australia. The BMC operates on early-intervention youth services at Camperdown under contract to Headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca, Janssen Cilag) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd, which aims to transform mental health services through the use of innovative technologies.

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