Published in final edited form as:

*Biol Psychiatry*. 2018 April 15; 83(8): e45–e46. doi:10.1016/j.biopsych.2018.02.013.

# Leveraging the Power of Genetics to Bring Precision Medicine to Psychiatry: Too Little of a Good Thing?

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Imagine, in 1968, a 56-year-old woman presenting to her primary care physician with a progressively worsening cough. Unrelatedly (in her mind)—and ominously (in her physician's) — she also reports a dull ache in her left hip. Over the next week, a detailed diagnostic evaluation reveals a large mass in her lungs and multiple bone metastases. She is both terrified and embarrassed when her physician first uses the “c word.” She is treated for her cancer with state-of-the art cyclophosphamide chemotherapy, whose adverse effects include unremitting nausea and vomiting and her hair falling out. Sadly, the treatment fails to alter the natural course of her illness and she dies approximately 6 months later.

If the same patient presented today, little beyond the initial diagnosis would look the same. The biopsy specimen would be tested for a range of driver mutations in genes commonly associated with lung cancer (including *EGFR, ALK, ROS1*, and *BRAF*). Her tumor might be found to contain an activating mutation in the *EGFR* gene and she would be treated with osimertinib, a third-generation inhibitor of the *EGFR* tyrosine kinase. Treatment could lead to complete resolution of both the primary tumor and her metastases (1).

In many ways, psychiatry remains closer to what oncology looked like in the 1960s than to how that field looks today. As yet, there are no biomarkers that allow us to definitively diagnose major psychiatric illnesses. Much of our clinical practice still relies on the “art” of medicine—we treat heterogeneous conditions with generalized interventions, forcing clinicians to make instinctive decisions that reflect complex probability functions, inferred in large part from our personal experience. But our field is evolving, and while broad biomarkers remain elusive, we are beginning to follow oncology's example in our ability to integrate a new and compelling source of data: genetics. A rapid expansion in methodological approaches, combined with the plummeting costs of these techniques, has led to an explosion of research in genetics. Large collaborations leveraging data from thousands of patients are yielding new insights from each of the four main branches of genetics (common genetics, epigenetics, pharmacogenetics, and rare genetics), each of which poses unique challenges and opportunities for reshaping clinical practice.

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The authors report no biomedical financial interests or potential conflicts of interest.

In the 20th century, research largely followed in the legacy of Mendel's original work. It was clear that psychiatric illnesses had large genetic components, and the hope at the time was that we might find one or a few genetic variants in the population that would account for the majority of disease burden, paralleling cystic fibrosis research from the mid-1980s. Of course, in psychiatry, this did not happen then. And while huge advancements have taken place in the intervening decades—the Human Genome Project is complete, and our methods have advanced from linkage studies to whole exome and whole genome sequencing—our data are leading to an ever more complex picture rather than a simpler understanding.

Contemporary work relating to schizophrenia offers a fascinating window to the state of the field. A recent article by Hilker *et al.* (2) used advanced statistical methods with a large national database to reaffirm that schizophrenia's heritability, a measure of the genetic contribution to a given disorder, was high, amounting to 79%. However, how we have come to understand this high heritability has followed a complicated path. Common variant studies were not yielding the results that the field initially anticipated. As discouragement about this method was starting to be the norm—we were not finding the gene(s)—large, multicenter collaborations transformed our basic understanding of the genetic underpinnings of schizophrenia. More than 100 common risk loci have now been identified (3), and risk for the disease emerges as a complex interplay between them (as can now be quantified using polygenic risk scores). As exciting as these results are, this approach explains only 5.5% of the variance in schizophrenia (4), underscoring its low ability to predict the disorder. While this type of research continues to emphasize the growing role of genetics in psychiatry, other branches offer greater short-term opportunity for clinical translation.

One of the most interesting aspects of modern genetics has been the increasing understanding of epigenetics—the ways in which our environment may shape the expression of genes. Epigenetic changes may play an important role in psychiatric symptomatology, such as how early adverse events may lead to a dyregulated stress response (5). In the context of trying to understand the cause of psychiatric illnesses, a striking recent finding is that epigenetic changes associated with trauma (or even simple fear conditioning) may be passed on from one generation to the next (6). As our knowledge about epigenetics expands and we learn more about how these epigenetic changes affect different tissues, we may gain additional insights into diagnosis and, ideally, the development of targeted treatments in the future.

The area of genetics that may currently be receiving the most attention in psychiatric clinics is pharmacogenetics. The basic principle is simple and compelling: Is it possible to identify genetic variation that could predict either how well individuals would respond to a particular medication or how likely they are to develop a particular adverse reaction? A number of commercial products are now available that purport to do exactly this. The underlying data, though, do not seem to match the aggressive marketing efforts that have pushed pharmacogenetics into common use. Other than the case for human leukocyte antigen genotyping of people of Asian ancestry to estimate the risk of serious adverse effects associated with carbamazepine, there are no clear indications at this time for the use of pharmacogenetics (7). Thus, while this remains an extraordinarily promising approach, the clinical applications are largely in the future.

There is one example, though, where the future is here today: the use of testing for rare genetic variants. Rare variants are defined as genetic changes that affect less than 1% of the population—and although individually rare, pathogenic copy number variants and single nucleotide variants may collectively explain up to 30% of cases of autism spectrum disorder (ASD). Because of this, genetic testing, specifically chromosomal microarray and fragile X testing, is now recommended by multiple professional medical societies as a key step in the workup of every individual with ASD (8). Although the frequency of rare genetic variants does not appear to be as high for other psychiatric disorders that also have a strong genetic burden, their potential clinical impact leads to the hope that disorders such as schizophrenia and bipolar disorder may be amenable to similar approaches in the future.

Conducting testing for rare genetic variants is not merely an academic exercise: establishing a diagnosis has significant consequences. Historical data from other patients with the same abnormality may yield valuable information about potential comorbidities and other symptoms that may emerge. This can allow for a range of preemptive treatment strategies such as avoiding potentially risky medications in patients with uniquely vulnerable organ systems (e.g., the endocrine and renal systems in individuals with 17q12 deletions) or customizing therapy approaches to more quickly target emerging cognitive or behavioral issues (8). Identifying pathogenic rare variants can lead to new insights into the biological mechanisms of these diseases and open the door to novel pharmacotherapeutic pathways (9). Perhaps most importantly, testing may allow us to communicate more effectively with patients and families. Though genetic testing is not without ethical concerns (including implications for relatives), establishing a diagnosis can put an end to a family's diagnostic odyssey and provide a sense of closure, while at the same time informing genetic counseling. It can connect families to additional resources and networks, including other families who share the same circumstances, and may instill a sense of community that would otherwise not be possible. Ultimately, understanding causality is a critical step toward alleviating the shame and stigma of psychiatric illness.

Yet despite these advances, the sad reality is that only a minority of patients with ASD are receiving these tests. The reasons for this are complex and multifactorial: community clinicians may not be aware of how to order and interpret tests and then act on the results; health care entitities and insurance companies may not have a streamlined process to support testing; and, of course, there are a range of broader policy, systems, and ethical issues. In many ways, this example may be seen as representative of the universal challenge of effecting broad, structural change to a field (10).

The time to make this transition is now. In order for us to take advantage of the full potential of genetics in psychiatry, we need to have a clear and accessible roadmap to guide clinicians. We can begin, today, by working toward the implementation and dissemination of the few clear examples where psychiatric genetics is already relevant and indicated— including genetic testing for ASD. We should also keep ourselves open to the other ways in which we can expect our field to evolve over the next 5 to 10 years, hoping not only for improved patient outcomes, akin to oncology, but to change the broader conversation about psychiatric illness in society.

## Acknowledgments

Clinical Commentaries are produced in collaboration with the National Neuroscience Curriculum Initiative (NNCI). David Ross, in his dual roles as co-chair of the NNCI and as Education Editor of *Biological Psychiatry*, manages the development of these commentaries but plays no role in the decision to publish each commentary. The NNCI is supported by the National Institutes of Health Grant Nos. R25 MH10107602S1 and R25 MH08646607S1.

## References

1. Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJ Jr, Wu YL, et al. Lung cancer: Current therapies and new targeted treatments. Lancet. 2017; 389:299–311. [PubMed: 27574741]
2. Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, et al. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish Twin Register. Biol Psychiatry. 2018; 83:492–498. [PubMed: 28987712]
3. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511:421–427. [PubMed: 25056061]
4. Power RA, Steinberg S, Bjornsdottir G, Rietveld CA, Abdellaoui A, Nivard MM, et al. Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. Nat Neurosci. 2015; 18:953–955. [PubMed: 26053403]
5. Dwyer JB, Ross DA. The Nature of nurture: How developmental experiences program adult stress circuitry. Biol Psychiatry. 2017; 81:e57–e59. [PubMed: 28317550]
6. Yehuda R, Daskalakis NP, Bierer LM, Bader HN, Klengel T, Holsboer F, et al. Holocaust exposure induced intergenerational effects on FKBP5 methylation. Biol Psychiatry. 2016; 80:372–380. [PubMed: 26410355]
7. Hirschtritt ME, Besterman AD, Ross DA. Psychiatric pharmacogenomics: How close are we? Biol Psychiatry. 2016; 80:e63–e65. [PubMed: 27663067]
8. Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJL, Nurnberger JI Jr, Hallmayer JF. Autism genetics: Opportunities and challenges for clinical translation. Nat Rev Genet. 2017; 18:362–376. [PubMed: 28260791]
9. Rapanelli M, Frick L, Bito H, Pittenger C. Histamine modulation of the basal ganglia circuitry in the development of pathological grooming. Proc Natl Acad Sci U S A. 2017; 114:6599–6604. [PubMed: 28584117]
10. Rogers, EM. Diffusion of Innovations. 5th. New York: Free Press; 2003.