Perspective on Beyond Statistical Significance: Finding Meaningful Effects

Howard J. Edenberg

Department of Biochemistry and Molecular Biology and Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA

Before I built a wall I'd ask to know
What I was walling in or walling out.
Mending Wall, by Robert Frost

Genome-wide association studies (GWASs) in psychiatry have recently identified many loci that affect a wide variety of disorders and related traits, although the number of associated loci varies widely among psychiatric and substance-use traits. The successes of GWAS have triggered thoughts about how to move beyond identification of loci (which contain a very large number of variants), to identification of the functional variants within them that actually contribute to the risk for the traits, and from there to identifying the genes, pathways, and mechanisms involved. The hope is that knowledge of the key genes and pathways will lead to better diagnosis, treatment, and prevention of these complex disorders. On September 2, 2020, three institutes within the US National Institutes of Health (NIH) sponsored a virtual meeting entitled “*Beyond Statistical Significance: Finding Meaningful Effects*” devoted to exploring these issues. The structure of the meeting – initial presentations followed by discussion sections on 3 sets of topics through which all willing participants cycled and a general discussion as a wrap-up – allowed for lively interaction and the presentation of many ideas. Dr. Elizabeth Hoffman opened the meeting by stating its objective was “To develop best practice recommendations for identifying, analyzing, and interpret-

ing meaningful effects by engaging researchers from a range of disciplines in discussions of meaningful science that go beyond statistical significance.” It should not surprise anyone that one conclusion was that these questions are difficult and there are no one-size-fits-all answers.

A good summary of the meeting has been posted at <https://apps1.seiservices.com/meaningfuleffects/>, with details of the presentations and the discussions. Some of these issues have been discussed in relation to the NIH Adolescent Brain Cognitive Development study [1] in a preprint recently posted to bioRxiv [2]. I will not recapitulate the meeting summary here, but rather provide a perspective on the key questions discussed, and potential future directions.

Background: Identification of Loci Affecting Psychiatric Disorders

The robust identification of loci affecting psychiatric and substance-use disorders and related traits is a relatively recent development. Before then, most studies were small in scale and focused on candidate genes thought to play a role in the phenotypes. Although the candidate gene era led to interesting biology, most of the candidate genes for psychiatric disorders did not prove significantly associated with them when analyzed by the unbiased approach of GWAS (e.g., [3]). There are, of course, excep-

tions: for example, functional variations in genes that metabolize alcohol (*ADH1B*, *ALDH2*) were shown to have a very large effect on risk for alcohol dependence many years ago in studies of small samples [4, 5] and have since been re-confirmed by GWAS [6–10]. More recently, a functional variant in the opioid receptor gene *OPRM1* has finally been confirmed as associated with opioid use disorder in a large GWAS [11]. But these are the exceptions; the general lack of replication of candidate genes in large GWAS has more recently led much of the field to focus on genome-wide significant findings, despite knowing that at current sample sizes we are still missing a lot of the biology.

Breakthroughs in the robust identification of risk loci began when the scientists involved realized that large-scale collaborations were needed to assemble the sample sizes required for reliable results. The Psychiatric Genomics Consortium [12] has led the way for many disorders, conducting meta-analyses across numerous individual studies to amass the required subject numbers. Schizophrenia was the first big success, starting with the 2014 article that identified 108 loci [13]. It has become clear that as sample numbers increase, there is an inflection point beyond which adding additional samples leads almost linearly to additional findings [12]. The number of cases that are needed to reach an inflection point depends on the heritability, heterogeneity, and genetic architecture of the disorder and varies greatly among them [14]. Schizophrenia required about 20,000 cases [13], major depression required over 100,000 [15]. None has yet reached an asymptote, so additional samples will lead to additional loci and to a better understanding of the disorders. Because we can still only explain a small portion of the heritability by the common variants analyzed by GWAS, in addition to larger samples we will need to include rare variants in our analyses.

Recently, large samples have come from biobanks, electronic health records, and consumer genetics companies. These additions have been of great value but have also introduced heterogeneity into the phenotypes. At times these sources use minimal phenotyping, sometimes a single question. A recent paper demonstrated that in the case of major depressive disorder, minimal phenotyping using self-reported items leads to association signals that are relatively nonspecific [16]. This emphasizes the need for additional carefully phenotyped samples to help dissect and understand the complex and heterogeneous psychiatric disorders.

There is a pressing need to expand studies to individuals of many different ancestries across the world, which

will allow us to look at a much broader range of the genetic variation among humans and will allow the benefits of these studies to reach more of humankind [17]. Studying populations in different environments is also of great value since psychiatric disorders are results of complex interactions among genes and between genes and the environment.

Focus of the Meeting

The meeting addressed the important topic: where do we go from here? Going “*Beyond Statistical Significance*” can be thought of in several ways, 2 broad categories of which were the focus of the meeting. A statistically significant locus typically has a very small effect on the trait in question. One thread in the discussions was the question posed at the opening by Dr. Hoffman: “*How do we know when a small effect is meaningful?*” A second set of challenges is how to go from identifying loci, each of which spans a very large number of variants, to the identification of the functional variants that actually (meaningfully) affect the trait. The organization of the genome into co-inherited blocks (linkage disequilibrium) and the fact that some variants act on nearby genes (*cis*-acting) while others act on distant genes (*trans*-acting) greatly complicates the identification of the functional variants.

The stage was set by brief introductory talks from the directors of the 3 NIH institutes that sponsored the meeting. Dr. Nora Volkow, director of the National Institute on Drug Abuse, opened the meeting commenting on the importance of reproducibility in science. She made the point that large datasets, such as the Adolescent Brain Cognitive Development study [1] and the Connectome project [18] can lead to many statistically significant findings, but their meaning depends on the scientific question asked. Dr. Volkow emphasized that the complexity of the human brain and the dynamic interactions across development and with different environments make the task of understanding psychiatric and substance-use disorders formidable. Dr. George Koob, director of the National Institute on Alcohol Abuse and Alcoholism, noted that the great recent advances in neuroscience were due in large part to big data and reinforced the importance of scientific rigor and reproducibility in their analysis and interpretation. Dr. Joshua Gordon, director of the National Institute of Mental Health, spoke about the complex biology and psychology underlying brain disorders and their symptoms, and the heterogeneity of the disorder.

ders. He noted that many small effects and many neural circuits are involved and that genes and their expression patterns, the pathways in which they participate, and the neural circuits at a layer beyond that all contribute to multiple phenotypes in complex ways. These are further complicated by the wide variety of environmental factors. Dr. Gordon noted that robust statistical associations, even if small in magnitude, can shape our knowledge of the relevant biology underlying the disorders and can be combined to make clinical predictors.

What Is a “Meaningful” Effect?

Small effects have sometimes been denigrated as having little or no meaning. Dr. Hoffman noted that a small effect can be meaningful if unbiased and replicable and noted several contexts in which meaning can be interpreted: statistical, biological, clinical, and public policy. This is an important point worth amplifying. The context is crucial, hence the Robert Frost quote atop this article. Talking about whether an effect is meaningful immediately raises the question of *meaningful in what context?* Some argue that meaningful is defined by the level of significance. Others say that the effect size is the main issue and that an effect of small size is not meaningful; here, one must explicitly consider the effect on what process or trait. Some emphasize that anything that tells us about the biology underlying a trait is meaningful. Still others focus on what can be used in the clinic, for prediction of risk for onset or likelihood to respond to a particular treatment. Still others look at what might have policy implications. All of these have merit in context; there is no way to set a threshold on what effect size may be meaningful.

Statistical significance is the first hurdle. If a finding is likely to occur by chance, using it for prediction or as a lead toward biology is obviously fraught. Many of the advances in understanding the genetics of psychiatric and substance-use disorders and related traits date from the time GWAS of large samples became the leading paradigm, with accepted criteria for genome-wide significance ($p \leq 5 \times 10^{-8}$). This reduces false positives, but at the cost of many false negatives. When sample numbers are low, there are few genome-wide significant loci, and these are often not reproduced by later studies or when additional cases and controls are added to the original studies. Larger samples are being assembled, so the number of loci reliably identified is growing steadily. As noted above, there is a pressing need for even larger samples, particularly of non-European ancestries. But we are al-

ready at the point where the issue of how to go *beyond statistical significance* should be addressed.

Effect sizes are important in many ways, but a key question is what effect is being measured, and on what scale. Effect size depends in part on the way a phenotype is measured and is sensitive to the environment – both the remainder of the genome and the external environment. In the context of risk for complex genetic traits, nearly all common loci have very small effects on the risk for a disorder [12]. For example, among the 108 significant single nucleotide polymorphisms (SNPs) for schizophrenia, only 2 had an effect size >1.2 [12, 13], and among 44 for major depressive disorder, the odds ratio ranged from 0.95 to 1.05 [15]. This implies that individual SNPs will rarely be good biomarkers or predictors of risk, but there is promise in combining them (see below). Even variations with large effect sizes, for example, copy number variants, show heterogeneity in the clinical symptoms they are associated with, presumably due to modification by the rest of the genome and the environment [19, 20].

Significantly associated SNPs can point toward the underlying *biology* of a disorder. Because the genome is inherited in blocks (linkage disequilibrium), the lead SNP need not be the one that has the largest effect (or any effect at all) on the trait. In most cases, it merely tags a large group of SNPs, some with *cis*- and others with *trans*-effects. Thus, identifying the SNP or SNPs that actually affect the trait is difficult (more on that later). Although the gene nearest to the lead SNP has often been described as if it was the associated gene, this is far from universally true. Studying populations of different ancestry, and thereby different linkage disequilibrium patterns can help narrow a locus. High throughput assays that identify functional SNPs are important methods for prioritizing SNPs for further study [21–23]. Identification of the functional SNP(s) and the gene or genes they affect provides a strong basis for studying the biology underlying the trait. From the genes, one can move to identifying the biological pathways involved, and the cell types in which they function. These insights can, in turn, provide firm bases for designing both diagnostics and treatments [24]. Dr. Dana Hancock pointed out that drug targets with GWAS support succeed twice as often as those without [25].

Clinical utility has often been thought of in the context of predicting risk. Given the small effect sizes of individual loci and the still small fraction of overall risk that can be explained at our current level of discovery, prediction is not yet robust. The most promising approach is to aggregate the effects of many loci into what have been called

polygenic risk scores (PRS) or genetic risk scores (GRS). There are many ways to do this and many ways to select which SNPs to include, ranging from only those that are genome-wide significant to all the SNPs in the genome. There are also some real cautions: for example, population stratification can lead to a confounding of genetics and environment in calculating a PRS even when the usual methods of correction are applied [26, 27]. PRS are not yet robust enough to predict on an individual level, particularly since genetics explains only a fraction of risk for psychiatric and substance-use disorders – there is also a major contribution from the environment. Those individuals within the group at the highest level of PRS may be several-fold more likely to develop a disorder, but PRS cannot determine who among them will.

There was discussion at the breakout sessions of whether the standards for predictive utility should be different depending on whether there is a proven intervention or not. For disorders in which there are clear and effective preventive measures that can be applied with little risk of ill effect (e.g., some cardiac disorders), prediction can be useful. But for psychiatric or substance-use disorders that is not yet the case, and there is a high risk of stigmatizing individuals identified as being at high risk, with the potential of causing great harm. For example, a recently proposed test for the risk of opioid dependence, aimed at physicians who might consider prescribing opioids for treatment of pain, has been carefully examined and found not to predict opioid dependence but rather to predict ethnicity [28]; thus, it could potentially exacerbate existing biases in the treatment of pain. We should move with great caution in predictions of risk in psychiatry. As we learn more, there is the potential for other types of clinical utility – genetics could eventually aid in differential diagnosis, in redefinitions of psychiatric disorders, and in pharmacogenetics (matching individuals to the treatment most likely to be effective).

Finding Functional Variants

As noted above, the most significant SNP in a locus need not be the one that contributes to the biology of the trait. A key step in finding *meaningful* effects is to discover which SNPs in an identified locus are functional and which are merely in linkage disequilibrium with the functional ones, and from there identifying the gene(s) affected by the variations. This is not a small task. It is sometimes discussed as finding “the” (one) functional SNP, which is unfortunate since many are likely to be. If

the biological effect is due to increasing or decreasing the activity (or localization) of a protein, many different variations may do that in different cells, tissues, individuals, and environments. The net effect of the entire pattern of variations (the haplotype and diplotype) is what will matter. Gene-based tests can aggregate the effects of multiple variants in a gene.

Some SNPs associated with complex disorders affect the amino acid sequence of a protein. Mapping those SNPs to the genes they affect is straightforward. One can then examine how that change affects the structure, function, and stability of the protein, and go on to make the same (or an analogous) change in a model organism to see how it affects cells, organs, and behavior. It will be important to consider cellular milieu in which to test the effects (raising the issue of gene $\times$ gene and gene $\times$ environment interactions).

Most common SNPs associated with psychiatric disorders do not, however, affect protein structure; they likely affect gene regulation in one or more tissues. Regulatory variation is much harder to study than coding variation. Recent advances in our ability to study gene regulation, particularly transcriptomics and epigenetics, were discussed by Dr. Hawrylycz. These have allowed us to better identify and understand regulatory loci, although as he emphasized, they must be used with great care to produce reliable and reproducible results. Transcriptomes can be studied to identify expression quantitative trait loci. DNA methylation can affect expression. Open chromatin and potential binding sites for regulatory proteins can be identified by techniques such as ATAC-sequencing [22]. High throughput assays of SNP function (as promoters, enhancers, silencers, and modifiers of RNA stability) [21–23] can make important contributions. Many of these approaches have been carried out in bulk tissues, and those studies have shown the importance of tissue-specific effects. The Genotype-Tissue Expression project [29] has been a valuable reference. There has been a recent move away from studying bulk tissues toward examining single cells within the tissues, which can give new insights into biology. Dr. Hawrylycz pointed out many technical cautions that must be addressed, including the stochastic and noisy nature of the data from single cells. The importance of the choice of cells and tissues in which to test the effects has become more apparent.

A particular problem for psychiatric disorders is that we do not have longitudinal access to the key tissue – the human brain. We are generally limited to studying blood samples, cell lines, cell types differentiated from induced pluripotent stem cells, or postmortem tissues. These not

only reflect pre-existing differences that could affect risk but also effects that have accumulated over the years of living with the disorders and/or with their treatment. They may also reflect conditions of tissue collection and/or cell culture. Animal studies can contribute valuable information about how variations affect physiology and behavior, since much (but not all) underlying biology is conserved, but one must be cautious when claiming a given behavior in a nonhuman organism “models” a psychiatric trait.

Going beyond Individual Genes

Finding the gene or genes that underlie a significant locus, difficult as it can be, is an important start. But genes do not function in isolation, so it is important to go beyond individual genes and examine the pathways and networks in which they function. Robustly identifying many genes that are associated with a trait provides an entry into this – one can look for commonalities in the pathways they participate in, again being careful to put these into the context of the cells and tissues involved.

Knowing the key pathways leading to risk (or treatment response, or recovery) can provide a firm basis for developing or evaluating potential drugs [24]. This is a clear situation in which the effect size of a variant is not relevant – if identification of a variant or variant(s), even of very small effect on the trait, leads to an understanding of a key pathway, the effect of a drug or other intervention on that pathway is in no way limited to the effect size of the variant(s) that led to its discovery. We are not even limited to targeting the particular step in the pathway that is modulated by the variant – similar overall effects on the trait might arise from targeting other steps in the same pathway. Similarly, a rare variant that has little effect on a population basis (although possibly a large effect on the rare individuals carrying it) can lead to understanding the biology of a disorder and to development of a drug that can have major impact across the wider population. For example, the fact that *PCSK9* variants affect low-density lipoprotein levels was initially discovered through rare mutations that caused autosomal dominant familial hypercholesterolemia [30], and now monoclonal antibodies that inhibit *PCSK9* are approved drugs to lower LDL and protect against atherosclerotic cardiovascular disease [31].

Of course, even the pathways within cells and tissues and across brain regions do not function in isolation. The environment plays a major role at all levels of function,

from intracellular milieu affected by the other genes and variants, through cell-cell and cell-tissue interactions, to whole-organism interactions with the external environment. The issue of which environments to measure and how to measure them is an important one – there are literally millions of things that could potentially affect outcomes, many in nonlinear ways that are hard to model. Dr. Erin Dunn emphasized the interplay of genes with many different environments across the lifespan. Much thought must go into which to attempt to measure and which to include in the modeling. Dr. Dunn emphasized that among those important to consider for psychiatric traits are socioeconomic status, sex, and race/ethnicity.

A factor that can confound genetic studies is that the environment of an individual is partially explained by the genotype (genetics) of other individuals [32, 33]. Parents provide not only genes but also much of the environment to their children during key formative years. Parents, siblings, and partners also provide indirect genetic effects [32, 33]. A recent analysis in the UK Biobank showed significant partner genetic effects on alcohol intake frequency, smoking status, and substance-use disorder; assortative mating might explain part but not all of this [32].

The balance between large exploratory studies (such as GWAS) and small confirmatory studies, both of which have value, was discussed. Dr. Dunn encouraged a balance between exploration and confirmation. The idea of basing confirmatory studies on solid results from large exploratory studies (i.e., following up significant findings from GWAS to examine mechanisms) was generally thought to be a good approach. In the discussion, the problem of hypothesizing after the results are known was raised. Dr. Jenn Pfeifer made the point that there are many degrees of freedom associated with the choices a researcher makes. She favors preregistration of more specific hypotheses and analytical approaches when doing confirmatory studies.

Meaningful Effects in Imaging

Given our inability to sample the brain of living individuals, imaging of the brain at rest and performing various tasks can aid our understanding of psychiatric disorders. The issues surrounding what is meaningful in neuroimaging studies were explored at some depth. The basic issues were similar – statistical significance, effect size, clinical significance, and the complexities of analysis.

Drs. Ragini Verma and Vince Calhoun discussed many ways that imaging can be analyzed, depending on

the modality, types of analyses (e.g., cross sectional, longitudinal, group-, or individual-based), and question posed. They illustrated many potential confounds that must be dealt with, including sex, age, diet, smoking, time of day and year, and how data were acquired (e.g., scanner differences may be nonlinear). They also noted that the confounds may interact, not necessarily in a linear manner. An important take-home message was that there is a lot of “healthy variation” and many potential measures and analyses, so much care is needed to avoid unconscious bias and produce reliable, reproducible results. They noted that there is no easy, uniform solution to the potential confounds. As an example, Dr. Calhoun pointed out that adjusting for smoking when studying alcohol use removes part of the real effect, due to comorbidity. The question of what is meaningful again depends on the goal of the study – if it is for precision medicine, sensitivity and specificity are key.

Confounds were further discussed in breakout sessions, and there are clearly no simple answers – strategies must be fit to the question and model being tested, which requires domain knowledge and much care to examine the sensitivity of results to different choices. Some suggested that machine learning approaches can help with confounds, but machine learning can also be misled by them and can be very sensitive to confounding due to ancestry differences [28, 34, 35]. Cross-validation and replication are critical. Collider bias (including that induced by the criteria for selection of study subjects – both cases and controls) can also substantially influence associations [36] but that was not addressed in detail.

Communicating with the Public

The issues discussed above, and others described in the meeting summary (<https://apps1.seiservices.com/meaningfuleffects/>), are complicated and subject to misunderstanding. Advances in psychiatric genetics are of great interest not only to other scientists and clinicians but also to the general public. Communicating with these various audiences in a meaningful way was the subject of the keynote talk by Jessica Wapner, a science journalist, that opened the meeting. Ms. Wapner noted how important it was for scientists to discuss their work in ways accessible to the broader public that finances the work, to expand knowledge, correct misinformation, and influence policy. This means avoiding hype and misleading information and communicating uncertainty. The concept of risk is particularly difficult to communicate carefully and

thoughtfully. The difference between relative and absolute risk can be great and can lead to serious misunderstanding and misplaced alarm; Ms. Wapner suggested that absolute risk is generally better to report. The difference between correlation and causation is also critical to convey, and all too often confused. Careful framing of behaviors makes a big difference in how they are understood and their impact. Ms. Wapner suggested that social media can be a positive tool to accurately disseminate findings and messages and to correct misinformation.

Ms. Wapner’s suggestions and cautions are important when discussing any scientific results, and particularly those relating to psychiatric and substance-use disorders and related traits because of the stigma often associated with them. It is important to try to convey 2 concepts that are often misunderstood as being mutually exclusive: genetics plays a substantial role in contributing to these disorders, but they are not completely determined by genetics. Understanding the contribution of genetics and, more generally, biology to these disorders can reduce stigma, showing them to be brain disorders rather than solely personal failures. But it is also important not to leave the impression that because there are biological underpinnings, the outcome is predestined; that can lead to a sense of the futility of prevention and treatment.

Moving Forward

Psychiatric genetics has entered a very productive phase, with large GWAS leading to robust findings. There is still a clear need for larger numbers – we are nowhere near asymptotic in our discoveries, so there is much more to be learned. Some of the large numbers of subjects can come from biobanks, consumer genetics companies, and population surveys, but these generally have a relatively low level of phenotypic detail and greater heterogeneity. The broader phenotypes can add power to gene discovery but may lead to less specific associations [16]. Therefore, accompanying these we need more and larger studies focused on severe cases with detailed phenotyping, to allow us to dissect the results and understand them in more detail. The high degree of comorbidity among psychiatric and substance-use disorders argues strongly that assessments should cover a wide range of traits. There is, however, a problem: the patience of subjects is limited, which limits how much detail one can obtain in an interview. One potential approach is to devise a consistent, minimal set of phenotypes that cover the broad range of psychiatric and substance-use disorders and gather at least that

minimal set across many studies, to complement the more detailed coverage of the specific disorder being investigated. Since many of the psychiatric and substance-use disorders and excessive use of alcohol and drugs contribute to a wide range of somatic disorders, information should be gathered in studies of those disorders also. Agreement on such common items will not be easy to achieve.

The need for studies of a much wider range of ancestries and environments bears reiterating. There are reasons both moral and practical. The results from the current, predominantly Euro-centric studies do not translate well to other ancestries, and could potentially widen existing health disparities. As has been pointed out many times, for the findings of genetic studies to aid people across the world, studies must include the broadest possible range of ancestries. In addition to this moral imperative, studying a broader range of ancestries also allows one to look at a much larger fraction of the genetic variability within humans. It is highly likely that the basic biological mechanisms underlying these and other disorders are similar across groups, even though the patterns

of variation and linkage disequilibrium vary. Cross-population studies can, therefore, greatly aid in narrowing down loci and identifying the functional variants within them. Different environments in which groups live can also affect results, so cross-population studies can also reveal much about gene $\times$ environment effects. Thus, diverse studies aid gene discovery and understanding that is relevant to all ancestries. Recommendations for how best to do this have been published [17]. Overall, this well-attended meeting provided much food for thought on an important set of questions.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

Funding Sources

Related work in the author's laboratory is funded by the US NIH (MH109532; AA008401); the sponsors had no input in the preparation of this manuscript.

References

- 1 Bjork JM, Straub LK, Provost RG, Neale MC. The ABCD study of neurodevelopment: identifying neurocircuit targets for prevention and treatment of adolescent substance abuse. *Curr Treat Options Psychiatry*. 2017;4(2):196–209.
- 2 Dick AS, Lopez DA, Watts AL, Heeringa S, Rutter C, Bartsch H, et al. Meaningful associations in the adolescent brain cognitive development study. *bioRxiv*. 2021. <https://www.biorxiv.org/content/10.1101/2020.09.01.276451v2>.
- 3 Johnson EC, Border R, Melroy-Greif WE, de Leeuw CA, Ehringer MA, Keller MC. No evidence that schizophrenia candidate genes are more associated with schizophrenia than noncandidate genes. *Biol Psychiatry*. 2017;82(10):702–8.
- 4 Thomasson HR, Edenberg HJ, Crabb DW, Mai XL, Jerome RE, Li TK, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. *Am J Hum Genet*. 1991;48(4):677–81.
- 5 Crabb DW, Edenberg HJ, Bosron WF, Li TK. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. *J Clin Invest*. 1989;83(1):314–6.
- 6 Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, Adkins AE, et al. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci*. 2018;21(12):1656–69.
- 7 Gelernter J, Zhou H, Nuñez YZ, Mutirangura A, Malison RT, Kalayasiri R. Genomewide association study of alcohol dependence and related traits in a Thai population. *Alcohol Clin Exp Res*. 2018;42(5):861–8.
- 8 Sanchez-Roige S, Palmer AA, Fontanillas P, Elson SL; 23andMe Research Team tSUDW-GotPGC, Adams MJ, et al. Genome-wide association study meta-analysis of the alcohol use disorders identification test (AUDIT) in two population-based cohorts. *Am J Psychiatry*. 2019;176(2):107–18.
- 9 Justice AC, Smith RV, Tate JP, McGinnis K, Xu K, Becker WC, et al. AUDIT-C and ICD codes as phenotypes for harmful alcohol use: association with ADH1B polymorphisms in two US populations. *Addiction*. 2018;113(12):2214–24.
- 10 Edenberg HJ, McClintick JN. Alcohol dehydrogenases, aldehyde dehydrogenases, and alcohol use disorders: a critical review. *Alcohol Clin Exp Res*. 2018;42(12):2281–97.
- 11 Zhou H, Rentsch CT, Cheng Z, Kember RL, Nunez YZ, Sherva RM, et al. Association of OPRM1 functional coding variant with opioid use disorder: a genome-wide association study. *JAMA Psychiatry*. 2020;77(10):1072–80.
- 12 Sullivan PF, Agrawal A, Bulik CM, Andreasen OA, Børglum AD, Breen G, et al. Psychiatric genomics: an update and an agenda. *Am J Psychiatry*. 2018;175(1):15–27.
- 13 Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421–7.
- 14 Sullivan PF, Geschwind DH. Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. *Cell*. 2019;177(1):162–83.
- 15 Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet*. 2018;50(5):668–81.
- 16 Cai N, Revez JA, Adams MJ, Andlauer TFM, Breen G, Byrne EM, et al. Minimal phenotyping yields genome-wide association signals of low specificity for major depression. *Nat Genet*. 2020;52(4):437–47.
- 17 Peterson RE, Kuchenbaecker K, Walters RK, Chen CY, Popejoy AB, Periyasamy S, et al. Genome-wide association studies in ancestrally diverse populations: opportunities, methods, pitfalls, and recommendations. *Cell*. 2019;179(3):589–603.
- 18 Toga AW, Clark KA, Thompson PM, Shattuck DW, Van Horn JD. Mapping the human connectome. *Neurosurgery*. 2012;71(1):1–5.
- 19 Chawner SJRA, Doherty JL, Anney RJL, Antshel KM, Bearden CE, Bernier R, et al. A genetics-first approach to dissecting the heterogeneity of autism: phenotypic comparison of autism risk copy number variants. *Am J Psychiatry*. 2021;178(1):77–86.

- 20 Binder EB. Genotype-phenotype predictions in autism: are we there yet? *Am J Psychiatry*. 2021;178(1):11–2.
- 21 Thapa KS, Chen AB, Lai D, Xuei X, Wetherill L, Tischfield JA, et al. Identification of functional genetic variants associated with alcohol dependence and related phenotypes using a high-throughput assay. *Alcohol Clin Exp Res*. 2020;44(12):2494–518.
- 22 Buenrostro JD, Giresi PG, Zaba LC, Chang HY, Greenleaf WJ. Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. *Nat Methods*. 2013;10(12):1213–8.
- 23 Ipe J, Swart M, Burgess KS, Skaar TC. High-throughput assays to assess the functional impact of genetic variants: a road towards genomic-driven medicine. *Clin Transl Sci*. 2017;10(2):67–77.
- 24 Breen G, Li Q, Roth BL, O'Donnell P, Didriksen M, Dolmetsch R, et al. Translating genome-wide association findings into new therapeutics for psychiatry. *Nat Neurosci*. 2016;19(11):1392–6.
- 25 Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, et al. The support of human genetic evidence for approved drug indications. *Nat Genet*. 2015;47(8):856–60.
- 26 Blanc J, Berg JJ. How well can we separate genetics from the environment? *Elife*. 2020;9:e64948.
- 27 Zaidi AA, Mathieson I. Demographic history mediates the effect of stratification on polygenic scores. *Elife*. 2020;9:e61548.
- 28 Hatoum AS, Wendt F, Galimberti M, Polimanti R, Neale B, Kranzler H, et al. Genetic data can lead to medical discrimination: opioid use disorder as a cautionary tale. *medRxiv*. 2020. <https://www.medrxiv.org/content/10.1101/2020.09.12.20193342v2>.
- 29 GTEx Consortium. The genotype-tissue expression (GTEx) project. *Nat Genet*. 2013;45(6):580–5.
- 30 Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34(2):154–6.
- 31 Warden BA, Fazio S, Shapiro MD. The PCSK9 revolution: current status, controversies, and future directions. *Trends Cardiovasc Med*. 2020;30(3):179–85.
- 32 Xia C, Canela-Xandri O, Rawlik K, Tenesa A. Evidence of horizontal indirect genetic effects in humans. *Nat Hum Behav*. 2020;5:399–406.
- 33 Kong A, Thorleifsson G, Frigge ML, Vilhjalmsdottir BJ, Young AI, Thorgeirsson TE, et al. The nature of nurture: effects of parental genotypes. *Science*. 2018;359(6374):424–8.
- 34 Bracher-Smith M, Crawford K, Escott-Price V. Machine learning for genetic prediction of psychiatric disorders: a systematic review. *Mol Psychiatry*. 2021;26(1):70–9.
- 35 Hedderich DM, Eickhoff SB. Machine learning for psychiatry: getting doctors at the black box? *Mol Psychiatry*. 2021;26(1):23–5.
- 36 Munafò MR, Tilling K, Taylor AE, Evans DM, Davey Smith G. Collider scope: when selection bias can substantially influence observed associations. *Int J Epidemiol*. 2018;47(1):226–35.