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Concluding Summary

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Introduction

As discussed throughout this volume, our understanding of the genetic basis of psychiatric disorders has advanced tremendously. This understanding now needs to be translated into actionable biology to help patients. The chapters in this volume represent an earnest attempt to clarify just how much our understanding has progressed, and what might be necessary to complete the translation process. As we noted in Chapter 1, during the course of the Forum, four distinct groups captured the progress to date and discussed pathways forward for next steps, tackling a set of questions the groups posed of themselves and then set about to answer. Here we will recap the progress made toward answering these questions in the four groups, summarizing the principal conclusions. We will then close by considering some cross-cutting themes that link ideas across multiple groups.

Delineating Additional Risk Factors

Discussion in the first group focused on whether and how to explore additional genetic risk factors. The progress and conclusions reached by Ronald et al. are detailed in Chapter 2. Despite the undeniable success in identifying hundreds of loci predisposing to multiple psychiatric disorders, Ronald et al. rapidly recognized that there remained considerable work to be done. First, they note that there remain relatively few known genetic risk factors for some less-studied disorders. Second, they recognized the evidence, reviewed by Robinson et al. (Chapter 3), that even for the well-studied disorders, there are likely more risk factors that can be identified in regions of the allelic spectrum that remain underexplored. There was a fair degree of consensus that the most important reason to continue the search for additional genetic risk factors was the lack of diversity in current genetic samples. Indeed, in considering next steps, Ronald et al. place the highest priority on ensuring that future data collection focus

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exclusively, or nearly exclusively, on incorporating individuals from genetically ancestral populations, to ensure both scientific progress and equity.

They also emphasize the need to consider the phenotypes being explored to maximize the return on investments in future gene discovery efforts. Phenotypes discussed included quantitative phenotypes related to brain and behavior; developmental and other longitudinally assessed phenotypes, including co-occurring disorders; and environmental exposures. Ronald et al. note that these and other nondisease, nonbinary phenotypes are more challenging (and expensive) to obtain at scale. They point to several seminal examples of the potential power of exploiting these phenotypes to reveal additional biological and environmental influences on psychiatric disorders. In the final section of Chapter 2, Ronald et al. identify several potential strategies to efficiently gather this phenotypic data. They also addressed the methodology to be used to characterize genetic variation. Here, consensus was more challenging to reach. Some argued that whole-genome sequencing was the appropriate level to interrogate genetic variation, maximizing the information to be gained from each individual and permitting a wide range of analyses to be conducted. Others noted that the trade-off in cost compared to whole-exome sequencing or chip-based genotyping and argued that it was more important to prioritize larger sample sizes and/or deeper phenotyping given potential budgetary constraints. Ronald et al. settled in on the notion that these trade-offs be considered when designing gene discovery projects and that the project should utilize the highest feasible level of genotyping depth possible.

Rare Variation

A second group was tasked with discussing pathways for translating knowledge about rare variants into neurobiological understanding and/or novel therapies. The deliberations and recommendations reached by Bearden et al. are included in Chapter 5. Recognizing the progress made in gene therapy for other monogenic disorders of the central nervous system, they note that much of this progress followed an understanding of the neurobiological consequences of these rare variants. Thus, they consider the pursuits of neurobiology and therapeutics to be intertwined.

Given the large number of rare variants that have now been shown to be causal for disorders such as autism (and to a lesser extent, schizophrenia), Bearden et al. discussed the need to prioritize among these variants for further follow-up. In Chapter 5, they detail a number of important factors to be considered in such a prioritization. These factors include those relevant to the clinical condition—including the strength of the association, the natural history of the illness, etc. —as well as biological variables—including the nature of the variant, its functional implications, and the dependence on gene dosage. Some of

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these factors are more relevant for studies aimed at understanding the neurobiology of the variants, while others are more relevant for therapeutic development.

Bearden et al. also considered the importance of identifying mechanistic convergence, both between different rare variant causes of a disorder as well as between rare and common variants. They note that in autism, in particular, there is already considerable evidence for convergence, both in terms of biological pathways and in terms of the tissues and developmental time periods during which risk genes are most likely to be expressed. Further, they delineate a number of model systems that might be utilized to identify these functional consequences.

Finally, Bearden et al. note that therapeutic development for rare variants is conceivable in the not-too-distant future, given advances in gene therapy and targeting methodologies. Accordingly, they considered the preparatory studies that are necessary to lay the groundwork for future clinical trials aimed at testing such therapies. Given the importance of understanding when and where such interventions should be targeted, Bearden et al. prioritize studies of the natural history of rare variant-associated illness as well as the development of biomarkers that could be used to identify individuals who might benefit from a particular treatment or to measure therapeutic effects during the course of treatment.

Common Variation

In terms of understanding the neurobiological and clinical consequences of common risk variants, the third group acknowledge the considerable, additional challenges that exist at present, as described in Chapter 8 by Won et al. The small effect size of each variant leads to questions of how this risk is summed mechanistically. Moreover, most of these variants are found in intergenic regions rather than within sequences that code for genes, leading to uncertainty as to which biological pathways are altered by the variants. As a result, Won et al. hold that unlike the case for common variation, where clinical and neurobiological implications can be explored simultaneously, further understanding of the biological consequences are the primary priority for rare variation. To help facilitate this understanding, Won et al. considered both experimental approaches and resources.

Experimentally, Won et al. note the importance of both human genetic and model system approaches. They articulate the need to establish a pathway leading from causal risk variant to gene that begins with increased sample sizes and increased diversity in existing genome-wide association studies (GWASs). Next, they note the necessity for refining approaches to statistical fine mapping to utilize these GWAS-derived data to identify the specific single nucleotide polymorphisms most likely responsible for the risk signal. Further, they describe a range of different approaches, including experimental in model

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systems, to validate these fine-mapping results and link them to altered gene and/or protein regulation. This pathway is crucial to understand the impact of common risk variants on cellular functions.

Refining this pathway of approaches is not in and of itself sufficient, in part due to the sheer magnitude of the task at hand. With hundreds and perhaps thousands of risk variants playing a role in psychiatric disorders, Won et al. recognize that a coordinated, resource-based approach will be key to elucidating a biological understanding. Accordingly, they suggest prioritizing the development of large-scale resources such as molecular atlases, validated gene ontologies specific to the brain, and stem cell banks and other biological material repositories linked to deeply clinically phenotyped individuals. These resources will assist at various points along the experimental pathway to speed progress and ensure a comprehensive treatment of the biological consequences of common risk variation.

Clinical Opportunities

The fourth group was tasked with discussing how to maximize the near-term potential for clinical opportunities stemming from progress in understanding of genetic risk. While acknowledging that the principal outcome of clinical benefit—novel therapies—is a long-term objective, Davis et al. recognize that there is a potential for more immediate impact, particularly regarding the explanatory power and predictive capacity of genetic testing. In Chapter 12, they consider the current and potential near-term future clinical use of various types of genetic information, the ethical and clinical implications of such use, as well as the barriers to effective use of genetic information in current clinical practice.

On several issues, Davis et al. achieved a principled consensus. Regarding rare variation, they note that in many countries, routine clinical care for autism and neurodevelopmental disorders already involves genetic testing for rare variants. The consensus was that this return of results was an informative and useful clinical endeavor. Regarding common variation, Davis et al. evaluated the clinical evidence for the utility of polygenic scores (PGSs) and found it lacking. They reached conclusions, including that current iterations of PGSs are not sufficiently predictive of psychiatric risk to be of utility in the general population; that the utility of PGS use in high-risk populations requires further study; and that equity in the application of PGSs in the future will require significant diversification of the samples used to conduct GWAS.

Cross-Cutting Themes

Several cross-cutting themes emerged that played significant roles in the discussions that took place across multiple groups at the Forum. First and perhaps

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foremost, each of the four groups independently recognized the importance of enriching diversity and considering community-driven goals as we progress along the path from genetics to biological knowledge and novel treatments. Diverse samples, especially those that include ancestral populations, serve multiple goals. Diverse samples may facilitate the discovery of additional genetic and environmental risk factors. Moreover, the inclusion of ancestral populations, with greater haplotype heterogeneity, can facilitate more precise fine mapping of known risk factors. Application of genetic information to clinical use requires diverse samples if the clinical utility is to be capable of being applied broadly across the globe. Finally, genetic studies that utilize diverse communities across the globe need to ensure that they are working in the service of those communities. The importance of engaging deeply with these communities to understand their needs and design genetic studies accordingly was emphasized in several chapters in this volume.

Another cross-cutting theme centered on the importance of moving beyond consideration of binary diagnostics and capturing deeper phenotypes. From ensuring that we fully capture meaningful genetic risk factors, to enabling a greater understanding of developmental events and capturing gene–environment interactions, deeper phenotyping has the potential to enhance dramatically our understanding of the biological implications of genetic risk. Moreover, increasing the breadth and depth of phenotyping has implications for clinical approaches. Characterization of genetic associations with neurodevelopmental phenotypes raises the possibility of novel preventative interventions, while physiological or behavioral phenotypes might lead to novel biomarkers. Meanwhile, translation of these genetically characterized phenotypes into model systems, such as human cell preparations or animal models, could enable progress in both clinical and biological spheres.

Developmental and translatable phenotypes are aspects of two additional themes that cut across the groups. All developmental events, phases of illness, and sequencing of co-occuring disorders are important for gene discovery, biological understanding, and clinical translation. Translatable phenotypes have the potential to confirm gene-phenotype associations, which will be especially useful for priorizing common variants. Moreover, translation of these phenotypes into model systems will facilitate exploration of biological pathways influenced by genetic risk, as well as testing of potential therapeutic targets.

A final cross-cutting theme that influenced much of the conclusions drawn by each of the groups is the importance of searching for convergence. With hundreds of risk variants, both common and rare, identifying convergent effects of these variants on biological mechanisms will allow neurobiologists to focus their efforts. Convergence between rare and common alleles will be particularly telling for clinical relevance; for most psychiatric disorders, rare alleles will likely only contribute to a minority of cases. The degree of convergence between the mechanisms implicated by rare and common variation will predict the degree to which knowledge and treatments that emerge from rare

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variants (which are much easier to study in model systems) will be relevant for clinical translation to the larger majority of individuals who have "idiopathic" illness that is not explained by a large effect size, rare variant.

Conclusion: Strategic Coordination to Speed Progess

These and other priorities articulated throughout this volume represent a potential strategic framework for advancing biological discovery and clinical translation in the wake of the many advances made in psychiatric genetics over the past decade. A noteable commonality worth underscoring here is the notion, articulated again across all the groups, that strategic coordination will be the key to accelerating furture progress. Both for large-scale efforts (e.g., developmental resources, multi-omics on single cells) and for smaller-scale efforts (deep phenotyping of individual variants, convergence from multiple common variants), vigorous coordination can ensure complete coverage of the variance space, reduce duplication, and ensure harmonization for rigor, reproducibility, and future meta- and mega-analyses. The enthusiasm for a coordinated approach was uniformly expressed and can be seen in the myriad recommendations detailed here and in the individual chapters. Such coordination, applied to the challenges and opportunities noted throughout the volume, holds the promise to transform the understanding, prevention, and treatment of mental illnesses over the coming decades.

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