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Developmental disorders special issue: biomarkers and targeted therapeutics

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Fueled by prospective studies of behavior and brain development in infants at high risk for neurodevelopmental disorders (NDDs) and by large-scale genetics registries supported by collaborations between private foundations and the National Institutes of Health, the last few years have witnessed considerable improvements in our ability to make early and reliable diagnoses of NDDs and to identify specific genetic causes for developmental concerns. However, earlier and more precise diagnoses also generate tremendous urgency for the development of effective and targeted therapeutics. Unfortunately, clinical trials in NDDs have been plagued by challenges that are rooted in features inherent to these developmental conditions: their clinical and etiological heterogeneity, their continuously evolving features based on age and experience, and the limitations in traditional behavioral assays to truly capture meaningful individual characteristics.

The manuscripts selected for this issue on developmental disorders highlight some of these core challenges and introduce opportunities to address them. We begin with two complementary perspectives on pharmacological interventions and clinical trials in autism spectrum disorder (ASD). Evdokia Anagnostou, (pp. 119–125) a child neurologist and clinical researcher, argues that our lack of pharmacological treatments for core features of ASD results not simply from a paucity of effective agents, but also from inadequate outcome measures, absence of biomarkers to help stratify participants, and a lack of developmental studies that take a life-span approach to understand symptoms and their treatments in ASD. Omar Khwaja, Global Head of Rare Diseases at Roche Pharmaceuticals, then provides an industry perspective on clinical trials and drug development, emphasizing that the explosion in autism genetics has opened the door for translational biomarkers as well as targeted therapeutics with agents that can modify basic processes in brain development.

These foundational articles are followed by a provocative call to action by neuroscientists Jill Silverman and Jacob Ellegood, (pp. 126–133) who argue for the need for more refined measures of both brain function and behavior in preclinical models of autism and genetic conditions, and for combination approaches that link brain structure/function to specific behaviors in these preclinical models to improve the process of testing targeted therapeutics. Clinical researchers Rujuta Bhatt *et al.*, (pp. 134–139) through a review of motor function in ASD, then provide an illustrative example of the limitations in standardized behavioral assays and reflect upon more quantitative measures of motor function in children. Finally, neuroimaging expert Alison Jack (pp. 140–148) introduces research in functional brain connectivity in ASD with focus on large-scale initiatives such as the Autism Brain Imaging Data Exchange, a publically available database of resting state MRI data collected across more than 20 international sites. This type of aggregate database can facilitate methods such as machine learning classification for patient stratification and identification of brain-based subgroups within the ASD spectrum that might then be amenable to specific types of treatments. Although these registries yield robust sample sizes, they face the constraint of considerable variability among study participants and differences across sites in data acquisition and processing protocols. These registries have, however, reinforced the necessity of large sample sizes to examine heterogeneous conditions and have, in turn, motivated the creation of multisite imaging/biomarkers consortia that can prospectively study brain and behavior in NDDs in a uniform manner, with the selection of biomarkers that are rooted in the presumed mechanisms underlying those conditions. Examples of such ongoing efforts include the Autism Biomarkers Consortium for Clinical trials and the European Autism Interventions – A Multicentre Study for Developing New Medications Consortium.

The ultimate goal in NDDs of precise diagnoses becoming immediately coupled with targeted

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treatments will only be realized through team science, direct translation, data sharing, and collaboration among patient advocates, clinicians, basic scientists, clinical researchers, and industry. As evidenced by breakthroughs in genetics and by the elucidation and quantification of neurobiological causes, we are accelerating toward an era of not simply symptom attenuation, but disease modification in NDDs.

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Conflicts of interest

There are no conflicts of interest.