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Developing Clinically Practicable Biomarkers for Autism Spectrum Disorder

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Abstract

Despite significant advances in understanding the biological bases of autism spectrum disorder (ASD), the field remains primarily reliant on observational and parent report measures of behavior to guide clinical practice, conduct research, and evaluate intervention outcomes. There is a critical need for objective measures to more sensitively and validly quantify risk for ASD, ASD symptomatology, and its change in clinical trials. To maximize public health impact, such biomarkers must be cost-effective and utilize accessible and scalable technologies. This letter describes concerns specific to the development of clinically practicable biomarkers for ASD and approaches to optimize understanding of these biomarkers through development of large-scale consortia and clinical networks.

Keywords

Biomarkers

In the nearly 75 years that have elapsed since Leo Kanner first described autism, the field has made significant advancement in understanding the biological bases of autism spectrum disorder (ASD; Kanner 1943). Autism researchers have myriad instruments at their disposal, and novel technologies offering fresh perspectives are being developed at a rapid pace. In contrast, autism clinicians remain reliant on the same tools that Kanner applied decades ago, clinical acumen and observation. Instruments to scaffold and structure clinical insights derived from observational assessments and parent interviews, such as the Autism Diagnostic Observation Schedule (Lord et al. 2012) and Autism Diagnostic Interview – Revised (Lord et al. 1994), enable impressive and unprecedented validity and reliability in clinical assessment.

Despite this progress, there are limits to the utility of clinical observation. Distinctions in biology that may be highly relevant to clinical practice may not be observable; some differences may never be evident in overt behavioral symptoms, and, given the

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developmental unfolding of the autism syndrome, we can expect that even detectable behavioral symptoms will not be consistently expressed throughout human development. Even with the sophisticated clinical tools that have been developed, there will necessarily be a certain degree of subjectivity inherent in all estimates based on human perception and description. Finally, the applicability of clinical insight is constrained by the availability of experienced clinicians, with often limited access in areas not proximate to academic and medical centers.

For these reasons, there is a critical need for biomarkers, or objective metrics to more sensitively and validly quantify risk for ASD, ASD symptomatology, and its change over time and in response to treatment. Here I describe an aspirational goal of developing such indices that are applicable in clinical settings, or *clinically practicable biomarkers*. I highlight scientific and practical challenges to its attainment and provide examples of scientific approaches that hold promise to advance this objective. In closing, I describe research in progress that is applying these principles to advance the objective of translational benefit to individuals and families affected by autism.

There are numerous scientific challenges to developing clinically practicable biomarkers for ASD. A primary difficulty is the *heterogeneity* evident in the manifestation of the condition. Individuals with ASD vary widely in clinically-relevant domains, such as cognitive ability and communicative function. In addition to the influence of developmental experience, this variable presentation likely reflects the existence of different biological etiologies. Given such phenomenological and ontogenetic variability, it may be unrealistic to anticipate discovery of biomarkers specific to autism and representative of all forms of autism. Aligning with the notion of Research Domain Criteria (Insel et al. 2010), it may be more fruitful to seek indices that characterize functional processes relevant to a condition, rather than diagnostic status, per se. It must also be considered that biomarkers may be relevant transdiagnostically. For example, social cognition is impacted in multiple disorders, including autism but also schizophrenia and anxiety, and biomarkers germane to treatment selection or outcome measurement may be common across disorders with overlapping clinical symptomatology. By seeking biomarkers that measure symptom-related processes, investigators may be more likely to detect specific relationships in the face of heterogeneous overall presentation. In terms of clinical practicability, little translational value is lost seeking biomarkers of this nature, as clinical decisions are typically made based on individual attributes rather than diagnostic category; in this way, biomarkers that capture functional processes may more closely align with clinical practice than biomarkers indicating diagnostic status. An important note regarding clinically practicable biomarkers and heterogeneity is that, though most published biomarker research reflects average differences among groups of individuals, for the purposes of personalized medicine, biomarkers must be stable and predictive at the individual level.

A second scientific challenge stems from variability within individuals over time, or *human development*. Because autism is a developmental disorder, symptom profiles vary longitudinally. For this reason, it is not certain that a single biomarker might capture variance in even a single domain of function across the lifespan. As an example, the systems subserving human face perception are presumed to move from subcortical to cortical sources

in infancy (Morton and Johnson 1991), suggesting that distinct biomarkers might be relevant for quantifying functionally equivalent cognitive processes over time. In seeking clinically practicable biomarkers, investigators must constrain judgement to the specific cohorts under investigation and planfully examine applicability in other developmental ranges. Because human brains change most significantly and rapidly during childhood, it will be necessary for biomarker studies to assay processes of interest at multiple developmental time points to establish intra-individual consistency in the absence of significant developmental or clinical change (i.e., test-retest reliability) and to demonstrate predictable relationships with observed developmental and clinical changes.

In addition to these scientific complexities, there are several important logistical considerations in developing clinically practicable biomarkers. A biomarker that can exert meaningful impact on clinical practice must have wide *applicability* in a clinical population. For example, as a lifelong condition, a biomarker to inform treatment selection in autism should be assayable in both children and adults. Furthermore, the metric quantified by the biomarker should be *robust to variation in behavior* during biomarker acquisition; a marker should be orthogonal or have measurable and consistent relationships with potential confounding factors associated with participant action or experience, such as behavior or arousal during biomarker acquisition. Though not relevant to purely biological biomarkers, such as levels of a blood metabolite, neuroimaging biomarkers, for example, would have decreased utility if they were influenced by task-irrelevant variability in visual attention during a scan or variable response to tolerating the confines of a scanner. In addition to applicability to variety of individuals with ASD, widespread *accessibility* is necessary for public health impact. For example, use of a biomarker derived through magnetoencephalographic recording would be limited by the scarcity of recording facilities. Biomarkers acquired via common medical procedures or instruments can be deployed in a more straightforward fashion. A third practical consideration, closely related to accessibility is *economy*. It will be necessary that clinically practicable biomarkers are acquired through low cost methods, either by virtue of economical technologies or reliance upon existing infrastructure, such as those readily available in pediatrician's offices or hospitals.

Although these scientific and logistical challenges are significant, they are not insurmountable, and ongoing research is designed to address them. Issues related to heterogeneity may be addressed by studies with large and deeply phenotyped samples, transforming the noise that obscures results in smaller samples into meaningful variation that can inform understanding of a biomarker's relation to individual differences. Longitudinal designs of such samples, with both brief and more extensive durations between time points, offer opportunities to quantify (a) the intraindividual stability of biomarkers in the short term and (b) change in relation to clinical status and development over longer time spans. By applying biomarker methods that are accessible, cost effective, and widely applicable in such research designs, investigators are poised to readily translate research findings into more clinical settings. Electrophysiological brain recording offers a desirable balance of these characteristics (McPartland 2016), and, though presently less accessible in existing infrastructure, tools such as eye-tracking and wearable autonomic sensors, hold great promise because they can be mass produced at low cost. Indeed, many of these techniques are already being applied in clinical trials (Dawson et al. 2017).

In summation, autism clinical practice has benefited from only a small subset of scientific discoveries, and the field lacks readily deployable clinically practicable biomarkers. Next generation biomarker studies, such as the EU-AIMS (Loth et al. 2014) and the Autism Biomarkers Consortium for Clinical Trials (ABC-CT; www.asdbiomarkers.org), are in progress and are positioned to deliver potentially practicable information about biomarkers derived from large samples with longitudinal sampling using accessible, cost-effective biomarker assays. The goal of such collaborative efforts is to provide an open-access resource for the field that will increase the likelihood of meaningful, reproducible results in future clinical research and trials. We are likely years away from application of biomarkers in clinical practice, with use in clinical trials as a probable preceding step. Nevertheless, ongoing large-scale projects that provide rigorous, reproducible appraisal of promising extant research offer hope for the advancement of clinical practice through scientific discovery.

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References

- Dawson G, Sun JM, Davlantis KS, Murias M, Franz L, Troy J, et al. Autologous Cord Blood Infusions Are Safe and Feasible in Young Children with Autism Spectrum Disorder: Results of a Single-Center Phase I Open-Label Trial. *Stem Cells Transl Med.* 2017; 6(5):1332–1339. DOI: 10.1002/sctm.16-0474 [PubMed: 28378499]
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry.* 2010; 167(7):748–751. DOI: 10.1176/appi.ajp.2010.09091379 [PubMed: 20595427]
- Kanner L. Autistic disturbances of affective contact. *Nervous Child.* 1943; 2:217–250.
- Lord, C., Rutter, M., DiLavore, PC., Risi, S., Gotham, K., Bishop, S. *Autism Diagnostic Observation Schedule*. Second. Torrance, CA: Western Psychological Services; 2012.
- Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental disorders.* 1994; 24(5):659–685. [PubMed: 7814313]
- Loth E, Spooren W, Murphy DG, consortium, E.-A. New treatment targets for autism spectrum disorders: EU-AIMS. *Lancet Psychiatry.* 2014; 1(6):413–415. DOI: 10.1016/S2215-0366(14)00004-2 [PubMed: 26361185]
- McPartland JC. Considerations in biomarker development for neurodevelopmental disorders. *Curr Opin Neurol.* 2016; 29(2):118–122. DOI: 10.1097/WCO.0000000000000300 [PubMed: 26844621]
- Morton J, Johnson MH. CONSPEC and CONLERN: a two-process theory of infant face recognition. *Psychol Rev.* 1991; 98(2):164–181. [PubMed: 2047512]