HHS Public Access

Author manuscript

Nat Rev Drug Discov. Author manuscript; available in PMC 2020 October 14.

Discovering translational biomarkers in neurodevelopmental disorders

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Abstract

Investment in drug development for neurodevelopmental disorders has suffered from recent failures in clinical trials that were based on promising preclinical findings. Here, we discuss development and validation of translational biomarkers of neurodevelopmental disorders that can enable more informative clinical experiments and translational success in these diseases.

Web summary

Investment in drug development for neurodevelopmental disorders has suffered from recent failures in clinical trials that were based on promising preclinical findings. Here, Sahin et al. discuss development and validation of translational biomarkers of neurodevelopmental disorders that can enable more informative clinical experiments and translational success in these diseases.

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Competing interests

The authors declare competing interests: see Supplementary information.

Supplementary information

Supplementary information is available for this paper at https://doi.org/10.1038/d41573-018-00010-7

Subject categories:

Health sciences / Diseases / Neurological disorders / Neurodevelopmental disorders; Health sciences / Diseases / Psychiatric disorders / Autism spectrum disorders; Biological sciences / Drug discovery / Biomarkers; Health sciences / Medical research / Translational research

Neurodevelopmental disorders (NDDs) are heterogeneous childhood-onset conditions that result from disrupted brain development and functioning. In the US, approximately one in six children are diagnosed with an NDD. Direct and indirect health-care costs associated with these disorders are substantial, and the lifetime cost of raising a child with autism spectrum disorder (ASD) and intellectual disability is estimated at $2.4 million in the US and £1.5 million in the UK.

Once a field limited to observation, description and supportive management, clinical investigation in NDDs has now become an exciting field with emerging mechanism-based treatments and preventive interventions thanks to advances in genetics, neuroscience, brain imaging and data science. However, several recent clinical trials have failed to show efficacy despite promising findings in animal assays thought to effectively mimic the clinical syndrome[1,2]. These failures have discouraged some pharmaceutical companies and funding agencies from pursuing drug development for NDDs and from investing in clinical trials, respectively. However, these negative results have prompted critical analyses of potential shortcomings in preclinical models and in clinical trial design. This critical reflection has unveiled an urgent need to develop and validate translational biomarkers of NDDs that bridge human and animal studies to improve chances of success. To this end, the National Institute of Neurological Disorders and Stroke convened a workshop on December 2017 to discuss biomarkers that can enable ‘clinical trial readiness’ and translational success in NDDs (see Supplementary Box 1).

Reasons for failure

Factors that may have contributed to the failed NDD trials include insufficient dosing and target engagement, lack of objective criteria for patient selection and the use of clinical end points that are not sensitive enough to detect a treatment response, especially within the short duration of most trials[2]. Biomarkers are needed to capture the pathways in humans that underlie the complex behavioural or cognitive outcomes assessed in NDD trials. Such markers can be indicators of target engagement and pharmacodynamic (PD) response, and provide early signs of treatment response in a trial. In addition, phenotypic heterogeneity is common even in Mendelian forms of NDD; biomarkers are needed to guide patient selection in trials or predict individual treatment response.

To address these needs, workshop participants considered the potential utility of the following biomarkers in accelerating progress in NDD clinical trials: electrophysiological (event-related potentials (ERPs) and oscillations, measured by electroencephalography (EEG) or magnetoencephalography (MEG)); imaging (structural and functional MRI); functional (eye tracking, pupillometry, transcranial magnetic stimulation, neurocognitive

measures and continuous monitoring with wearable sensors); and biochemical and molecular (genetic sequencing, proteomics, transcriptomics).

Developing the right biomarkers

According to the biomarker criteria defined in the FDA's BEST (Biomarkers, EndpointS and other Tools) Resource, the biomarkers now being developed in NDD research are not ready for use as surrogate end points or even as predictive markers, partly because there are few FDA-approved treatments that can be used to validate these measures in trials. Nonetheless, a number of promising biomarkers under development — including measures of neural oscillations, ERPs, and structural and functional imaging — may prove very useful in dosing and patient selection, and in providing crucial evidence of PD responses. However, continuing effort is needed to assess which subset of these biomarkers shows greatest promise for later-stage validation and standardization.

Furthermore, many of the current biomarker studies focus on revealing phenotypic or genotypic differences between patient populations rather than on demonstrating sensitivity and/or specificity at the individual patient level[3]. Such 'fit for purpose' development is crucial for effective biomarkers in drug discovery.

The search for biomarkers is also linked to efforts to understand the biology underlying NDDs and the pathways and circuits that bridge genotype to phenotype. Understanding the mechanisms and clinical relevance of biomarkers to assess a meaningful outcome will not be feasible without parallel and iterative studies in animal models and humans using equivalent platforms[4,5].

Providing the right framework

Clinical trials in NDDs often involve young children and participants with impaired or atypical communication and/or cognitive abilities, and other understudied populations in which new mechanism-targeted interventions may be most relevant. The feasibility of using biomarkers will vary between populations and with age. A critical gap in our understanding of brain development is the evolution of biomarker expression in paediatric populations. Addressing this gap will be crucial for defining biomarkers of NDD and interpreting any changes with intervention. For example, electrophysiological signals including ERPs are used to examine excitability and functional connectivity in the brain. However, such markers may change with age, brain region, specific task and the exact methodology used. Therefore, longitudinal studies of development using consistent methodology are needed. Currently, detailed developmental atlases are rare for many biomarkers in the typically developing population and even rarer in genetic disorders.

Although it is crucial to establish reliable pharmacokinetic (PK) and PD properties of drugs in animal studies, this work is rarely done in academic laboratories when testing compounds. By leveraging preclinical information about PK/PD, clinical trials have a greater chance of achieving safe and appropriate levels of drug exposure and inducing an efficacy signal in humans. The development of translatable biomarkers to assess PK/PD properties of candidate therapies, particularly when used in parallel in preclinical and clinical studies,

would yield valuable information about blood–brain barrier penetration and target engagement in the brain, providing an enormous boost to drug development for NDDs.

Given that many genetic disorders that give rise to NDDs are rare diseases, multi-site studies are necessary to enrol enough patients. Many biomarker studies include single-site studies with few patients, which raises concerns about the generalizability and reproducibility of the findings. Multi-site studies require biomarkers that are reproducible not only between sessions within the same patient but also across sites, which requires rigorous data acquisition standards, portability, feasibility, and reproducibility across sites. For example, traveling human imaging phantoms are often required to ensure that the acquired data from the same patient on different platforms at different sites are comparable. This is often a challenge for MRI when accounting for variation due to scanner type, acquisition algorithm, software upgrades and more. The Alzheimer's Disease Neuroimaging Initiative has established procedures for addressing this challenge. Similar hurdles exist for EEG and MEG so that the compatibility of recordings from different systems (such as different types of electrode and amplifier) needs to be determined in advance. Ideally, EEG can be cross-referenced with MEG to increase confidence in the localization of the signals. Developing rigorous standards for data acquisition and analysis, including on-site setup and training, detailed manuals of procedures for data collection, real-time feedback to sites of quality control and uniform data processing pipelines, will result in reliable biomarkers. Establishing consortia projects will help to determine the reproducibility of effects across sites. Finally, dissemination and discoverability of newly identified biomarkers to real-world trials and clinical practice are needed.

Future directions

In addition to electrophysiology and imaging, other markers may be very useful, including eye tracking, actigraphy, multimodal sensors of respiration and autonomic function, cognitive markers, personalized analysis of neural cells from inducible-pluripotent stem cells and molecular pathway assays. These technologies, especially those that can provide continuous multi-modal functional data in naturalistic settings, such as in the home or school, may be very powerful and may lead to discovering novel biomarkers. However, such emerging technologies will need to undergo assessments similar to more conventional clinic-based tools. Finally, multi- component biomarker signatures (such as combining and integrating analysis of EEG and imaging signals in a study) may eventually prove more predictive and provide greater confidence in the assays than single biomarkers.

The enormous heterogeneity of ASD and the advances made in the molecular understanding of several rare, genetic forms of NDD associated with ASD has brought these genetic syndromes to the forefront in treatment trials. A Biomarker Atlas that catalogues the longitudinal trajectory of the most promising biomarkers, such as MRI and EEG, in a number of key genetic disorders would significantly reduce the risk of failure of clinical trials in these disorders. A multidisciplinary approach will be needed to accomplish this goal with clinicians, basic scientists, data scientists and technologists working on complementary and coordinated aspects of biomarker development. Once validated in genetic syndromes,

such biomarkers will catalyse the investment in drug development for other objectively measureable traits, and also for non-syndromic forms of NDDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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