

Chapter 4: Which Treatments & Interventions Will Help?

Aspirational Goal: Develop a range of interventions that optimize function and abilities across the lifespan to achieve meaningful outcomes and maximize quality of life for people on the autism spectrum.

Section 1: Introduction

Our aspirational goal progressed from the *2009 IACC Strategic Plan* (“Interventions will be developed that are effective for reducing both core and associated symptoms, for building adaptive skills, and for preventing the disabilities associated with ASD.”) to the 2013 update (“...effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD.”). This evolution, with a shift in focus from “preventing disabilities” to “building adaptive skills, and for maximizing quality of life and health” reflected a growing recognition of the diversity of ASD—owing, in large part, to the increasing participation of individuals with ASD as members of the IACC. Now, in 2017, we again amend our aspirations, emphasizing the construction of lifespan approaches and utilization of meaningful treatment outcomes for individuals living with ASD and their families.

This change recognizes the shifting landscape of treatment opportunities driven by exciting discoveries from cognitive neuroscience, revealing breathtaking developmental reorganizations of brain structure, function, and connectivity in adolescence and young adulthood. For instance, we now know that brain structure, function, and connectivity develop through early adulthood, with executive and social brain networks exhibiting the greatest rates of functional maturation during adolescence. This “Growth spurt” in adolescence is accompanied by increased neural reactivity to emotions and rewards as well as an increased reactivity to socio-affective contextual influences adolescent on decision-making. The confluence of these factors may set the stage for adolescence/young adulthood as a sensitive period for socio-emotional and self-control development. These discoveries do not negate the importance of early childhood intervention. Instead, they suggest that the period from adolescence into young adulthood, with an associated period of increased brain plasticity, may offer an important new window of augmented opportunity for individuals with ASD, their families, scientists, and clinicians to co-construct novel approaches for improved outcomes and superior quality of life.

This new science of adolescent/young adult brain development has arrived in the nick of time to help us turn an incredibly vulnerable period into a new window of opportunity. Writing about Question 6 (“How can we meet the needs of people with ASD as they progress into and through adulthood?”) elsewhere in this report, our colleagues note that each year, approximately 50,000 individuals with ASD turn 18 years old. And across the next decade, there will be an estimated 123% increase in the number of young people with ASD leaving high school. This generation of young adults with ASD will overwhelm our current transition and service systems. As such, there is a critical need to leverage state-of-the-art science to develop approaches that will maximize opportunities for these young people to build fulfilling, self-determined lives. Our colleagues further consider that the heterogeneity of the autism spectrum, amplified across time, makes it unlikely that any one program, or even one dozen approaches, will meet the needs of most individuals with ASD across all phases of life.

Section 2: Progress

Since the *2013 IACC Strategic Plan Update*, we have witnessed an explosion of behavioral intervention studies and there have been several advancements in intervention science including continued progress in the development of multiple intervention types. Key advancements include improvements in community implementation of effective interventions, greater numbers of fully powered randomized trials, comparative efficacy studies, implementation science studies that are hybrid in nature (in other words, child outcomes are still included in the study design, in addition to whether the staff can implement methods at fidelity), and increased diversity of samples that now include low income, minority families as well as populations previously excluded or overlooked in ASD research, such as minimally verbal children and girls. We also have seen great progress in brain-

behavior measures as predictors of outcomes of interventions, as well as the development of adaptive interventions, recognizing that sequential and multiple interventions are often required to improve child outcomes. Finally, technology has been used more frequently, both as a tool within an intervention (such as iPads for communication and storyboarding) and to deliver an intervention using telehealth methods.

Intervention Types

Evidence-Based Practice. The concept of evidence-based practice comes from the evidence-based medicine movement and has three dimensions. First, it is based on the premise that there are behavioral/developmental interventions that have evidence of their positive and strong effects for children, youth, and adults with ASD and practitioners (e.g., psychologists, speech pathologist, teachers) should use them in their work with families. Second, when strong evidence for an intervention or treatment to address a specific goal or outcome does not exist, the practitioner should look for the strongest available intervention, although the empirical efficacy may fall below an established standard. Third, clinical and/or professional expertise plays a major role in selecting an intervention or practice to address a specific goal or more generalized outcomes and is especially useful for adapting the intervention for the individual with ASD when needed.

Behavioral Interventions. Focused intervention practices are instructional or therapeutic approaches applied to an individual's goals (e.g., making social initiations to peers, reducing self-injury), designed to produce outcomes related specifically to the goal, and are implemented until an individual meets his or her specific goal (e.g., over a relative short-time period). Examples of these practices include reinforcement, prompting, visual supports, and time delay. Comprehensive treatment models (CTMs) are designed to address broader outcomes (e.g., increases in cognitive abilities, adaptive behavior, social and communication skills), consist of many focused intervention practices organized around a conceptual framework, are documented through treatment protocols, and exist over an extended time period (e.g., years). Examples include the Lovaas Model and Early Start Denver Model. Practitioners use these two classes of interventions/treatments in different ways. They may select multiple focused intervention practices to build individualized programs for children, youth, and adults with ASD, or they may fully adopt a comprehensive treatment program in which the focused interventions and their use are already proscribed.

A multidisciplinary committee of scientists organized by the *National Academy of Sciences* examined the literature on "educating children with autism, and published their findings in a landmark report. One feature of that report identified 10 comprehensive treatment models that met their criteria, but indicated that few, aside from the Lovaas model, had efficacy data. In association with NSP, Odom, Boyd, Hall, & Hume reviewed the literature on comprehensive treatment models, and revisited the literature in a 2014 report. They identified 30 comprehensive treatment models that met their inclusion criteria then evaluated them on procedural features and empirical support. They found that a subset of the programs was well-designed and had some empirical support. However, few at the time had Randomized Controlled Trial (RCT)-level data demonstrating efficacy. Since that time, research has continued to be published, with RCT level data documenting efficacy for a number of programs. Examples include the Lovaas Model, Early Start Denver Model (ESDM), Joint Attention, Symbolic Play, Engagement & Regulation (JASPER), LEAP, Pivotal Response Treatment (PRT), First Words Project, Floortime, and STAR.

Although multiple CTMs have been shown to be efficacious, they may be implemented less often by practitioners than focused intervention practices. The National Standards Project and the National Professional Development Center on ASD (NPDC) have conducted critical and rigorous reviews of the intervention research literature and identified sets of focused intervention practices that have evidence of efficacy. The NPDC work specifically focused on practices that could be implemented in school and/or community settings. Although the number of practices differed for the two projects (NSP = 11; NPDC = 27), there was substantial overlap. Similarly, deBruin and colleagues conducted a meta-analysis of school-based interventions in high schools, finding evidence for many of the same focused intervention practices (i.e., antecedent-, video-, and consequent-based

interventions). Other reviews have documented the efficacy of school-based, focused interventions on challenging behavior, the use of peer-networks to foster social engagement; social skills training); and academic interventions.

School-Based Interventions. There has been an increase in moving interventions from laboratories to school based settings. It can take over a decade and a half for evidence-based interventions to take hold in the community when developed in the lab. One solution is to test interventions in the community context right from the beginning with the goal of sustaining the intervention beyond the study period. Two recent studies demonstrate that similar outcomes can be obtained in the community and the lab. A randomized wait list design conducted in public preschool classrooms and adapted to small group instruction found that the immediate treatment group increased significantly in their initiations of joint attention gestures, joint engagement, and mean length of utterance compared to those in the waitlist condition. Another study using a similar hybrid implementation approach with toddlers in publically funded school programs found that toddlers improved in their play, joint engagement and language outcomes compared to a wait list control. Both of these studies implemented JASPER aimed at improving core impairments in social communication. These studies also noted sustainability of the intervention over a short term follow up. While several other studies were reported in the literature in school or community settings, most were pre-post designs, and thus, subject to a number of experimental design flaws in evaluating efficacy (e.g.,). As a whole, these findings highlight the effectiveness of teacher-implemented interventions in school settings on improving one of the core problems in ASD and paving the way for more school-based intervention research.

Parent-Mediated Interventions. As children with ASD are identified at earlier and earlier ages, researchers have tested a number of parent mediated interventions in order to meet the need for interventions that can be implemented as early as possible. Most of these are in the newly vetted grouping of ABA-based early interventions, labeled Naturalistic Developmental Behavioral Interventions (NDBIs;). Several recent studies have yielded significant improvements over earlier studies that found little difference between experimental and control groups (e.g.,). Wetherby and colleagues noted that toddlers improved in receptive language and social communication skills in a parent coached intervention based on the SCERTS model, and Kasari and colleagues noted improvements in core social communication impairments of joint attention, play and engagement in toddlers receiving the JASPER intervention. Similarly, a preschool aged, low resourced sample of children receiving JASPER also showed improvements in joint attention, engagement and play.

Critically, all three of these studies compared the experimental treatment to an active control group involving parent education but no hands-on coaching. These studies, therefore, represent a shift in design in which two experimental treatments are compared rather than treatment as usual (TAU). These design improvements are particularly useful since we still do not have an accepted standard of care for early interventions in autism so that when comparing an active treatment to TAU, the TAU group can vary on dose, approach, and effectiveness. Such variability makes it difficult to determine the active mechanism underlying why a treatment provides benefit or not. One conclusion of the recently completed comparative efficacy studies is that active hands-on parent coaching for social communication outcomes is more effective than parent education models where the same information is provided but no active coaching.

This conclusion is further supported by another recent study of toddlers at-risk for ASD (under 30 months). This study involved 12 sessions of a parent education model (Focused Playtime Intervention-FPI) delivered in home once per week, and aimed at improving parental responsiveness to their young children for the purpose of improving communication and language outcomes. FPI delivered limited hands on coaching. The model was compared to 4 sessions of general parent education on communication and behavioral strategies. Compared to the comparison group, gains were found in parent responsiveness for the FPI group but no measurable gains for child social communication. These initial parent gains did not sustain to the follow up, speaking to the need for longer-term, more intense, or more hands-on intervention.

A parent mediated intervention study based on the DIR/Floortime approach was also recently published, suggesting efficacy of this model for improving parent and child outcomes. In this study, a monthly parent consultation model based on DIR/Floortime was compared to a community control of treatment as usual. This

large RCT of 128 families yielded greater parent responsiveness and child initiations in interactions with their parents at the end of the year for the DIR/Floortime group, but no differences in standardized scores.

All of the studies were conducted one-on-one with a parent-child dyad. In other research, parent group interventions yielded significant parent and child benefit using PRT. This study also used an active control parent-group that focused on information on ASD. This randomized study of 53 parents found improvements on prompted utterances of children and parent report of communication improvement on a standardized measure, the Vineland Adaptive Behavior Scales over 3 months. While more cost effective than 1:1 therapy sessions, more research is needed to determine the generalizability and sustainability of this method for meaningful child behaviors.

Altogether, the foregoing studies add to positive outcomes of parent-mediated interventions, but raise issues about meaningful outcomes (i.e., spontaneous versus prompted outcomes), and the specific active ingredients of treatment (i.e., hands on coaching, dose, approach).

In the future, researchers will need to better understand for whom an intervention works best, and why an intervention provides benefit. Understanding mechanism of behavioral interventions gets us closer to knowing the active ingredients of an intervention. Two studies tested mechanism of parent mediated interventions. Pickles and colleagues found that parent synchronization was the mechanism that led to reduced ASD symptoms in preschoolers with ASD. Gulsrud and colleagues found that mirrored pacing was the underlying mechanism leading to greater child initiated joint engagement in a parent mediated JASPER trial with toddlers. Thus, these two related variables begin to suggest some important elements or active ingredients of parent mediated interventions.

Interventions for Minimally Verbal Individuals. Of note during this review period are studies that focused on low rate communicating preschoolers, and children still minimally verbal at school age. Two preschool studies were small sample, randomized controlled trials, and both compared two active treatments, thus representing an experimental design improvement. Both studies focused on improving communication outcomes. One compared two behavioral interventions and the other compared PRT to PECS for improving expressive language. Neither study found differences between treatments, and only minimal progress was made on independent language tests. No power analyses were included, but it is likely the trials were underpowered. Still the lack of external validity for these interventions does not support their community adoption at this point.

One study on school aged, minimally verbal children took a different methodological approach. Kasari and colleagues applied an adaptive treatment approach, testing whether JASPER combined with a behavioral language intervention with and without an augmentative device (AAC; e.g., iPad with proloquo2go software) facilitated greater spoken language over 6 months. After 3 months of intervention, children who were responding slowly based on pre-determined assessment cutoff scores, were re-randomized to receive additional sessions per week or to include the AAC device if they did not receive it in the first randomization. Fast responders continued in their initial assigned treatment. Results were impressive. The children who received the AAC device from the beginning of treatment significantly improved in spoken language; thus, suggesting important implications about the treatment approach and timing of providing an AAC device.

Unique Intervention Needs of Females with ASD. Another under-studied group are girls with ASD. Recent studies find few developmental differences between preschool aged boys and girls with ASD. However, studies of older children find girls with ASD who have lower IQs also have more impairing symptoms of ASD than boys. In contrast, girls with higher IQs report better friendships and social skills, and fewer repetitive behaviors than boys. School playground observations of girls with ASD find they are more subtly overlooked and neglected by their classmates whereas boys with ASD are often overtly rejected. In part, these differences between girls and boys with ASD are due to the ability of girls to camouflage their interaction difficulties. Girls often stay in close proximity to peer groups whereas boys are more likely to be isolated, or alone on the playground, and therefore more readily identifiable. These findings suggest that gender should be included as a tailoring variable when individualizing interventions for children with ASD.

Pharmacological Treatments. In contrast to the many behavioral intervention options available, currently, only two drugs, risperidone and aripiprazole, have Food and Drug Administration (FDA) indication for use in ASD,

specifically for the symptom of irritability. There are no approved treatments for the core symptoms of ASD. Although clinical trials of pharmacological interventions for core symptoms of ASD are now underway, they require several years for completion, analysis, and reporting, thus there few published findings to date. Advances in genetics and neurobiology have led to an increase in the number of clinical trials testing medical treatments for ASD. While the majority of such trials are still drug trials, neurostimulation (discussed separately below) is also gaining momentum as a modality to alter brain activity and neuronal connectivity.

The literature contains an abundance of open label, single-center drug trials that report effectiveness in small samples. Unfortunately, many of these results cannot be replicated in subsequent larger, randomized, placebo-controlled trials. Many of the drug trials in ASD exclude individuals with intellectual disability and also very young children. There are ethical and practical challenges with trials that include these groups. However, a mechanism-based intervention that is supposed to improve core symptoms of ASD may be more effective if administered relatively early in life and may be most effective in those most severely affected. Therefore, it is crucial that such individuals are also included in upcoming trials.

Many different genes may contribute to the susceptibility of developing ASD. This heterogeneity of underlying causal mechanisms makes it difficult to identify convergent molecular pathways and brain circuits involved in all individuals with ASD. One promising target is the oxytocin system. Oxytocin, a neuropeptide (a molecule that brain cells use to talk with each other) expressed in the hypothalamus, is involved in social cognition and has been investigated in a number of studies of ASD. The short half-life of the peptide and the low ability to penetrate the blood-brain barrier are potential challenges for its therapeutic use. Work to determine the best doses and compare methods of delivery are desperately needed. Moreover, given the contextual specificity of oxytocin's effects, work aimed at understanding how oxytocin might enhance responses to evidence-based behavioral interventions is recommended.

Other randomized, placebo-controlled treatment trials have targeted mechanisms such as oxidative stress, glutamatergic, GABAergic, and serotonergic dysfunction proposed to contribute to the pathophysiology of ASD. N-acetylcysteine (NAC), an antioxidant treatment, was well tolerated and had the expected effect of modulating oxidative stress markers, but had no impact on social impairment in youth with ASD. D-cycloserine, a partial agonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, was tested in combination with social skills training. No difference was found in the drug treatment group compared with placebo. The serotonin partial agonist buspirone was used to target core symptoms during the developmental period of low serotonin synthesis capacity in young children with ASD. Low, but not high, dose buspirone showed significant improvement in a measure of restricted and repetitive behaviors. Finally, a double-blind clinical trial using the diuretic bumetanide that reduces intracellular chloride, thereby augmenting GABAergic inhibition, showed that bumetanide significantly reduced clinical symptoms of ASD in children 3-11 years old and was well tolerated. Furthermore, bumetanide combined with a behavioral intervention resulted in a better outcome in children with ASD than a behavioral intervention alone.

Larger trials are needed to validate these initial findings. Moreover, given the importance of context and a developmental perspective on ASD, it will be very important to conducting well-powered studies that combine pharmacological treatments with EBP including behavioral approaches, cognitive behavioral therapy, and social skills training.

Given that the rates of ASD are rising and that there are no effective drugs to treat its core symptoms, the unmet need in ASD is enormous and urgent. Undoubtedly, to address this unmet need, we need to increase the involvement of private industry and encourage industry-academic collaborations. While we focus on the pharmacological industry for the most part in this section, it is important to recognize that other industrial partners, such as those in software, electronics, robotics, can contribute significantly to finding effective treatments for ASD.

Major pharmaceutical companies have reduced their CNS drug research and development programs significantly. This is at least in part due to the greater risk in CNS drug development compared to that of other therapeutic areas. How do we de-risk drug discovery in ASD and attract more private industry? There are several

challenges in the ASD therapeutics pipeline that need to be navigated. First, predictive animal models are difficult to come by. There are significant issues with reproducibility of results published by single academic labs. One way to address this issue is to provide incentives for replication of critical results in order to provide the pharmaceutical companies a portfolio they can trust. Current investigator-initiated research funding mechanisms do not favor applications that propose replication. Thus, collaborative multi-institutional efforts that aim to validate certain critical models and findings need to be supported.

Second, there are additional challenges for clinical development in ASD, such as heterogeneity of symptoms, lack of validated outcome measure and relevant biomarkers and dearth of previous experience with registration studies. While there is a relative sizeable literature of single-site, short-duration, open-label studies that report positive outcomes, very few end up being replicated in controlled trials. This landscape highlights the need to take into account methodological problems, such as placebo effects related to patient, care-giver and/or investigator bias. As much as possible, multi-site, longer duration, placebo-controlled studies should be prioritized in order to produce more reproducible results, such that private industry will take on the challenges of conducting large Phase III registration studies.

A third strategy to encourage private industries involvement is to support the findings of pilot studies with translatable biomarkers. Such biomarkers (discussed in detail below) may have the potential to demonstrate target engagement by the intervention and help select individuals who may respond to that treatment. Outcome measures may also be bolstered by technologies that enable continuous and objective monitoring of certain symptoms rather than the episodic assessment by clinicians in an artificial setting or care-giver questionnaires. Incorporation of such technologies provides another avenue to increase the involvement of private industry in ASD research.

In order to overcome the reluctance of the pharmaceutical industry in CNS drug discovery, we may be able to leverage private-public partnerships and pre-competitive consortia of several stakeholders. A key driver of such initiatives is funding, which can have a variety of sources, such as the NIH Blueprint grants, patient advocacy groups, venture capital and philanthropy.

Direct Brain Stimulation. Transcranial magnetic stimulation (TMS) is a promising method for identifying neural mechanisms and treating aspects of cortical dysfunction in ASD. ASD has been hypothesized to involve an imbalance in cortical excitation/inhibition as well as deficient cortical plasticity. TMS can provide direct measures of corticospinal excitability and cortical plasticity in humans and, as such, offers a non-invasive tool to study aspects of the altered physiology underlying ASD. Treatment strategies involve using TMS to modulate brain cortical plasticity and network activity. In particular, repetitive TMS (rTMS) can alter brain excitability and network activity beyond the duration of a stimulation session or treatment study, and is being examined as a treatment that could potentially reduce core and associated ASD symptoms. Such rTMS-induced changes in cortical network activity may reflect TMS-induced changes in GABAergic interneurons.

Preliminary studies have investigated whether neuromodulation via rTMS or transcranial direct current stimuli (tDCS) can induce neurophysiological and clinical benefits in individuals with ASD. In open-label trials, Casanova et al. have used low-frequency, sub-threshold rTMS to dorsolateral prefrontal cortex (DLPFC) to demonstrate reductions in irritability and repetitive behavior associated with delivery of TMS in individuals with ASD. Using a similar TMS paradigm, improvements have also been reported in electroencephalography (EEG) measures indexing target detection and error monitoring. These measures tap executive functions related to the ability to respond flexibly to changing demands. In one of the few double-blind, randomized trials, Enticott et al. examined the effects of deep rTMS in adults with ASD. Treatment was based on rTMS applied daily to bilateral dorsomedial prefrontal cortex (5 Hz) for two weeks. Those in the active condition showed a significant reduction in symptoms related to social impairments and self-reported social anxiety. Another study employed high-frequency (8 Hz) rTMS in a series of small, sham-controlled studies with children with ASD with intellectual disability. Significant improvements in eye-hand coordination following left premotor cortex HF-rTMS were reported, and these effects were enhanced when behavioral eye-hand integration training was also provided. Amatachaya et al. evaluated ASD symptoms using the Childhood Autism Rating Scale (CARS) after anodal tDCS in individuals with ASD using a

cross over design comparing sham and tDCS stimulation over the left DLPFC. Results showed a decrease in CARS score, as well as an increase in overall clinical functioning (Children's Global Assessment Scale).

In summary, the results of preliminary studies suggest that TMS might be of therapeutic value for improving core and associated symptoms of ASD. However, most studies to date have been based on small samples and employed open-label designs. There is a need for well-controlled, randomized trials with adequate sample sizes to better understand whether TMS is efficacious and safe and whether there are subgroups of individuals with ASD that might benefit from treatments based on TMS.

Mechanistically Based Approaches. The prospect of better understanding a specific disease pathophysiology in order to develop specific, targeted treatments, i.e., precision medicine in ASD, is a tantalizing one. Genetically defined disorders such as Rett Syndrome (RTT), Fragile X Syndrome (FXS) and Tuberous Sclerosis Complex (TSC) provide a unique opportunity to develop mechanism-based treatments for ASD.

The most common cause of classic RTT is a *de novo* mutation in the X-linked gene MECP2 (methyl-CpG-binding protein 2). MECP2 mutations are inherited in X-linked dominant fashion, and females are almost exclusively affected. MECP2 protein binds to methylated DNA. In light of the basic science discoveries in the pathogenesis of RTT, researchers have proposed multiple routes to treatment for the disorder based on knowledge of MECP2 function. These strategies are designed to address either the underlying gene defect or downstream pathways implicated in the disorder. Clinical trials are underway evaluating the use of two different NMDA (N-methyl-D-aspartate) receptor antagonists, dextromethorphan and ketamine, to improve outcomes like epilepsy in RTT. Among neurotrophic factor effectors downstream of MECP2, IGF-1 has been studied. Double-blind, placebo controlled trials of rhIGF-1 and NNZ-2566 (a synthetic version of the terminal tripeptide fragment of IGF-1) have recently finished and are being prepared for publication. The cholesterol pathway has recently been identified as being involved in RTT, and lovastatin is currently under investigation in an open label trial for females with RTT. Finally, directly or indirectly manipulating faulty copies of the MECP2 gene, transcript, or protein is an appealing approach for treating RTT. Read-through strategies as well as gene transfer approaches using adeno-associated viral vectors are being actively pursued.

FXS is an X-linked, trinucleotide repeat expansion disorder involving FMR1 (fragile X mental retardation 1) gene. This is a leading single gene cause of ASD. FMRP protein encoded by this gene regulates protein synthesis in neurons. Advances in our understanding of the pathophysiology of FXS have led to the development of numerous targeted trials. The most prominent theory of FXS, mGluR theory, posits that many symptoms of the FXS are due to exaggerated responses to activation of mGluRs. The prediction of this model was that reduced activation of mGluR would remedy the symptoms of FXS. Recent clinical trials (phase II and III), however, with two different mGlu5 inhibitors (basimglurant and mavoglurant) showed no therapeutic benefit in FXS patients for reasons as yet unclear. Driven by lessons learned from previous trials of mGluR antagonists, investigators are planning a multicenter placebo-controlled trial of mavoglurant for children with FXS ages 2 ½ to 6 years of age. This trial will examine outcome measures, including language, for all participants with a parent implemented language intervention provided to all participants and psychopharmacologic intervention provided only to some.

Approximately 50% of the patients affected with TSC also develop ASD and 90% will have seizures sometime in their life. Importantly many patients with TSC will be diagnosed with this disease very early in life, usually in the newborn period, due to the presence of heart tumors. This provides the unique opportunity to investigate the development of ASD in this high-risk group during the first year of life. A recent study shows that an abnormal EEG signature has 100% positive predictive value for clinical seizures, 2-3 months prior to the onset of these seizures. These data have led to the initiation of a "prevention" trial in the high-risk infants with TSC using the anti-seizure medication vigabatrin. TSC patients have hyperactivation of the mTOR pathway, which controls neuronal protein synthesis similar to FMRP. The hypothesis that overactive mTOR signaling in TSC may be amenable to mTOR inhibitors has led to trials involving the use of this class of medications in patients with TSC. A large phase III trial demonstrated that adjunctive mTOR inhibitor treatment was effective for refractory focal epilepsy in TSC patients. Whether mTOR inhibitors will also be effective in improving neurodevelopmental symptoms including ASD is not yet known. A phase II trial was recently completed; results are pending.

Taken together, advances in the study and treatment of RTT, FXS and TSC have laid the groundwork for similar mechanism-based treatment trials in genetic disorders associated with ASD. Translating successes from animal studies have not been straight forward to date. Intellectual disability commonly affecting individuals with these neurogenetic disorders is an additional obstacle in study design in this field. Next steps will have to include biomarkers to help detect objective improvements in response to treatment and to identify optimal developmental periods to apply the treatment trials.

Technology-Based Interventions. Digital-based technology interventions for individuals with ASD have continued to increase in accessibility, breadth, and depth of use. Scientific evidence for the effectiveness of technology-based or technology-enhanced interventions has increased, with a larger number of RCTs appearing in recent years. Notable trials highlighting the breadth of technology applications in ASD research as well as their increasing rigor include: 1) a study of 61 minimally verbal children with ASD, 5 to 8 years of age, showing more rapid gains in spontaneous spoken language in a blended developmental/behavioral intervention began with speech-generating devices, as compared to beginning with spoken words alone ; 2) a study of 50 adult employees with ASD showing significantly decreased hours of job coaching when training was started with a personal digital assistant for vocational support ; 3) a study of 80 children with ASD 7 to 17 years of age with dental fear showing that specific classes of electronic screen media combined with content (specifically, video goggles of a favorite movie during a visit or video peer modeling provided on video goggles before a visit) reduced anxiety during a return dental visit; 4) a study of 49 dyads of teachers and children with ASD showing improved educational outcomes for children whose teachers were randomized to a consultation-based intervention delivered either face-to-face or via videoconferencing; 5) a comparison of 36 5- to 12-year-old children with ASD randomized to robot, rhythm, or control conditions showing no advantage of robots over rhythm training and some advantages of robots over control; and a study of 45 2 to 13 year-old children showing the effectiveness of a technology-enhanced mattress in promoting sleep quality.

In the field of robotics, recent work has highlighted potential advantages of robots over human agents for promoting communication, development towards creation of "closed-loop" autonomous systems for providing skill acquisition support, and accelerating intervention progress more broadly. Yet several reviews, surveys, and commentaries have highlighted a number of challenges and gaps also shared by speech generating devices, virtual reality, video games and computer-assisted instruction, mobile applications, and telemedicine. These challenges and gaps include the need for a greater number of studies (especially RCTs) involving more participants and greater methodological rigor; more focus on generalization in experimental design and interpretation; greater attention towards participant characteristics in result interpretation and study design and increased efforts towards personalization and adaptive systems; more careful consideration of stakeholder needs and limitations and incorporating stakeholder feedback in the technology development processes; increased focus on applicability of systems to individuals who are minimally verbal and/or have substantial comorbidities including motor and intellectual impairments; deeper cross-disciplinary integration of clinical/educational perspectives with technology/engineering expertise and vice versa; development of richer quantitative measures of response and change; research towards the development of practical service systems supporting developed technologies, including identification of pathways for translating research tools into sustainable products (e.g., see) ; leveraging of data mining and machine learning methods with attention towards rigorous computational and statistical methods; increased acceptance and facilitation of both replication studies as well as the dissemination of negative or unexpected results especially in well-designed studies.

Innovative Combinations of Therapeutic Modalities. Few examples exist in the combination of therapeutic modalities. One example would be the combination of psychopharmacology and behavioral treatments. A few of these types of studies are in progress, but none reported during this review period. This is obviously an area of great need, especially for comorbidities, such as anxiety, aggression, and depression. The core impairments of ASD (e.g. social communication) have not been responsive to drug therapies yet, but the possibility of combining drug with behavioral interventions still holds promise for improvement in these core areas.

Outcome Measures & Biomarkers

Metrics to Measure Treatment Response. Over the past few decades, significant progress has been made in the development of new behavioral interventions and identification of novel drug targets aimed at reducing core and associated ASD symptoms and improving quality of life across the lifespan. A major challenge in determining whether new treatment approaches are efficacious has been the measurement of treatment response. Because ASD is a heterogeneous disorder involving symptoms that vary depending on an individual's symptom profile, sex, cognitive and language abilities, and development level, measurement of treatment response is particularly complex in ASD. Moreover, many existing assessment measures were developed for screening and diagnosis and therefore are not sensitive to assessing change in symptoms over time. Over the past several years, considerable effort has been directed toward evaluating which existing measures are suitable for clinical trials and developing new quantitative, objective, and sensitive measures of treatment response. Increasingly, the input of key stakeholders, including caregivers and persons on the autism spectrum, is solicited to ensure that outcome measures reflect the priorities and needs of persons for which the treatments are being developed. Several reviews and consensus statements have been published that have evaluated the appropriateness of existing parent report and observational measures for clinical trials, including measures of social communication, anxiety, and repetitive behaviors. Studies validating observational measures of ASD symptom severity based on the Autism Diagnostic Observation Schedule have also been published, and a brief observational assessment of social communication change has also been recently developed.

Metrics to Better Reflect Stakeholder Perspectives. Beyond measures that allow us to better tailor our treatments to address mechanisms of change and understand core deficits in ASD, much more attention has recently been given to the quality of life outcomes for addressing the needs of individuals with ASD, including: academic success, autonomy and self-sufficiency, financial stability, health and well-being, inclusion, independent living, meaningful employment with fair wages, pursuit of dreams, recreation and leisure, respect and dignity, safety, self-identity and acceptance, social connections, and subjective well-being

Using such outcomes allows professionals, parents, and individuals to develop plans and efforts to help a person with ASD to advance daily in each of the quality of life indicators. It also allows planning to move away from seeking a goal such as “the individual will be employed upon completion of schooling” to “the individual will have achieved academic success, maximum independence, maximum self-sufficiency and is able to pursue their dreams to obtain a meaningful employment opportunity.” Quality of life indicators allows for defining the specific results and outcome of quality of life indicators and thus, when such indicators are maximized, the individual is able to fully live a life maximizing long term success. Measuring such outcomes can occur both short and long term and can be developed based on the needs of the individual in terms of their level of skills, functioning and ability. For example, for some on the autism spectrum, a long-term outcome of independent living might be that the “individual is able to fully live on his or her own without support.” Short term outcomes for such an effort would be related to incremental steps in getting to the long-term goal such as understanding responsibility of living independent, cooking skill development, budgeting, etc. Likewise, for some on the autism spectrum, a long-term outcome of independent living might be that the person is able to live alone as an adult with various levels of support related to needs of that individual. Short term goals might be helping the person with proper hygiene, grooming and life skill development, minimal cooking skill development, making decisions properly and effectively, etc. It is always best to use existing research on how best to measure outcomes as well as short and long term outcome settings related to quality of life indicators. Such research will help a professional, family member, and/or the individual be able to see how short term outcomes once met can lead to long term outcomes for each indicator

Biomarker Discovery. Biomarkers of treatment success as well as “stratification” biomarkers for matching people to the best treatment for them at the best time are desperately needed. Until it becomes possible to biologically measure treatment response, negative results from pharmacological and behavioral interventions will be difficult to interpret and positive results may not definitely indicate the requisite dose or duration of treatment. Predictive biomarkers, those that help to match individuals to particular treatments, will help us to create more precise treatments, and help the individuals and families we serve to avoid wasted time and resources. Ideally, biomarkers should be: 1) grounded in an understanding of basic developmental mechanisms; 2) sensitive, reliable

measures of targeted atypical processes; 3) useful at the individual level; 4) predictive of response and informative of mechanism(s); 5) useful as levers to improve treatment response; and 6) practical for implementation in medical settings.

Initial efforts have focused on developing measures that are linked indirectly or directly to underlying neural circuitry, which can offer insight regarding whether the treatment is influencing specific aspects of neural circuitry (target engagement), inform us of the neural mechanisms that might underlie the treatment effects, and predict treatment response. These measures include eye tracking (ET), electrophysiological (EEG) responses, and functional magnetic resonance imaging (fMRI), among others. Such measures can also serve as an early efficacy signal that can detect response to treatment before changes in more distal measures such as language and social abilities are evident. Early efficacy markers can be used to identify which individuals are most likely to benefit from a given treatment and/or in adaptive study designs to indicate early in the trial whether modifications in the treatment (e.g. dose) should be made.

ET is a class of techniques used to determine where someone is looking. Modern eye tracking systems typically use infrared cameras to track pupil position. Applications of eye tracking to ASD research have robustly identified diminished looking at social information in individuals with ASD relative to control groups (for a review, see ref), with effects evident across the lifespan from infancy (e.g. refs), through toddlerhood (e.g. refs), school age (e.g. refs), and into adulthood (e.g. refs); across multiple social targets including biological point-light displays (e.g. refs), emotional and non-emotional faces (e.g. refs), and complex naturalistic scenes (e.g. refs); and in multiple configurations including fixed camera setups to track looking at computer screens (e.g. prior references in this section), tablet screens (e.g. ref), and live displays of real-world actions (e.g. ref), as well as wearable eye tracking systems for more flexible use in real-world interactions (e.g. refs). Eye tracking has also been used to index atypical information processing and attentional processes in ASD via blinks (ref), pupil size changes (e.g. refs), search tasks (e.g. refs), and psychophysical methods (e.g. ref). Several studies have associated specific patterns of looking in ASD with atypical brain activation (e.g. ref, though see refs) as well as with concurrent or later deficits in language, nonverbal cognition, social interaction, or pragmatic skills (e.g. refs).

ET has great potential for acting as an early indicator of treatment efficacy by tracking changes in social attention (ref). While applications of eye tracking to clinical trials and interventions are still relatively new, results have been promising. A study of parent-mediated intervention for infants at high-risk for ASD (Video Interaction to Promote Positive Parenting) used ET to identify faster attentional disengagement in the treatment group, suggesting improved information processing speed and attentional flexibility (ref). Still, other studies have found that ET has limited associations with behavioral treatment outcomes (ref), suggesting further refinement or development of ET methodologies to match specific treatment targets may be warranted. ET studies have also shown that administration of intranasal oxytocin to adults with ASD leads to increased looking at faces, especially the eyes of faces, both in computer-based identification tasks (refs) and in live-interviews enabled via video streams (ref). ET studies of oxytocin in children with ASD have been primarily observational, with limited evidence that lower salivary oxytocin levels may be associated with lower attention towards eyes (ref). Studies of the effects of the anxiolytic propranolol on face scanning in ASD, in contrast, indicated decreased mouth looking in response to propranolol administration, with increased mouth looking associated with greater nonverbal communication impairment in the study (ref). Recently, an experimental ET battery comprised of prior tasks developed in the scientific literature was used by Roche pharmaceuticals to examine pre-post changes in attention in adults with ASD subsequent to the intravenous administration of a novel arginine vasopressin receptor 1a (V1a) antagonist. While the results should be treated with caution, given the exploratory nature of that study, this randomized double-blind placebo-controlled study indicated increased orienting towards biological motion in the group administered the V1a antagonist. Finally, a recent study using ET to track 6- and 12-month outcomes after a single infusion of autologous umbilical cord blood in children with ASD found increased looking at eyes and a positive correlation between improvements in Vineland socialization scores and increases in looking at eyes (ref). These results, taken together, highlight the increasing maturity of ET as a method for measuring response across a wide range of treatments.

Promising future directions for developing ET as a marker of change include furthering data-driven, computational, and machine learning approaches towards subtyping and stratification with the autism spectrum (ref) and for improved discrimination between individuals with ASD and controls (ref); the design of ET batteries with the express goal of treatment measurement use as opposed to explication of theoretical mechanism (ref); the adaptation and advancement of eye tracking metrics in technology-driven/technology-interactive interventions, such as virtual reality, robotics, and simulators (refs) as well as in novel adaptive paradigms designed to change gaze strategies (refs); and advancement of methodological considerations including the promotion of big-data studies, facilitation of replication, and increasing adherence to more rigorous and universal technical and methodological standards (ref).

Previous studies have shown that children and adults with ASD have distinct electrophysiological signatures, offering the possibility of using such measures to detect treatment response. For example, children with ASD exhibit atypical event-related potential (ERP) responses to faces vs. objects (e.g.), facial expressions (e.g.), and biological motion (e.g.), as well as differences in EEG patterns of neural coherence (e.g.). In future work, prior to these measures being useful as potential biomarkers, it will be important to demonstrate their ability to reliably predict a signature of dysfunction at the individual subject level, as opposed to group averaged data.

A few studies have demonstrated changes in these EEG signatures in response to treatment in randomized, controlled trials. Using an EEG measure derived from an early study of preschool aged children, it was found that early intensive behavioral intervention based on the Early Start Denver Model was associated with normalized patterns of EEG brain activity, as evidenced by a shorter Nc latency and increased cortical activation (decreased alpha power and increased theta power) when viewing faces. Greater activity while viewing faces was associated with improved social behavior. Expertise training with faces in adults with ASD was found to be associated with electrophysiological changes to faces (P100 ERP component;). In a randomized controlled trial of families with an infant at familial high risk for ASD age 7-10 months, the effects of a parent-delivered intervention designed to promote social and communication development on parent-child interaction, attention disengagement, adaptive function, and event-related potentials to vowel change were examined. Improvements in infant attentiveness to the parent, improved attention disengagement, and parent-rated infant adaptive function. Contrary to expectations, there was a negative effect on language measures and ERP responsivity to vowel change. In a second randomized, controlled trial, high risk infant siblings who received a parent-delivered intervention that provided increased social stimulation showed a significantly greater increase in frontal EEG theta power and faster habituation to faces between 6 and 12 months. Van Hecke et al. found that adolescents with ASD, who were provided with an evidence-based social skills training program (PEERS), exhibited shifts from right-hemisphere gamma-band EEG asymmetry to left-hemisphere EEG asymmetry. Changes in EEG, including peak alpha frequency and ERPs related to error and novelty detection, have been documented after treatment with TMS. These studies suggest that EEG, which is a non-invasive measure that can be used to record patterns of brain activity throughout the lifespan, offers promise as a metric of treatment response related to neural circuitry. Furthermore, distinct EEG signatures have been found among genetic subtypes of individuals with ASD and related disorders which could be used in future clinical trials testing drugs that are targeted to individuals with ASD with specific genetic syndromes.

Magnetic Resonance Imaging (MRI) techniques, including fMRI and Diffusion Tensor Imaging (DTI), have provided a wealth of information regarding the neurobiological underpinnings of ASD. Specifically, task-based fMRI studies have pointed to atypical social-brain functioning and activation in ASD while resting-state functional MRI and DTI have pointed to deficiencies in integrative social information processing as indicated by white matter atypicalities and diminished long-range connectivity (see refs for review).

Despite the potential for brain imaging techniques to elucidate mechanisms underlying behavioral treatment response (ref), few studies have directly used it for treatment monitoring or prediction of treatment efficacy. However, this appears to be rapidly changing, with several recent studies expanding on earlier work (for reviews see refs). Notably, a case-series study using a biological-motion fMRI task to examine the effects of pivotal response treatment (PRT) in young children with ASD found individualized changes in social brain function towards that seen in typically developing children (ref). These findings were built upon in a larger study where it was

observed that half the children with ASD at baseline exhibited hypoactivation and the other half hyperactivation of the right posterior superior temporal sulcus in response to observing biological motion (the movements of another person); these groups exhibited differential profiles in response to treatment consistent with scaffolding mediated either through social reward learning (hypoactive group) or improved emotional regulation (hyperactive group) (ref). A related study demonstrated that brain responses to coherent versus scrambled biological motion could serve as a robust biomarker of ASD in male (but not female) children. The team then applied this biomarker approach to predict and explain the neural mechanisms of treatment response to a 16-week course of PRT. Similarly, following up on prior research showing changes in brain areas associated with compensatory neural mechanisms for face processing in response to a computer-based facial-emotion training system, the Frankfurt Test and Training of Facial Affect Recognition (FEFA) (ref), a recent study has shown, in adolescents and adults with ASD, increased activation in social brain regions, including areas associated with face processing and emotional response, subsequent to FEFA training when compared to an ASD no-training group (ref). Finally, a study of children with ASD undergoing an intensive reading intervention showed, via resting-state fMRI, increased functional connectivity of Broca's and Wernicke's, with enhanced connectivity of these components within an identified "reading network" associated with improvements in reading comprehension (ref). A follow-up fMRI study using a sentence imagery task found post-training increases in visual and language area activity, with additional subcortical and right hemisphere activity suggesting compensatory routes for language comprehension in participants undergoing treatment.

Considerable progress has also been made recently in regards to the use of brain imaging techniques for understanding *in vivo* pharmacological neural action in individuals with ASD. Studies have shown that administration of intranasal oxytocin to children with ASD results in increased activation in key social brain areas implicated in autistic psychopathology including reward circuitry, social attention, and mentalizing areas (ref), with recent work suggesting both increased connectivity between reward and socioemotional processing networks (ref) as well as modulation of brain pattern activation dependent on socially-interactive context (refs). Studies of other compounds include findings of propranolol-induced decreases in resting-state fMRI functional connectivity in ASD in dorsal medial prefrontal cortex attention network components and increased connectivity in medial temporal lobe components (ref); and bumetanide-associated increases in brain activation in face encoding, expressive face processing, and reward system brain networks together with well as improvements in emotion recognition.

In summation, advancements in developmental neuroscience, including the charting of developmental trajectories in infants at high-risk for developing ASD stratified by outcomes (ref), are beginning to provide the context for expanding the scope and applicability of brain imaging techniques for monitoring treatment across the lifespan, including before the signs of ASD are overtly apparent. Given the many successes yielded from the application of MRI methods to the development of biomarkers in ASD and related fields, considerable opportunity exists for further research and development in this area.

Digital technologies, such as mobile devices, provide another approach for developing quantitative, objective, and sensitive measures of treatment response. These tools provide opportunities to study biomarkers in combination with self-report data, often in more naturalistic contexts such as the home. Novel analytic methods, such as machine-learning and computer vision analysis, can provide new insights into patterns of behavior. Examples of the application of digital phenotyping approaches to ASD include the use of actigraphy to track and quantify sleep, autonomic measures, such as pupillary responses, heart rate variability, and electrodermal responding, computerized video tracking to measure social approach, automated vocal analysis, and the use of computer vision analysis to measure attention and facial expressions. Although early in their development and application to ASD populations, such measures have the advantages of being scalable, objective, and feasible. Thus, studies that explore their utility as a method of treatment monitoring should be pursued.

Recently, a number of substantial investments have been made to support large, collaborative efforts aimed at validating biomarkers and outcome measures for use in ASD clinical trials. These consortia involve public-private partnerships among academia, advocacy and other nonprofit organizations, government, and industry with a goal of de-risking investments into pharmacological ASD trials and optimizing the success of such trials. These projects

are examining a wide range of potential biomarkers and their relationships with observational and caregiver-report measures of behavior in large samples of individuals with ASD vs. typical development over time. Furthermore, regular communication, data-sharing agreements, and shared measures across the existing consortia will increase the scientific utility of these investments.

EU-AIMS (European Autism Interventions—A Multicentre Study for Developing New Medications) is an international consortium of scientists, led by Roche and King's College London. Among the primary goals of EU-AIMS are to develop and validate translational measures that can be used to test novel ASD therapy and to create a robust clinical trial infrastructure to conduct clinical trials. In the United States, Janssen has invested in the development of the Janssen Autism Knowledge Engine (JAKE™), which is being validated in a multi-site study to provide quantifiable and reproducible measures for use in treatment monitoring and identification of ASD subgroups. JAKE is a mobile and web-based application that includes an ASD symptom inventory coupled with biosensors, which is designed for large scale clinical trials. JAKE is specifically designed to be used by community-based clinicians who do not have an extensive background in biosensor methodologies, such as EEG and eye-tracking. ABC-CT (Autism Biomarkers Consortium for Clinical Trials) is an NIH-, FNIH-, and Simons Foundation-funded consortium of sites that aims to develop, validate, and disseminate objective measures of social function and communication for ASD with the ultimate goal of advancing these measures as markers and predictors of treatment response. The ABC-CT is led out of Yale University and includes collaborating implementation sites at Boston Children's Hospital, Duke, UCLA, and University of Washington.

In sum, multiple laboratories are conducting studies to develop better ways of measuring treatment response. Continued investment in such studies will ensure that, as new behavioral and medical treatments are developed, we will have the capability of testing their efficacy. Such investments will also be essential for developing improved methods for identifying subgroups that are responsive to specific treatments and identifying neural mechanisms underlying treatment response.

Section 3: Accelerating Discoveries & New Objectives

Accelerating Research & Increasing Access to Evidence-Based Interventions

While research in interventions for individuals with autism has shown consistent growth and advancement, opportunities exist for accelerating the pace of research. First, high-quality intervention studies are expensive to conduct and require substantial specialized expertise to oversee. Increased funding can expand the breadth, depth, reach, and rate of progress of intervention science. The stability of research funding is also important, as funding instability diminishes incentives for research infrastructure investment, can result in abandonment of developed research capacity, can interfere with the ability of researchers to maintain positive ties with their community, and can force researchers (especially early investigators) to leave for alternative careers. Commitment to building and maintaining research infrastructure, such as support for longer-term investigator-, center-, or network-focused funding mechanisms, can mitigate the impact of funding uncertainties.

Trends in personalized medicine (Ng & Weisz, 2016) provide additional inspiration for accelerating discovery. Next generation trials may explicitly augment the question of "does this treatment work?" with "for whom does this treatment work?" For example, advancement of new or reconceptualization of existing treatments into modular therapies (where therapies are organized into therapeutic modules each targeting that can be combined and reused in flexible arrangements) can provide finer granularity and more tractable opportunities for understanding individual change. Similarly, adaptive interventions (e.g. Sequential Multiple Assignment Randomized Trials (SMART); see Kasari et al., 2014) are personalized based on a patient's response or non-response and can be further tuned and optimized by enriching samples at different points in the adaptive treatment strategy (Liu, Wang, & Zeng, 2016), allowing for time-varying intervention intensity based on intermediate responses (Dai & Shete, 2016), leveraging pilot studies (Almirall, Compton, Gunlicks-Stoessel, Duan, & Murphy, 2012), and identifying more powerful, repeatable, flexible, and usable tailoring variables (see our previous discussion of *Biomarker Discovery*). These adaptive and more flexible study designs can make more efficient use of existing clinical, research, and participant resources, providing more information to researchers

and potentially greater benefit to participants. To encourage adoption, investment in study design methodology research (including dissemination of methods and development of trial design resources) will be of significant value.

Additional opportunities may emerge from standardization of reporting and protocols so as to facilitate aggregation or comparison of clinical trial data at meta-analytic levels. Careful inspection of evidence gaps at macroscopic or microscopic levels may thereby identify holes in research evidence. For example, if participants are discontinued when they display no progress for 6 weeks, no evidence will exist for what happens when the intervention is continued for 10 weeks. Designs where clinical uncertainty is matched with appropriate variation along key implementation parameters may provide more comprehensive information about treatment effectiveness when the evidence is examined from higher analytic levels. Sharing data at finer level of detail, e.g. at the level of participants' assessment items, specifically tracked behaviors, or medical indicators, may additionally facilitate data mining investigations that may help to identify more streamlined assessment (e.g. Bone et al., 2016) or nuanced precursors and predictors of treatment response (e.g. see Shih, Patterson, & Kasari, 2016). Application of statistical or computational methods, from computational neuroscience (Wang & Krystal, 2014) to text mining applied to medical records (Abbe, Grouin, Zweigenbaum, & Falissard, 2016), can synthesize and transform extant sources of data into relevant knowledge (Huys, Maia, & Frank, 2016). These methods and models may not only lead to generative models for testing and advancing new hypotheses, but may facilitate the development of more multilevel systems approaches for understand autism, including genetic (Brandler & Sebat, 2015), neural (Yang et al., 2016), and behavioral components.

The development of interventions using digital technologies offers new opportunities to accelerate research progress. The ability of technology-based systems, such as mobile applications, wearables, and internet resources, to automatically record and generate measures from will increasingly provide richer, denser, and more meaningful information to researchers. Additional emphasis should also be placed on transforming these signals into digestible and useful forms to maximally aid and personalize ongoing, real-world treatment of issues faced by individuals with ASD. As the understanding of these data streams matures, new methods and systems will need to be created to harness the power of this data and to filter and control the massive flows of information reaching data consumers. Analogously, the proliferation of technology-based platforms purporting to help individuals with ASD points to a need for new, efficient, and scalable methods and infrastructure for evaluating technology-based interventions.

Additional infrastructure investments are likely to yield compounding gains in autism intervention research progress. Creating and sustaining networks of institutions, investigators, clinicians, and families committed to shared, large-scale implementation of interventions or experimental research (e.g. the Autism Treatment Network (ATN)/Autism Intervention Research Network on Physical Health (AIR-P) ("The Autism Speaks Autism Treatment Network," 2013), Simons SPARK ("SPARK," 2016)) will combat fundamental heterogeneity issues in ASD research, leading to more reproducible and robust scientific findings and, consequently, opportunities to impact policy. These networks can be leveraged to promote testing of novel interventions, exploration of unique scientific perspectives, and commitment to a culture of non-exclusive innovation transcending traditional boundaries. Additional investment should focus on knowledge transfer for bridging gaps between scientific evidence and clinical applications, including specific attention towards "Valleys of Death" in translational research between basic science findings and clinical interventions and between evidence-bases and effective community implementations (Szatmari, Charman, & Constantino, 2012).

Extra resources should be directed towards promoting the development of applied scientific tools, including more robust statistical methods, data mining techniques, basic science methods, laboratory techniques, and optimized pipelines for discovery. Interdisciplinary collaboration should be promoted, and barriers to sustained partnerships identified and overcome (e.g. see Kim, Paul, Shic, & Scassellati, 2012), especially mismatches in discipline-specific foci of success (e.g. NSF vs. NIH perspectives). However, while collaboration is desirable, multidisciplinary mentorship may be even more valuable, creating a new generation of scientists capable of bringing their unique perspectives to challenge fundamental questions in autism research. Identifying methods for promoting direct integration of scientists from underrepresented fields into autism research is warranted.

Approaches could include clinical mentorship, dedicated training programs, intensive workshops, and creation of training resources. Additional resources could also be spent at the tail end of intervention science, on the wider dissemination of implementable discoveries. Examples would include encouraging Phase II transitions to Phase III trials, identifying appropriate industry partnerships to foster larger-scale intervention implementation (e.g. see Shic et al., 2015), and *in vivo* studies of ongoing new intervention integration efforts. Incorporation of business and operations perspectives into autism research infrastructure development may help to optimize intervention deployment efficiency, enabling more studies to be conducted in a sustainable fashion. By focusing on practical barriers to ultimate treatment deployment, barriers which include insurance, provider adoption willingness, and marginal expenses, a more robust, efficient, and complete pipeline from idea to effective individual treatment can be realized.

Cultural shifts in scientific perspectives can also accelerate the pace of progress. A willingness to accept publication of studies with negative findings is critical, as is ensuring rigor in psychological and medical trials. Positive developments include the development of the Registered Reports publication format (Nosek & Lakens, 2014) and facilitation and appreciation of replication (Simons, 2014). Decreasing the turnaround to scientific results dissemination will also catalyze research progress. Just as the open access journal movement (e.g. PLoS One, PeerJ) has provided more global access to research results, the increased prominence of non-peer reviewed preprint repositories in physics (arXiv) and life sciences (bioRxiv) is providing more rapid access to new findings before formal peer review. These trends, though not without their critics nor without flaws, are part of a movement towards faster, more open, and more comprehensive sharing of research results. A focus on overcoming concerns, e.g. regarding predatory publishing, a perception of pay-to-publish, risks of scientific scooping, low-quality reporting, and opportunities for unethical research conduct, will help realize potential gains in accelerated research progress.

Empowering stakeholders, including families and individuals with ASD, to act as active directors in the research process could also accelerate scientific progress. Development of tools to help stakeholders manage and maintain research, educational, behavioral, and clinical records could help them better advocate for participation in studies most relevant to their needs or most aligned with their personal visions. With a focus on usability and controlled data sharing, such tools could become interfaces by which information could be bi-directionally shared with researchers and relevant providers, reducing redundancy in information requests, streamlining study deployments, and reducing participant burden. Currently, several incarnations of such systems have been developed, including Microsoft HealthVault and Apple HealthKit, but efforts towards tailoring interfaces, cross-platform interoperability, and common standards should be pursued so as to best meet the specific needs of the autism community, to prevent data from becoming unnecessarily locked to proprietary platforms or formats, and to better enable data exchange. Creation of user-friendly research registries that promote awareness of relevant ongoing intervention studies or technologies, that can be personalized by user preferences (including constraints on geography, participation characteristics, and study facets), that are updated regularly and managed in a sustainable fashion, and that facilitate connections between legitimate researchers and qualified research participants (with appropriate governance of privacy and participant rights) would further enable stakeholders to direct their research agenda. Adaptation of stakeholder-held records, including genomic information (see SPARK, above), for the purposes of creating an interface that would facilitate recruitment of participants with extremely specific characteristics (e.g. pharmacological trials targeting specific gene mutations, see Crawley, Heyer, & LaSalle, 2016) may be critical for appropriately powering highly-targeted studies and for providing stakeholders access to the most tailored and innovative science. Throughout these processes, the involvement and feedback from the autism community should be emphasized so as to provide continuous context for research endeavors. It may be beneficial to provide more unified forums for soliciting stakeholder feedback and discussion. Such a focus could reveal areas of need which should be targeted more directly by the weight of scientific inquiry or point to areas where additional rationale and scientific dissemination should be provided so as to clarify the intention and ultimate promise of ongoing research. Still in other situations, such open discourse may reveal that for subsets of the autism spectrum specific interventions are not warranted, nor appreciated.

Finally, a focus on the comprehensive environment of support for individuals with autism, including friends, families, educators, clinicians, and other supportive members of the community, could lead to a greater understanding and acceptance of treatment research by the community, reducing barriers to implementation and increasing access to target populations. In a similar vein, broader promotion of autism awareness among the general population is still needed so as to foster greater understanding of neurodiversity and greater appreciation for the criticality of concerted and continued autism research. Research focused on the promotion of positive change for individuals with ASD is just half the story. Even as we move to accelerate research progress in intervention science, a similar emphasis needs to be placed on accelerating outreach and improving knowledge, tolerance, acceptance, and inclusion of autism into mainstream society. It is through this two-sided push – interventions targeting not only individuals with ASD but also everyone else – that we may expect to see the most rapid gains towards improving the quality of life for individuals with ASD and their families.

Three New Objectives

We close this 2017 update with the proposal of three new objectives as outlined below. The new objectives are followed by a delineation of five cross cutting themes, that we recognized to be essential to all three new objectives, and applicable to many of the previously established objectives. The new objectives are:

- **New Objective 1: Develop and improve pharmacological and medical interventions to address both core symptoms and comorbidities in ASD.**
- **New Objective 2: Create and improve psychosocial, developmental, and naturalistic interventions for the core symptoms and comorbidities in ASD.**
- **New Objective 3: Maximize the potential for technologies and development of technology based interventions to improve the lives of people on the autism spectrum.**

Cross cutting themes are:

1. We recommend prioritizing the understanding of the brain basis and mechanisms underlying all therapeutic approaches.
2. Consider designs and recruitment strategies that allow for testing the ways in which we might maximize effectiveness and precise matching of treatment plans to individual needs and neurobehavioral profiles by combining therapeutic approaches.
3. Develop more robust, standardized outcome measures, including adaptive measures, predictive measures, biologically-based metrics, measures that address heterogeneity, and measures of practical outcomes that will help better target therapies to individual needs and goals.
4. Ensure support for the entire intervention research pipeline including the training of the next generation of multidisciplinary intervention scientists.
5. Strive to put more in the hands of practitioners through translation of research to community based practice and use of effective, novel dissemination strategies.

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