

2013 IACC Strategic Plan Update – Draft Conclusion – Prepared by Tom Insel, OARC and John Robison

Progress

The *2013 Strategic Plan Update* details the progress that has been made on the scientific questions and investment recommendations of the IACC Strategic Plan. Of the 78 specific Plan objectives, 72 have fully met or partially met the recommended budget. Overall, approximately \$1.5B in public and private research funding has been dedicated to ASD projects over the past 5 years, with an average funding increase of 39% across the Strategic Plan Questions for the period following its initial release in 2009. This increased investment has brought forth a range of scientific advances at all levels of the Plan.

The state of the science has dramatically changed in the ASD field since 2008, reflected in a significant increase in the number of publications. While biological differences in individuals with ASD were hypothesized earlier, now there are data demonstrating specific changes in the genome and epigenome, gene expression, cell structure and function, brain connectivity, and behavior that have been linked to the causes and underlying biology of ASD. Over the past 5 years, genetic studies have revealed that genetic variation ranging from changes in single bases to alteration of large regions of DNA or even extra chromosomes can contribute to ASD risk, and that both inherited and spontaneous mutations can play a role. Several environmental factors have emerged as potential contributors to ASD risk in the past five years, including: prenatal maternal infection, preterm birth, advanced maternal and paternal age at conception, short inter-pregnancy interval, as well as some data suggesting that exposure to air pollution, phthalates and pesticides during pregnancy may also increase risk. Vitamin intake, particularly folic acid, during the pre-conception period has been identified as a possible protective factor against ASD risk, while both the genetic and environmental data now point to the early months of gestation as a critical period for the development of ASD.

Advances in screening tools such as the Modified Checklist for Autism in Toddlers (M-CHAT) and the Infant-Toddler checklist, with an emphasis on early and repeated screenings, now provide a realistic future goal to identify 95% of children with ASD before the age of 24 months. New technologies to detect differences in eye-tracking patterns, and new research on white matter tract development and posture control in infants also introduce the potential to detect ASD as early as 2-6 months of age. This ability for early ASD detection, however, will depend on large community based validation studies of screening in the general population and only become clinically useful if efficient, cost effective tools can be designed around these new capabilities. It will also be critical to ensure that following an early screening, parents readily seek diagnosis and intervention, and that there are effective early interventions available. Recent clinical trials of behavioral interventions have demonstrated their positive impact on outcomes and begun to provide the evidence base needed to support the widespread use of these advances in the community. However more needs to be done to make these therapies affordable and scalable to large and diverse community settings, and efforts are needed to increase the number of children who progress from identification in early screens to diagnosis and early intervention. Disparities in access to diagnosis and treatment based on resources, ethnicity, and gender remain another significant challenge.

Studies of animals with gene mutations that cause syndromic forms of autism have demonstrated that symptoms can be reversed in animal both in early development and in adulthood. While these studies may not translate to humans, they indicate that some symptoms of autism may be amenable to treatment even later in life, identify possible drug targets, and they provide a pathway for developing treatments for the core symptoms of ASD. Clinical trials in toddlers have demonstrated the value of early behavioral intervention, with gains in behavior and function as well as the first demonstration of measurable changes in brain activity in response to intervention. Several trials are currently underway, ranging from exploratory trials of novel interventions to tests of currently used treatments. Over the past five years, a large clinical network has been developed, several pharmaceutical companies have become engaged in ASD research, and new technologies have emerged that may prove transformative. This field still requires standardized, sensitive outcome measures and biomarkers that can both stratify the heterogeneous ASD population and serve as rapid indicators of clinical response.

Recent studies have revealed the tremendous service needs within the community, with data showing that young adults transitioning out of the educational system frequently lose their services access and often have limited opportunities for employment and independent housing. While more data are needed on the needs of adults with ASD so that services can be more appropriately targeted, there is already an opportunity to collect data on the effectiveness of current services being delivered in the community and through projects such as federally funded state demonstration projects, and in some cases, to do comparative studies that could begin to make improvements in services for adults in the near term.

One of the most encouraging signs of progress has been the increased research infrastructure over the past 5 years, helping the scientific community embrace a culture of data integration and sharing. Several large scale government funded research centers, privately funded efforts, and some public-private collaborative projects have been built in the past five years. The National Database for Autism Research (NDAR), a hub that stores and shares aggregate data, from exomes to images, has grown to over 70,000 human subjects. Efforts such as the NIH Neurobiobank and the Autism Brain Net have been established to try to expand the supply of available brain and other tissue samples for ASD and brain disorder research. In addition, the Interactive Autism Network (IAN) and Autism Genetic Resource Exchange (AGRE) give families the opportunity to share data and participate in new models of more rapid, interactive clinical trials, expanding the possibilities for future research.

Relative to many other areas of biomedical research, ASD science is still a young field. While the past five years have seen rapid growth and substantial scientific progress, the Committee recognizes the large gap that still remains between advances made in research settings and practical benefits that are ready to be delivered to individuals and families living with ASD today. We remain far from the aspirational goal of research to yield tangible improvements in quality of life for people with ASD across all settings and communities. An intensified effort will be needed to ensure that recent promising discoveries are rapidly translated into clinical practice and services that will improve quality of life for individuals with ASD.

In conducting this review, the Committee recognized several core needs that spanned across multiple areas on the research portfolio:

- **Scaling Up:** Many of the screening tools, interventions and services approaches that have been developed to date are effective in research settings, tested in small groups. In order for these tools and approaches to have the potential to impact the community, they must be scaled up to be useable in the full range of community settings.
Population Inclusion: Screening tools are frequently tested in the siblings of ASD children. Children with no family history of ASD, adolescents, and adults must all be considered in future screening and diagnostic tool development. For other studies, many participants have mild disability and are in areas with good access to medical care. It is vital that participants across the full range of ASD disability, across all periods of the lifespan, and from underserved populations are included so that tools developed will have broad applicability.
- **Research to Practice:** In the arenas of interventions and services, there are already many practices that are being utilized within the community, and there are interactive networks of individuals and families available, providing an opportunity to study the use of these interventions and services in a real-world setting. More academic and community partnerships and new clinical trial approaches are needed to leverage these resources and gain valuable insight into what works well in the community. The new Patient Centered Outcomes Research Institute may be an opportunity for such studies.
- **Addressing heterogeneity:** A remaining challenge is to address the heterogeneity of ASD which is comprised of different conditions resulting from different underlying biology and causes. The development of predictive and early efficacy biomarkers that can identify subtypes of ASD that will respond to different treatments will be essential to move to a precision medicine approach for ASD.
- **Leveraging Existing Infrastructure:** In the past five years, both public and private resources have been invested in establishing infrastructure for surveillance, clinical research, environmental studies, and data sharing. To fully utilize these resources and gain the maximum value from these investments, agencies and organizations should consider building new studies onto these existing resources.
- **Applying Strategies from Other Fields:** Scientific disciplines relevant to autism are making considerable advances in the study of other health conditions. Over the past five years, there has been much success in learning about ASD biology from research on related disorders. Similarly, ASD researchers may be able to adopt successful strategies from other disease fields to solve issues such as how to detect trace chemicals in small biosamples effectively or how to effectively reach underserved populations with tools and services. Finally, the data collected by longitudinal studies and the data available through NDAR need to be exhaustively analyzed.
- **Standardized Outcome Measures:** In order to truly determine the effectiveness of interventions and the outlook across the lifespan, measurements of outcomes that are responsive to interventions and quality of life measures that can help determine the effectiveness and impact of services must be identified and standardized.

Future Directions

History may identify the past five years as an inflection point for our understanding of ASD. Increased investments (especially from private sources), improved resources for research, and expanded communities of scientists entering this field all provide hope that recent progress will accelerate. Many new areas of science, from microbiomics to social prosthetics, may transform

our understanding of ASD with entirely new tools for interventions. One of the greatest challenges will be finding the right balance between science that can immediately improve quality of life for individuals with ASD and science that offers a deep understanding of ASD with the promise of prevention or cure. The ASD community has a diversity of views on how to set this balance, with some focused on identifying the causes with the goal of preventing ASD, reducing disability or finding a cure, while others focus on accommodation, inclusion, and acceptance. In the near term, science can serve both sets of goals to develop a deeper understanding of the many forms of ASD and enhance interventions, services and supports that can offer individuals with ASD opportunities for independence and full participation in community life.